

Short Review

Effects of Benzimidazole derivatives on digestive system and cardiovascular system

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Abstract

One of the goals of medicinal chemistry research and drug discovery is to provide a rational basis for the design of new medicinal agents. Organic compounds and their reactions have been utilized by people since antiquity. Due to the increasing demand for bioactive molecules, organic chemists are increasingly required to synthesize new compounds of biological interest. As Benzimidazoles are very useful intermediates for the development of molecules of pharmaceutical or biological interest, this review study was conducted to explore the effects of Benzimidazole derivatives on digestive system and cardiovascular system.

Keywords: Benzimidazole, Digestive System, Cardiovascular System

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1. Introduction

Benzimidazole nucleus has been considered an important pharmacophore in drug discovery since substituted benzimidazole derivatives have found applications as in diverse therapeutic agents including antiulcer, antihelminthic, antihypertensive, anticoagulant, antiallergic, analgesic, antiinflammatory, antipyretic, antibacterial, antifungal, antiviral, antiparasitic, antioxidant, anticancer and anti-anxiolytic. Benzimidazol (Figure 1) is a fused aromatic imidazole ring where a benzene ring is fused to 4 and 5 positions of an imidazole ring.

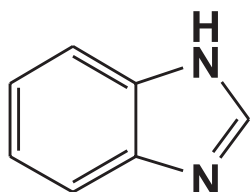


Figure 1. Benzimidazole

Benzimidazoles are very useful intermediates for the development of molecules of pharmaceutical or biological interest. Substituted benzimidazole derivatives have found applications as in diverse therapeutic agents including antiulcer, antihelminthic, antihypertensive, anticoagulant, antiallergic, analgesic, antiinflammatory, antipyretic, antibacterial, antifungal, antiviral, antiparasitic, antioxidant, anticancer and anti-anxiolytic. Because of their significant medicinal importance, the synthesis of substituted benzimidazoles has become a focus of synthetic organic chemistry. Benzimidazoles are listed with various effects on human body and are used to treat multiple system disorders.

2. Review

2.1. Effects of Benzimidazole derivatives on digestive system

2.1.1. Benzimidazole derivatives as antiulcer agents

Antiulcers are a class of drugs that are used to treat gastric ulcer. Peptic ulcer and related diseases are the major health problems of mankind. Peptic ulcer occurs in that part of the gastrointestinal tract which is exposed to gastric acid and pepsin, i.e., the stomach and duodenum (First part of the small intestine). The etiology of peptic ulcer is not clearly known. It results probably due to an imbalance between the aggressive (acid, pepsin and *H. pylori*) and the defensive (gastric mucus and bicarbonate secretion, prostaglandins, nitric oxide of the mucosal cells) factors. Reduction of acid is the main approach to ulcer therapy.

The physiological studies regarding acid secretory pathway have proved that proton pump being the ultimate mediator of acid secretion, H^+ , K^+ -ATPase enzyme a prime component of the gastric proton pump responsible for acid secretion in the stomach, is localized in specialized acid secreting tubulovesicular system of the parietal cells in the gastric mucosa and catalyzes the electro neutral exchange of intracellular H^+ and extra cellular K^+ coupled with the hydrolysis of the cytoplasm ATP (Sachs et al., 1978). Hyper secretion of this enzyme in the stomach leads to hyperacidity, reflux and ulcer. Therefore, this regulatory enzyme was found to be a pharmacological target for many anti-ulcer drugs. Development of proton pump inhibitors was an important issue in aspect of acid-related diseases treatment. Nowadays benzimidazole derivatives are found to be potential anti-ulcer agents (Richter, 1997). The most known drugs of this group, representing 2-(2-pyridylmethylsulfinyl) benzimidazole derivatives, are Omeprazole (Figure 2) (McTavish et al., 1991), Pantoprazole (Figure 3) (Bliesath et al., 1994), Lansoprazole (Figure 4) (Sachs et al., 1995) and Rabeprazole (Figure 5) have been marked as irreversible inhibitors of the gastric H^+ , K^+ -ATPase, and have shown to be effective in the treatment of peptic

ulcer (Gustavsson et al., 1983). Domperidone (Figure 6) produced an antiemetic (nausea and vomiting) effect related to its blocking action upon the peripheral dopamine receptors. This

action eliminates the inhibiting effect of dopamine on the motor function of the gastrointestinal tract and increases the evacuation and motor activity of the stomach.

