



Different Potential Biological Activities of Benzimidazole Derivatives



Asma S. Al-Wasidi¹, Moamen S. Refat^{2,3}, Ahmed M. Naglah^{4,5}, Ahmed A. Elhenawy^{6,*} 

¹ Department of Chemistry, College of Science, Princess Nourah Bint Abdulrahman University, Riyadh 11671, Saudi Arabia, asalwasidi@pnu.edu.sa

² Department of Chemistry, Faculty of Science, Taif University, P.O. Box 888, Al-Hawiah, Taif 21974, Saudi Arabia, msrefat@yahoo.com

³ Department of Chemistry, Faculty of Science, Port Said University, Port Said, Egypt

⁴ Department of Pharmaceutical Chemistry, Drug Exploration & Development Chair (DEDC), College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia, anaglah@ksu.edu.sa

⁵ Peptide Chemistry Department, Chemical Industries Research Division, National Research Centre, 12622-Dokki, Cairo, Egypt

⁶ Chemistry Department, Faculty of Science, Al-Azhar University (Boys' Branch), Nasr City, Cairo, Egypt

Abstract

It has been demonstrated that most of the various derivatives of benzimidazole have distinct biological activity that gives clear promises to treat many different diseases, and for this wonderful reason, all the different new formulations based on benzimidazole remain of high concentration of interest to most scientists interested in the pharmacological fields. In this review article, we focused on mentioning many different derivatives of benzimidazole and studying its biological activities for humans and animals alike. In addition, in this reference article we have also focused on the more active benzimidazole derivatives that have shown significant pharmacological effect among patients.

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

2. Introduction

Benzimidazole is a heterocyclic aromatic compound. It is a critical pharmaceutical compound and has a distinct structure in the field of medicinal chemistry. Moreover, nowadays, many options make it have many pharmacological properties. Alternatively, the most prominent benzimidazole compound in nature is N-ribosyl-dimethylbenzimidazole, which has a distinct cobalt linkage to vitamin B12 [1]. Historically, the use of benzimidazole goes back many years in the past, when various structural modifications of the newly constructed compounds have been studied, and thus the different pharmacokinetic effects of these modern derivatives have been studied. Alternatively, many different derivatives of benzimidazole were newly synthesized, as both fluorine and propylene as well as

tetrahydroquinoline was replaced, which gave impressive results from a biological viewpoint, as it led to a high increase in biological activity [2–4]. It is worth noting that most of the different chemical derivatives of benzimidazole play an effective and critical role in the medical field as a distinct treatment for many different diseases, for example anti-all types of infections [5], and anti-various types of microbes [6], and it is used as a diuretic. It contains urine in humans and animals [7], as well as antivirals [8], and is considered a powerful antidote to various cancers [9], and its success has been proven as an antiprotozoal [10], anti-ulcer [11], antioxidant [12], and anti-asthma [12, 13], antidiabetic [14], cystocide [15], analgesic [16], antihypertensive [17], anthelmintic [18], anti-HIV [19], anticonvulsant [20], and deodorizing Antispasmodic [21]. Most of the

*Corresponding author e-mail: elhenawy_sci@hotmail.com

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various benzimidazole derivatives showed strong activity that gives hope for a successful treatment of many diseases. In addition, for these reasons, the great interest of all scientists and those interested in the field of pharmacological study has been noted to focus research on the construction of benzimidazole derivatives. Also, in general, it has been observed through our recent references that synthetic organic chemistry has a distinct biological activity in all different application directions [22–57]. For this reason, we focused in this review on the knowledge of several different benzimidazole derivatives while studying their pharmacological activities.

3. Compounds having benzimidazole

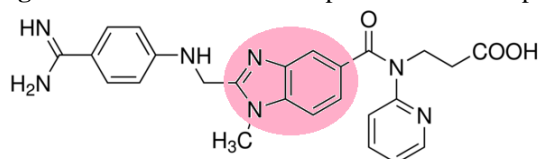


Fig. 1. Structure of Dabigatran

nucleus

3.1. As oral anticoagulants

Dabigatran (Fig. 1) is a premium anti-coagulant that is administered orally. It is worth noting that it acts as a direct inhibitor of thrombin (Factor IIa). However, it can be used successfully to prevent and reduce stroke in most patients who periodically suffer from a trial Fibrillation. This drug was developed to play an important role as an alternative to warfarin. In addition, the use of Dabigatran has been reported to be a strong inhibitor of the formation of various blood clots in the veins, and this observation is only in adults, especially those who have undergone surgery to replace one of the hip or knee joints [58].

