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STUDY OF THE PRACTICAL SIGNIFICANCE OF BENZIMIDAZOLE AND SOME OF ITS DERIVATIVES

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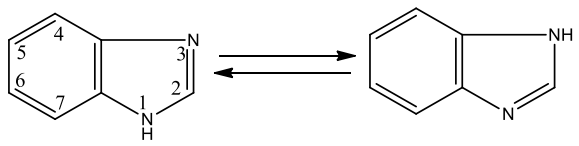
Abstract: Biologically active compounds and their derivatives have been the basis for many studies and are of great practical importance due to their versatile biological activities, including antifertility, antiviral, anticancer, antioxidant, antitrypanosomal, antimicrobial and antimalarial activities. The article explains the practical importance of one such compound - benzimidazole and some of its derivatives.

Keywords: crystal, bicyclic, tautomer, condensation, hygroscopic, anthelmintic, antioxidant.

Benzimidazole derivatives have attracted great interest due to their biological functions and a wide range of pharmacological applications. Benzimidazole derivatives have various therapeutic properties such as antiulcer, anthelmintic, antihypertensive, anticoagulant, antiallergic, analgesic, anti-inflammatory, antimicrobial, antiviral, antiparasitic and antioxidant.

Benzimidazole was first described by Hobrecker in 1872. It is a bicyclic derivative of imidazole condensed with benzene and is a colorless crystal with a melting point of 172 °C. Benzimidazole is good in alcohol, water, ether and diluted acid and alkali solutions, it is difficult to dissolve in non-polar solvents [1-2-3].

In benzimidazole, the 1,3-tautomeric equilibrium state between I and II is equivalent:



I II

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Currently, two approaches are most common in the synthesis of benzimidazole. The first of them includes methods based on the Phillips-Ladenburg reaction, and the second on the Weidenhagen reaction. The Phillips-Ladenburg reaction is an acid-catalyzed condensation of 1,2-diaminobenzene with carboxylic acids or their derivatives (ethers, amides, nitriles), and the Weidenhagen reaction is the condensation of 1,2-diaminobenzene with aldehydes and ketones. In modern modifications of the Weidenhagen reaction, instead of aldehydes, for example, primary alcohols and primary alkylamines, it is possible to obtain benzimidazole derivatives using arylcarboxylic acids and their derivatives (in the Phillips-Ladenburg reaction) and arylmethylketones, arylcarbaldehydes and their synthetic equivalents (in the Weidenhagen reaction).

The laboratory method of synthesizing benzimidazole is the reaction of o-phenylenediamine with formic acid or trimethylorthoformate. 2-Alkylbenzimidazoles are obtained from the interaction of fatty acids with o-phenylenediamine in the presence of hydrochloric acid. 2-Arylbenzimidazoles are obtained by the Weidenhagen reaction, that is, by condensation of o-phenylenediamine with aromatic aldehydes, followed by oxidation with copper (I) acetate [4-5].

With the ions of some metals (Ag, Co, Cu, etc.), benzimidazole forms salts in ammonia solution. Benzimidazole is resistant to oxidizing agents. But CrO_3 in 80 % H_2SO_4 oxidizes at 80 °C to form imidazole-4,5-dicarboxylic acid. Acting with sulfur, benzimidazole turns into benzimidazole-2-thione, 1-alkylbenzimidazole, and 1-alkyl substituted compounds.

Benzimidazole is alkylated with alkyl halides and dialkyl sulfates in the presence of bases in the 1st state. When N-alkylbenzimidazoles are alkylated, 1,3-dialkylbenzimidazole salts are formed. Arylation of benzimidazole in case 1 with haloarenes usually proceeds under harsh conditions. N-acyl derivatives are obtained under the influence of acyl chlorides and acid anhydrides.

The main drugs with benzimidazole derivatives are: dibazol, albendazole, medamine, mebendazole, omeprazole, droperidol, domperidone (motilium). Table-1 lists their names and chemical formulas.