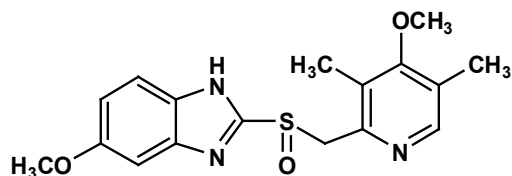


Figure 2. Omeprazole

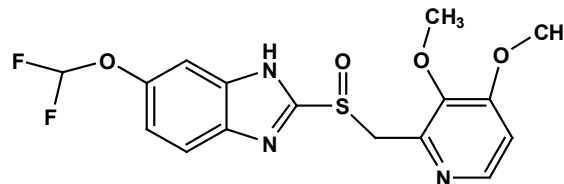


Figure 3. Pantoprazole

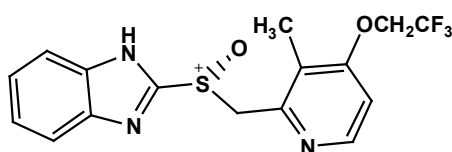


Figure 4. Lansoprazole

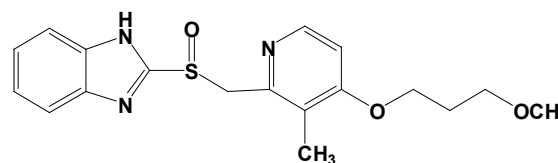


Figure 5. Rabeprazole

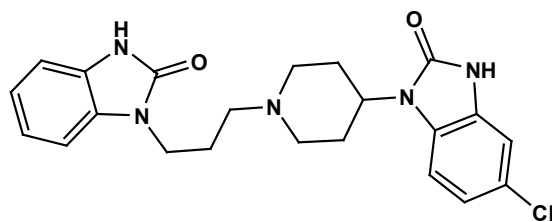


Figure 6. Domperidone

Benzimidazole derivatives used as antiulcer and antiemetic drugs

1.2. Benzimidazole derivatives as antihelminthic agents

Antihelminthics are drugs that either kill or expel infecting helminthes. Human body gastro intestinal tract is the adobe of many helminthes, but some also live in tissues, or their larvae migrate into tissues. They harm the host by depriving him of food, causing blood loss, injury to organs, intestinal or lymphatic obstruction and by secreting toxins. Helminthiasis is rarely fatal, but is a major cause of ill health. Original results of investigations devoted to the antihelminth properties of benzimidazole derivatives were published within the time period from the middle 1960s to the beginning 1970s. One of the first drugs repre-

senting these compounds, now widely used in helminthology, was Mebendazole (Figure 7) (Chavarria et al., 1973). At present, more than twenty benzimidazole derivatives are used as antihehnhinth preparations in the world medical practice, including Thiabendazole (Figure 8) (Eyster, 1967), Oxfendazole (Figure 9) (Tolliver et al., 1993), Albendazole (Figure 10) (Barger et al., 1993), Fenbendazole (Figure 11), Nocodazole (Figure 12) (Morgan et al., 1993), Triclabendazole (Figure 13) (Stitt et al., 1995), Oxibendazole (Figure 13), Cambendazole (Figure 14), Parbendazole (Figure 15) (Lyons et al., 1994), Luxabendazole (Figure 16), Flubendazole (Figure 17), Cyclobendazole (Figure 18), Oxibendazole (Figure 19), Benomyl (Figure 20) (Surin, 1995) etc.