3.2. As oral antidiabetic

Schimke and his group in 2007 have demonstrated that the use of oral diabetes medications of type 2, a disorder involving insulin resistance secreted

during the treatment phase. They also demonstrated that antidiabetics contain benzimidazole as well as Rivoglitazone (Fig. 2) [59].

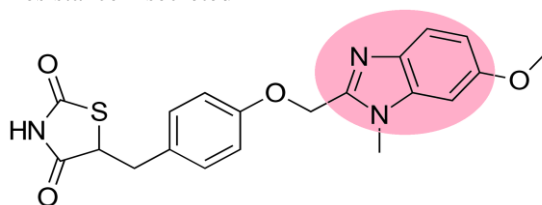


Fig. 2. Structure of Rivoglitazone

3.3. As oral antiviral

It is a scientifically proven fact that medicines used as antivirals of all kinds are a class of medicines used to treat viral infections, for example, human

immunodeficiency virus, influenza, viral hepatitis, herpes virus, and human cytomegalovirus. Maribavir is a critical example of an antiviral benzimidazole-containing (Fig. 3) [60].

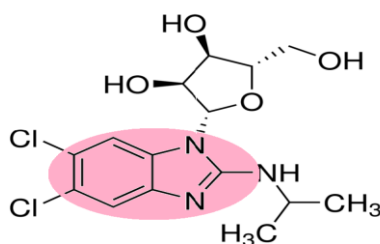


Fig. 3. Structure of Maribavir

3.4. Drugs in HSDD

HSDD (hypoactive sexual desire disorder) is the most common sexual disease, especially for

females. Flibanserin (Fig. 4) is an important and effective drug benzimidazole-containing and has been used with success in treating HSDD.

Flibanserin is a newly important 5-HT_{1A} receptor agonist and a 5-HT_{2A} receptor antagonist and for this reason it is used as a distinct treatment and is considered non-hormonal for women with HSDD

of all ages, especially in the premenopausal period. It is worth noting that Flibanserin was studied and reported as a drug for treating depression at the beginning of its discovery [61, 62].

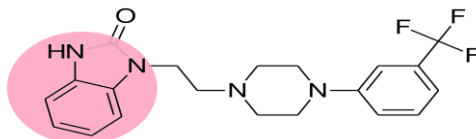


Fig. 4. Structure of Flibanserin

3.5. As anti-hypertensive

Medicines that are used among patients as antihypertensives can be defined simply as drugs used to treat high blood pressure and reduce to the normal range. One of the most important advantages of antihypertensive treatment is that it protects patients from complications of high blood pressure.

3.5.1. Candesartan

Candesartan (Fig. 5) is an important example as an angiotensin receptor blocker, and this drug is also used for treating high blood pressure and has also been shown to be successful in treating congestive heart failure. However, a patent was registered for

Examples of these complications are serious stroke and myocardial infarction [63]. Candesartan, Candesartan cilexetil, and Telmisartan, (Fig. 5, Fig. 6 and Fig. 7), respectively, are a group of clinically important antihypertensive drugs, and all these drugs have the advantage of having a chemical formula that they contain benzimidazole [64].

this drug in 1990, and it was approved for medical use in patients in 1997 [65]. An important and reported note is that candesartan is also available along with thiazide diuretics (of various brand names), always hydrochlorothiazide, to achieve an additional antihypertensive effect [66, 67].

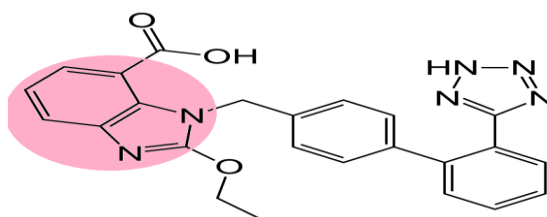


Fig. 5. Structure of Candesartan

3.5.2. Candesartan cilexetil

Candesartan cilexetil (Fig. 6) is completely metabolized by the application of esters in the intestinal wall, while this drug is absorbed into the active part of Candesartan. Moreover, the use of a different form of prodrug increases the important bioavailability of Candesartan. In addition, its bioavailability is poor, ranging from 15% (from Candesartan Celexetil tablets) to 40% (from

Candesartan Celecetil solution) [68]. Candesartan cilexetil can be considered as, an effective treatment for patients suffering from high blood pressure and proteinuria. Moreover, it does not lead to any damage to the renal function. It is for this reason that it has been reported that the use of Candesartan Silicetil in patients helps maintain permanent renal function [69, 70].