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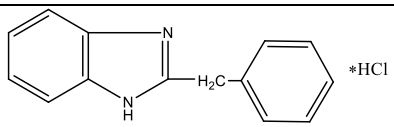
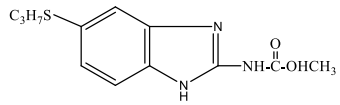
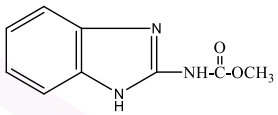
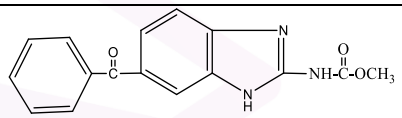
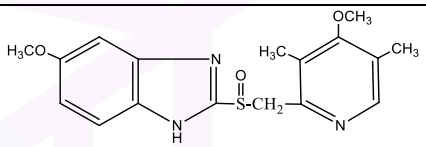
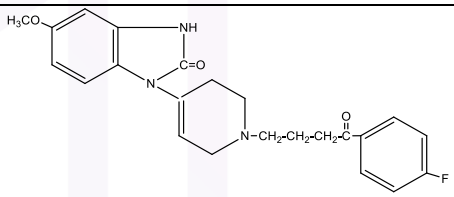
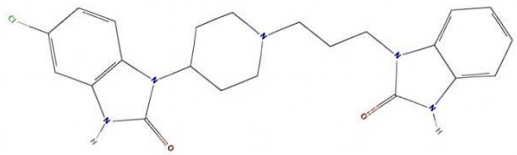
Table 1 Name and structure of some benzimidazole derivatives

№	Name	Chemical formula
1	**Dibazol** - Dibazolum; 2-Benzylbenzimidazole hydrochloride	
2	**Albendazol -**Albendazolum; 2Methoxycarbonylamino-5-propylthio-1N-benzimidazole	
3	**Medamin –** Medaminum; Carbendazim; Mercarzol; Carbendazole; 2-Methoxycarbonyl-aminobenzimidazole	
4	**Mebendazol –** Mebendazolum; Methyl-5-benzoyl-1N-benzimidazol-2-yl-carbamate	
5	**Omeprazol –** Omeprazolum; (5-Methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methanesulfinyl]-1H-benzimidazole	
6	**Droperidol-** Droperidolum; 1-{1-[4-oxo-4-(4-fluorophenyl)butyl]-1,2,3,6-tetrahydro-pyridin-4-yl}-1,3-dihydro- 2N-benzimidazol-2-one	
7	**Domperidon**-Motilium; 6-chloro-3-[1-[3-(2-oxo-3H-benzimidazol-1-yl)propyl]piperidin-4-yl]-1H-benzimidazol-2-one	

1. Dibazol - in 1948, Leningrad chemists B.A. Poray-Koshits, A.S. Efros, O.F. The Ginzburgs synthesized dibazole, a compound that dilated blood vessels worse than papaverine and was considered less toxic.

As it turns out, the new drug Dibazol is a sweet, savory, white or slightly yellowish crystalline powder, difficult to dissolve in water and chloroform, easily soluble in alcohol, slightly soluble in acetone. It liquefies at a temperature of 182-186 °C. Has hygroscopic property [6-7-8].

Dibazol is used for spasms of mucous membranes of internal organs (gastric ulcer and intestinal spasms, etc.), for bronchial asthma (to prevent angina attacks), but Dibazol is especially effective in relieving spasms of blood vessels.

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2. Albendazole - invented by Robert J. Gurick and Vassilios J. Theodorides, patented in 1975. It was introduced in Australia in 1977 as an anthelmintic for sheep and was introduced for human use in 1982.

White or almost white-yellow fine crystalline powder. It is easily soluble in strong acids and alkalis, glacial acetic acid, chloroform, acetone, practically insoluble in 95% ethyl alcohol, chloroform and water.