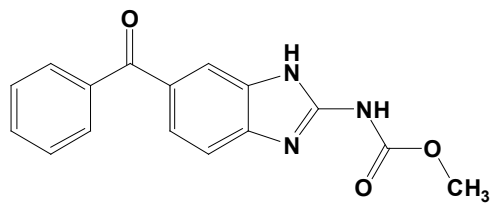


Figure 7. Mebendazole

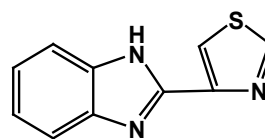


Figure 8. Thiabendazole

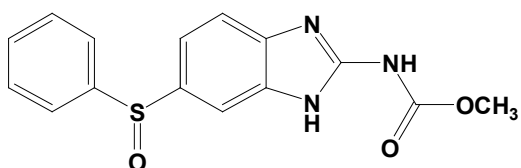


Figure 9. Oxfendazole

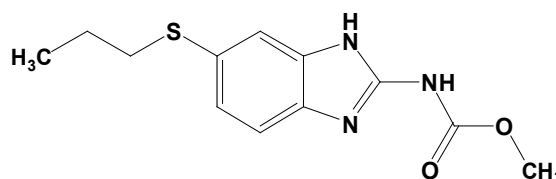


Figure 10. Albendazole

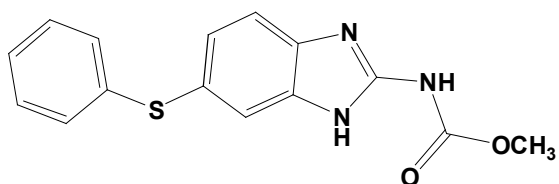


Figure 11. Fenbendazole

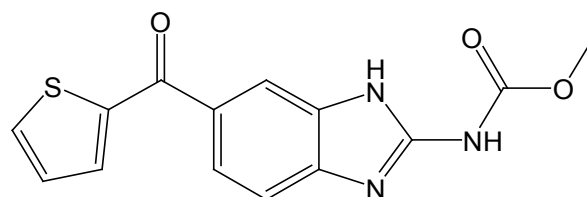


Figure 12. Nocodazole

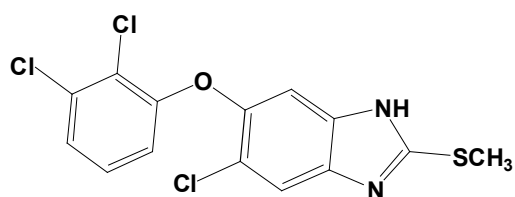


Figure 13. Triclaendazole

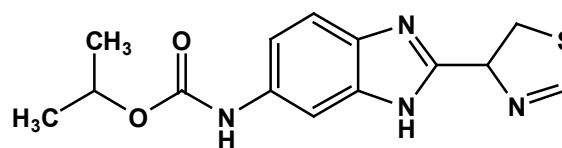


Figure 14. Cambendazole

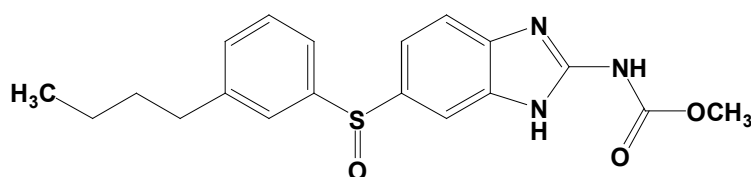


Figure 15. Parbendazole

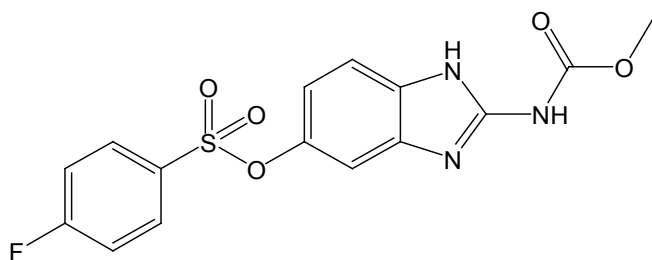


Figure 16. Luxabendaazole

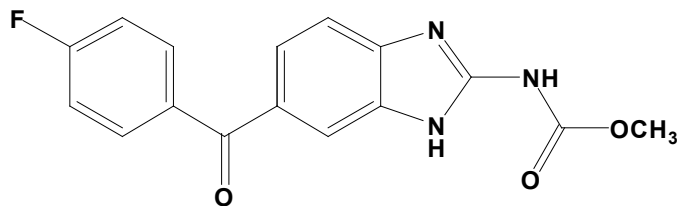


Figure 17. Flubendazole

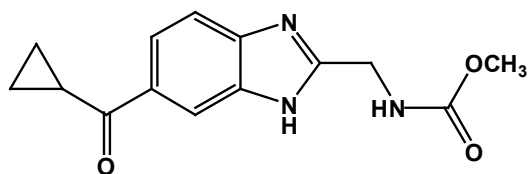


Figure 18. Cyclobendazole

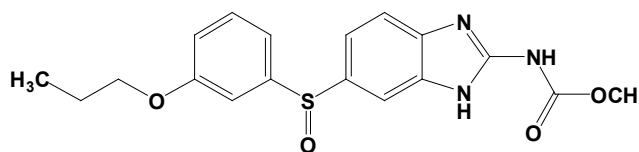


Figure 19. Oxibendazole

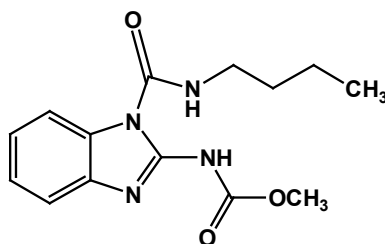


Figure 20. Benomyl

Benzimidazole derivatives used as antihelmintics drugs

2.2. Effects of Benzimidazole derivatives on cardiovascular system

In the 1940s, a group of researchers including Ginzburg and Efros synthesized 2-benzylbenzimidazole, which was capable of decreasing the tone of smooth muscles of the blood vessels and internal organs. This compound, called Dibazole (Figure 21), is widely used as a spasmolytic and hypotensive remedy (Pavlova et al., 1947).

2.2.1. Benzimidazole derivatives as Antihypertensive agents

Antihypertensives are a class of drugs that are used in medicine and pharmacology to treat

hypertension. Hypertension is most commonly referred to as “high blood pressure”. Hypertension is considered to be present when a person’s systolic blood pressure is consistently 140 mmHg or greater, and/or their diastolic blood pressure is consistently 90 mmHg or greater (Chobanian, 2003). Recently, as of 2003, the Seventh Report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (ALL-HAT Officers and Coordinators, 2002) has defined blood pressure 120/80 mmHg to 139/89 mmHg as “prehypertension.” Prehypertension