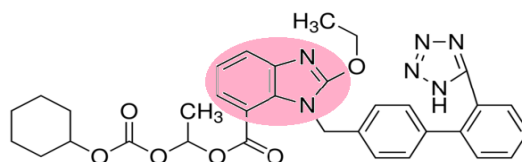


Fig. 6. Structure of Candesartan cilexetil

3.5.3. Telmisartan

Telmisartan (Fig. 7) is an effective anti-angiotensin II receptor antagonist used in the successful

management of hypertension [71–73]. Moreover, by comparing this drug with other angiotensin receptor blockers, it was observed that Telmisartan was not associated with an increased risk of developing

cancer. For this reason, this study provides complete reassurance to patients who take Telmisartan for the short term only [74].

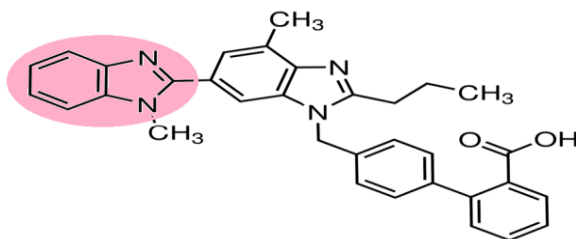


Fig. 7. Structure of Telmisartan

3.6. As anthelmintics

These are drugs that are used to treat a wide variety of helminth infections. The best examples of these drugs are Albendazole (Fig. 8), Mebendazole (Fig.9), and Thiabendazole (Fig. 10). These medicines

contain benzimidazole, they are deemed a wide variety of anthelmintic drugs, and these drugs are also effective against multiple nematode infections [75, 76].

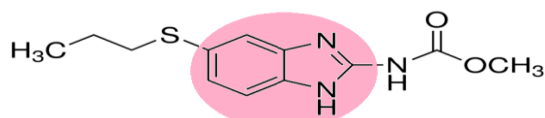


Fig. 8. Structure of Albendazole

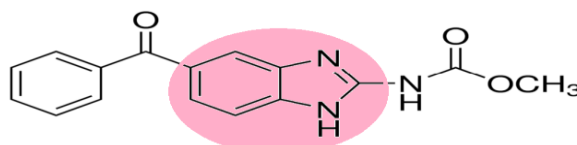


Fig. 9. Structure of Mebendazole

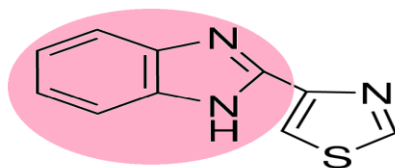


Fig. 10. Structure of Thiabendazole

3.7. As fungicidal

Carbendazim (Figure 11) this drug is one of the most popular examples of fungicides. It has the advantage of having a preventive and curative effect. It has been reported that it is absorbed by green root groups and tissues. It was also noted that it works by finally inhibiting beta-tubulin synthesis, making it a

successful drug in inhibiting germ tube development as well as inhibiting the growth of fungi. It has also been reported to be compatible with most different types of insecticides. It has also been reported that this drug has many important benefits for various plant diseases, for example, sheath blight, powdery mildew, scab, and other various plant diseases [77].

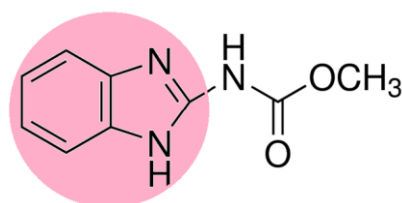


Fig. 11. Structure of Carbendazim

3.8. Drugs in git

Domperidone (Fig. 12) is a widespread example of an important drug benzimidazole-containing, a peripheral blocker, and dopamine receptor blocker. Domperidone has been successful as a treatment for relief of human

nausea and vomiting, To increase the passage of various foods through the stomach. It is also useful in gastroparesis in women to improve the level of breastfeeding of the newborn, as it increases milk production in the breast of a nursing mother and is done by releasing more prolactin. It is also used as an essential neurotransmitter for all parts of the body [78].