It is used as an anthelmintic agent. It affects tissue parasites, including Ascaris lumbricoides, Trichuris trichiura, Enterobius vermicularis, Ancylostoma duodenale, Necator americanus, Strongyloides stercoralis, nematodes: ascariasis, trichocephalosis, hookworm, enterobiosis, nonkatorosis, toxocarosis, strongyloidiasis, opisthorchiasis, giardiasis, microsporidiosis (and others). used to treat symptoms.

For example, active substance in 5 ml of Pangelm drug: albendazole - 200 mg; excipients: sodium benzoate, xanthan gum, sucrose, sodium methylhydroxybenzoate, sodium propylhydroxybenzoate, glycerin, polysorbate-80, disodium edetate, erythrosin supra dye, raspberry and fruit mixture flavoring, purified water. Pangelm suspension belongs to the pharmacological group of drugs for the treatment of nematodes.

3. Medamin - Odorless, white or pale pink, gray fine crystalline powder. Density 1.45 g/cm^3. Very little in chloroform, practically insoluble in 95 % ethyl alcohol and water (Solubility in water 8 mg/l). It liquefies at 307-312 °C.

Antihelminth is a tool. The drug is used to treat intestinal nematodes caused by roundworms (ascariasis), hookworms (ankylostomiasis), oysters (enterobiosis), trichocephalosis, strongyloidosis. It is used as a fungicide in some countries.

4. Mebendazole - Light golden powder. Ice easily dissolves in acetic acid, chloroform, acetone, practically insoluble in 95% ethyl alcohol and water.
Antihelminth is a tool. It is used in enterobiosis, ascariasis, trichostrongylidosis, trichuriasis, trichinellosis, teniosis, mixed helminthosis.

5. Omeprazole - white or whitish-yellow granules. Omeprazole has been developed since the late 1970s. Omeprazole is used in the treatment of gastroesophageal reflux disease, gastric and duodenal ulcers, erosive esophagitis, Zollinger-Ellison syndrome, and eosinophilic esophagitis. Omeprazole can exist in two tautomeric forms: 5-methoxy or 6-methoxy benzimidazole [9-10-11].

6. Droperidol - discovered by Janssen in 1961. It is a neuroleptic agent. White or pale yellow-brown amorphous or microcrystalline powder. It darkens under

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the influence of air and light. Practically insoluble in water and ether, slightly soluble in 95 % ethyl alcohol, soluble in chloroform.

7. Domperidone - Domperidone was discovered in 1974 and has been used in medicine since 1979. Domperidone is available without a prescription in many countries, such as Europe. It is used to treat gastrointestinal disorders such as nausea and vomiting and gastroparesis. It increases the level of prolactin in the human body and is used to increase the production of breast milk. Domperidone effectively increases esophageal motility, increases gastric motility and peristalsis [12-13].

Biologically active substances - necessary for maintaining the vital activity of living organisms, having a high physiological activity at low concentration against certain groups of living organisms or their cells, malignant tumors, selectively affecting or accelerating their growth or chemicals that completely stop the development. Most of them are found in food, for example: alkaloids, hormones, vitamins, biogenic amines, neurotransmitters. All of them are pharmacologically active and most are potent pharmacology agents. Biologically active compounds are found in different forms, often together with foreign substances, sometimes in pure form [14].

Biologically active compounds are important for living organisms. They play a major role in the normal functioning of all vital processes in the body. It directly participates in the growth of the body, carbohydrate and lipid metabolism. Biologically active compounds include nucleic acids, hormones, vitamins, etc. Currently, the processes of action of biologically active substances at the level of molecules, cells and systems are being studied.

With the discovery of new physical and physico-chemical methods, supramolecular complexes and new derivatives of biologically active compounds are being synthesized, these researches are important for ensuring the normal functioning of the human body, increasing the resistance of cultivated plants to diseases, and obtaining new medicinal substances.

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