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
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 antitumor, antihelmintic, 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](image)

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.

Benzimidazole derivatives as antihelmintic agents

Antihelmintics are drugs that either kill or expel infecting helminthes. Human body gastro intestinal tract is the abode 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. Helminthisis 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 representing 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 antihehninth 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
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 (ALLHAT 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]benzimidazolinedihydrochloride ritmidazole), which is a calcium antagonist acting simultaneously upon the incoming sodium and outgoing potassium currents. The compound AKS-180, or 2-(3,4-dimethoxyphenyl)-(13-diethylaminoethyl)imidazo[ 1,2-b]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 an nonpeptide angiotensinII receptor antagonist (Wienen et al., 1993). The 4-(1H-benzimidazole-2-carbonyl)piperidines are histamine H1/tachykinin NKI receptor antagonists with significantly improved physiochemical 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).
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. Potency 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.

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.

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5. References