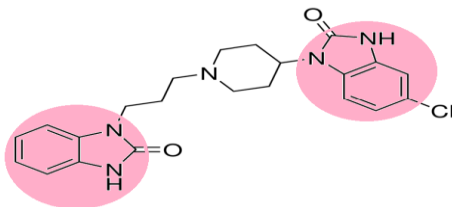


Fig. 12. Structure of Domperidone

3.9. Drugs in allergic conjunctivitis

3.9.1. Emedastine

Emedastine (Fig. 13) is a widespread second-generation antihistamine drug shown to be used in eye drops, to treat allergic conjunctivitis. Moreover,

it works as a successful H_1 receptor antagonist, and it has been reported that this drug works by completely blocking natural substances, histamine are the main cause of allergy symptoms [79, 80].

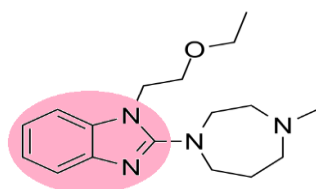


Fig. 13. Structure of Emedastine

3.9.2. Mizolastine

Misolastine (Fig. 14) is a powerful antihistamine that is only dosed once per day, and moreover it is non-sedative. There is no doubt that it blocks H_1 receptors and it has been observed that this drug has

a fast action. It was recently observed that it does not block the actual release of histamine from any mast cells, but only prevents its binding to all types of receptors [81].

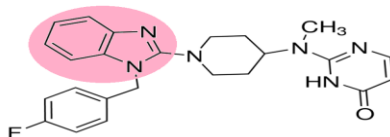


Fig. 14. Structure of Mizolastine

3.9.3. Clemizole:

Clemizol (Fig. 15) is a distinct drug as an H_1

antihistamine [82], meaning that it is a drug used to treat all kinds of different allergies [83].

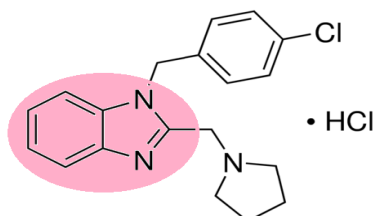


Fig. 15. Structure of Clemizole hydrochloride

3.9.4. Astemizole:

Astemizole (Fig. 16) is an essential drug that is used as a long-acting H_1

antihistamine, and it is selective with minimal to most of the multiple central effects and various anticholinergics. It

has also been reported that this drug is used in the effective treatment of

conjunctivitis as well as treatment of allergic rhinitis and urticaria [84].

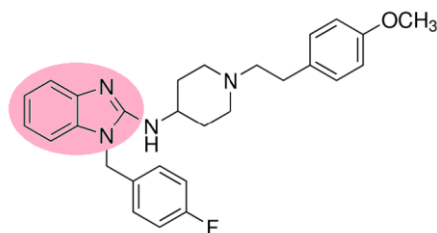


Fig. 16. Structure of Astemizole

3.10. As antipsychotic

A patient with psychosis has complete difficulty understanding everyday reality as well as his own circumstances. These medications are used regularly in a mental illness called schizophrenia as well as

chronic psychosis. Among the most important examples of drugs that treat psychosis and contain benzimidazole are as follows: - Droperidol (Fig.17), Pimozide (Fig.18), and Benperidol (Fig.19) (85–87).

3.10.1. Droperidol

Droperidol (Fig. 17): It has been discovered as an anti-vitamin drug that is used as an antiemetic and an

antipsychotic. Droperidol is also used as an anesthetic and a powerful nerve reliever when treating intensive care [88].

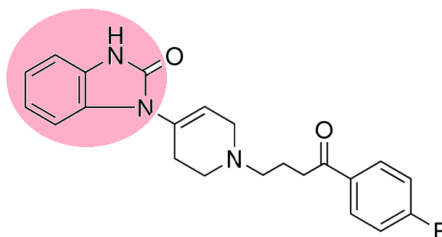


Fig. 17. Structure of Droperidol

3.10.2. Pimozide

Pimozide (Fig.18) is a popular drug as an antipsychotic and is a drug of the diphenylbutylpiperidine class. It has been observed

that Pimozide is used in oral preparation in patients suffering from schizophrenia, as well as in patients with chronic psychosis and Tourette's syndrome, as well as in various tics of involuntary resistance [89].