is not a disease category; rather, it is a designation chosen to identify individuals at high risk of developing hypertension. A pronounced antihypertensive activity is characteristic of a series of compounds including Condesartan Cilexetil (TCV-116) (Figure 22), Condesartan (CV-11194) (Figure 23), BIBR 277 (Figure 24), TAK-536 (Figure 25). The mechanism of their action is related to a selective antagonism to the angiotensin II receptors (Ogihara et al., 1994). Another interesting compound is Ro 40-5967, which is capable of blocking calcium channels. A systematic search for active compounds in the series of imidazo[1,2-a]benzimidazole derivatives led to substances possessing antiarrhythmic properties, increasing the antihypoxic stability of myocardium and enhancing the nonspecific resistance of the heart and the entire organism with respect to stressor damage. The maximum antiarrhythmic activity among the substances studied was observed for 9-(2-diethylaminoethyl)-2-tert-butylimidazo[1,2-a]benzimidazole dihydrochloride (ritmidazole), which is a calcium antagonist acting simultaneously upon the incoming sodium and outgoing potassi-

um currents. The compound AKS-180, or 2-(3,4-dimethoxyphenyl)-(13-diethylaminoethyl)imidazo[1,2-a]benzimidazole nitrate, also produced a maximum positive effect upon the stability of myocardium with respect to hypoxia: the drug restricted myocardial damage related to an oxygen deficiency caused by coronary occlusion. The benzimidazole derivative BIBR 277 (Figure 24) is a nonpeptide angiotensin II receptor antagonist (Wienen et al., 1993). The 4-(1H-benzimidazole-2-carbonyl)piperidines are histamine H₁/tachykinin NK₁ receptor antagonists with significantly improved physicochemical properties and oral efficacy. The synthesis of benzimidazole-7-carboxylic acid derivatives such as candesartan (CV-11974), novel and potent nonpeptide AT₁ selective AII receptor antagonists. The prodrug of candesartan, candesartan cilexetil (TCV-116) (Figure 22), is an orally active, highly effective, and longacting AII receptor antagonist, and it is now under clinical trial as an antihypertensive agent. TAK-536 (Figure 25) is also potent and orally active as TCV-116 (Figure 22) (Kubo et al., 1993).

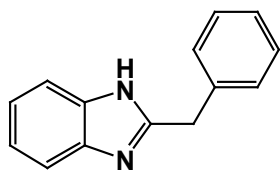


Figure 21. Dibazole

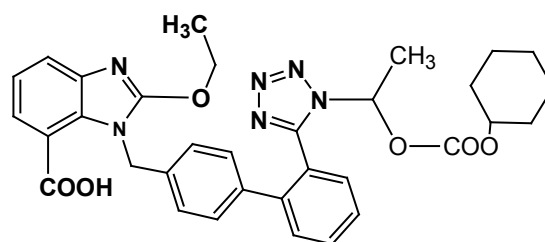


Figure 22. Condesartan

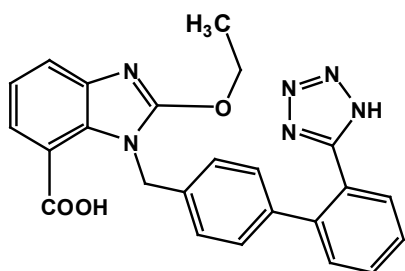


Figure 23. Condesartan (CV-11974)

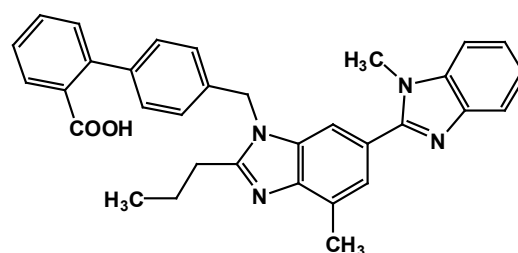


Figure 24. BIBR 277

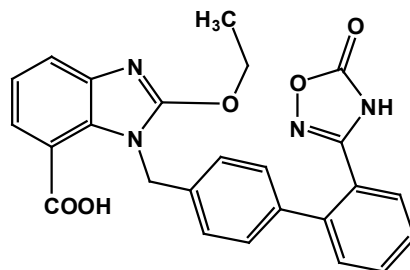


Figure 25. TAK-536

Benzimidazole derivatives used as antihypertensive drugs

2.2.2. Benzimidazole derivatives as anticoagulant agents

A substance that prevents coagulation; that is, it stops blood from clotting. Chlorothiophene benzimidazole emerging from a screening library, a series of 5(6)-substituted tethered amides was designed resulting in the discovery of neutral and achiral factor Xa inhibitors. Po-

tency depends on the length and nature of the linker between benzimidazole and P4 residue (Werner et al., 2004). Dabigatran (Figure 26) and Chlorothiophene benzimidazole (Figure 27) are the drugs used as anticoagulants. The benzimidazoles with substituted aminocarbonylmethyl groups as the side chain showed potent FXa inhibitory activity.

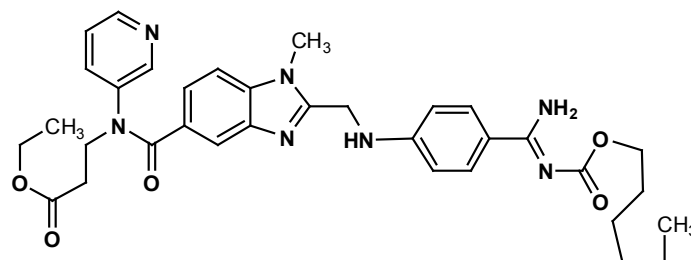


Figure 26. Dabigatran

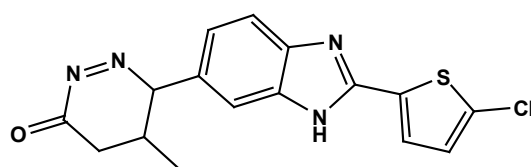


Figure 27. Chlorothiophene benzimidazole

Benzimidazole derivatives used as potent anticoagulant agents

3. Conclusion

This review study showed the importance of some benzimidazole derivatives with very

strong effect on human digestive system and cardiovascular system. Some of the mentioned derivatives are used as regular drugs for human digestive system and cardiovascular system therapies. Because of these significant

medicinal importances, the synthesis of substituted benzimidazoles has become a focus of synthetic organic chemistry.

4. Acknowledgements

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5. References

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