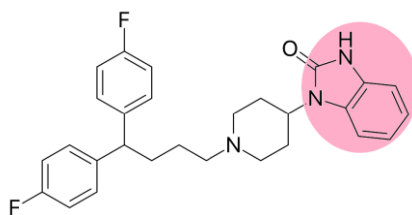


Fig. 18. Structure of Pimozide

3.10.3. Benperidol

Benperidol (Fig.19): It is an antipsychotic drug, which can be used to treat patients suffering from schizophrenia, on the other hand, it is effectively used

for successful control of antisocial sexual behavior. It is essential for the release of these criminals, and moreover it is considered an alternative to anti-androgens, for example cyproterone [90].

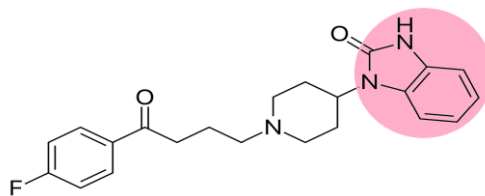


Fig. 19. Structure of Benperidol

3.11. As analgesic

Bezitramide (Fig.20): It is a strong anesthetic analgesic drug. Bezitramide is also a primary drug that can be completely broken down in the

gastrointestinal tract into its main metabolite, called despropionyl-Bezitramide [91].

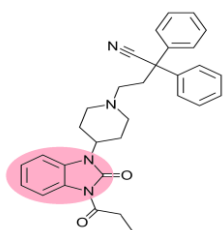


Fig. 20. Structure of Bezitramide

3.12. As antimicrobial

Ciprofloxacin (Fig. 21): It is the most popular and widely used antibiotics [92] and it belongs to the family of drugs known scientifically as quinolones [93]. It is used as a distinct treatment of various infections caused by some types of bacteria [94]. This drug has been reported as the most common among all medicines for treating various infections of the

skin, as well as for treating various sinus diseases, as well as most bone diseases, as well as lung infections, as well as ear infections, most abdominal diseases and nephritis, and moreover it is a successful treatment for diseases of the prostate, bladder and this drug can treat most different types of urinary tract infections [92–103].

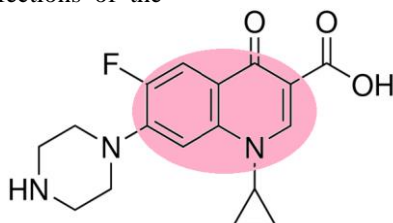


Fig. 21. Structure of Ciprofloxacin

3.13. As anti-diarrheal

Rifaximin (Fig. 22): It is an excellent drug as a semi-synthetic antibiotic. The use of this drug for treating

traveler's diarrhea has been reported and its success in treating hepatic encephalopathy [104].

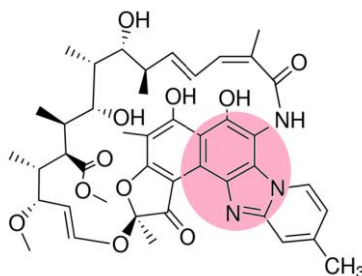


Fig. 22. Structure of Rifaximin

3.14. As anti-neoplastic

Nocodazole (Fig. 23): It is an important drug as an

anti-tumor agent and its effect is clearly demonstrated in human cells by direct interference with the

polymerization of most microtubules [105].

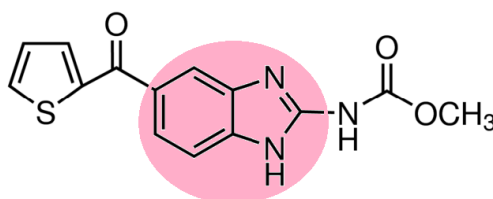


Fig. 23. Structure of Nocodazole or Oncodazole

3.15. As antiulcer drug

This is the enormous group of drugs used as a short-term treatment for all symptoms of duodenal ulcers as well as erosive gastroesophageal reflux disease and ulcerative. It is also used for treating stomach ulcers, and this drug treats peptic ulcer diseases, (Zollinger-Ellison syndrome). In addition, moreover it has been noted that this drug can eradicate *Helicobacter pylori* and for this reason it is a successful treatment in reducing the multiple risks of recurring duodenal ulcers. The common examples of some medicines that contain benzimidazole are Rabeprazole (Fig. 24), Omeprazole (Fig. 25), Lansoprazole (Fig. 26), and

Pantoprazole (Fig. 27). Alternatively, these medicines belong to a class of proton pump inhibitors [106–108].

3.15.1. Rabeprazole

Rabeprazole is a well-tolerated proton pump inhibitor. This drug has proven effective in treating peptic ulcers and reducing their relapse. Moreover, this drug is an important alternative as an anti- H_2 . Furthermore, an additional therapeutic option as an inhibitor of the other proton pump in the management of various disorders associated with gastric acid [109].

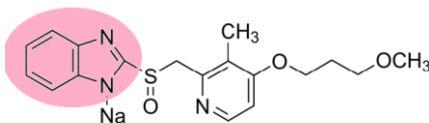


Fig. 24. Structure of Rabeprazole, Pariprazole

3.15.2. Omeprazole

Omeprazole (Fig. 25): It is a drug that plays an important role as a proton pump inhibitor and therefore it is used as a successful treatment for indigestion, as well as peptic ulcer disease.

Furthermore, moreover it treats gastroesophageal reflux disease and combats laryngopharyngeal reflux disease and treats Zollinger-Ellison syndrome [110].

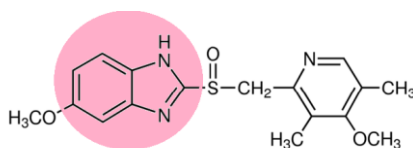


Fig. 25. Structure of Omeprazole, Antra, Losec

3.15.3. Lansoprazole

Lansoprazole (Fig. 26): This drug reduces high stomach acidity [111]. This drug is used to treat most of the various diseases of the digestive system [112]. This drug affects similar to other proton

pump inhibitors [113]. This drug is taken orally [111]. The onset is within a few hours and the therapeutic effects continue for up to two days [111].

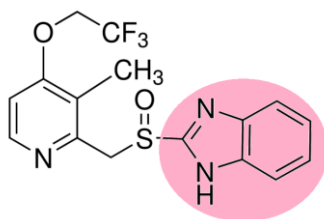


Fig. 26. Structure of Lansoprazole

3.15.4. Pantoprazole

Pantoprazole, a drug used to successfully treat stomach ulcers, is also a commonly used drug as a short-term treatment for patients with erosive esophagus. Moreover, it is used to treat pathological conditions of hypersecretion (Zollinger-Ellison syndrome) [114]. In addition, it is also be used with other medicines to eliminate the stomach bacteria called *Helicobacter pylori* [115]. Also, Pantoprazole has been shown to be a drug of equal efficacy with other proton pump inhibitors [116]. This drug can be administered

orally and intravenously [114]. The importance of Pantoprazole has also been reported as a short-term treatment in cases of erosion and esophageal ulceration in adult patients and children over five years of age [115]. In addition to the above, Pantoprazole can be used simultaneously with various antibiotics used to treat ulcers (caused by the bacterium *Helicobacter pylori*) [118]. This drug can be used to prevent stomach ulcers, especially in patients who are taking anti-inflammatory drugs (especially NSAIDs) [115].

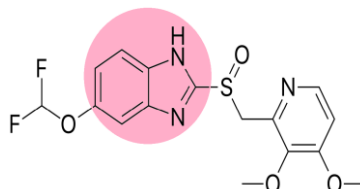


Fig. 27. Structure of Pantoprazole

3.16. As calcium sensitizer

Pimobendan: It is a drug that is used as a calcium-sensitizer, so this drug has the advantage of having positive effects for reducing muscle contraction. As well as for vasodilation, it is also an important drug

used as a selective phosphodiesterase III (PDE3) inhibitor. Pimobendan is used in the field of veterinary medicine (treating heart failure in dogs) [119, 120].

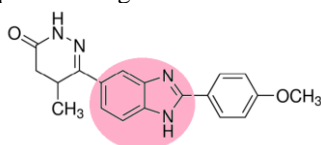


Fig. 28. Structure of Pimobendan

4. Conclusion

Benzimidazoles find many diverse applications in many different fields of applied chemistry. The location and type of substitutes on the benzimidazole ring are responsible for the multitude of diverse combinations of various biological activities of a human, animal, or plant. In

the future, it will be interesting to note the possibility of using these modifications of Benzimidazoles derivatives as highly effective therapeutic agents in addition to the wide diversity of biological activity of these different derivatives of benzimidazole.

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