



## Preparation Of 2-Propionylaminobenzimidazole and Its Anthelmintic Activity

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<p><b>KEYWORDS</b></p> <p>2-propionylaminobenzimidazole, glycerol, polysorbate, suspension, Na-carboxymethylcellulose, stability, helminth, nematode, trematode, fastioliosis, nematodiosis, marshallagiosis, anthelmintic, form, suspension, powder.</p>	<p><b>ABSTRACT:</b></p> <p>In current work studied interaction of methylbenzimidazol-2-ylcarbamate with propionic acid. The reaction with propionic acid was carried out by boiling (141°C) of carbamate in excess acid for eight hours. It should be emphasized that the reaction in propionic acid, in contrast to acetic acid, proceeds with the formation of a product at the exocyclic 2-propionylaminobenzimidazole yield of is quantitative (96%). The structure of the obtained compound was proved by IR, <sup>1</sup>H NMR-spectroscopy and mass spectra.</p> <p>Based on the synthesized 2-propionylaminobenzimidazole, an effective stable suspension form was obtained for animal husbandry using local raw materials. At the same time, a decrease in the toxicity of the drug was achieved.</p> <p>The article also contains information on the study of the anthelmintic properties of powder and suspension forms of 2-propionylaminobenzimidazole against ovine helminthiasis. In particular, it was noted that the powder form of the drug gives a high anthelmintic effect against fastioliosis, nematodiosis and marshallagiosis, which are the main helminthiasis, and the suspension form of the drug has a high anthelmintic property against fastioliosis of this Code.</p> <p>The article found that the use of 2-propionylaminobenzimidazole in an amount of 200 mg/kg is highly anthelmintic, but not toxic and cumulative for the body of sheep.</p> <p>At the same time, the article notes that the drug 2-propionylaminobenzimidazole, produced in the Republic of Uzbekistan, is a highly effective anthelmintic agent of a wide anthelmintic spectrum and is a class of vaccine in Nematode and Trematode, which are considered livestock helminths that cause great economic damage to the sheep industry.</p>
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**Introduction:** Heterocyclic compounds are essential for life and extensively distributed in nature. A significant role has been played by heterocyclic compounds in the metabolism of all living cells. The nitrogen based heterocyclic compound play important role for mankind. Particularly benzimidazole has an immense importance not only biologically but also industrially among the entire nitrogen based heterocyclic compound. Among heterocyclic pharmacophores, the benzimidazole derivatives is quite common. Although there is great interest in benzimidazole ligands and structural chemistry, the main interest is in their biological activities [1, 2].

Since Woolley proposed in 1944 that benzimidazole may behave similarly to purines, stimulating various biological reactions, the therapeutic potential of benzimidazole nucleus has been known [3]. Many heterocyclic nuclei are present in antiparasitic drugs,

such as 5(6)-substituted benzimidazoles and 2-aminonitrobenzimidazoles [4, 5]. The 2-aminobenzimidazole core is found in albendazole, the most common antiparasitic drug and the drug of choice for anti-infectious chemotherapy against anaerobic protozoa and other parasites [6].

Benzimidazole-based drugs exhibit a wide range of different biological activities as a result of changing the groups on the core structure. These biological activities include anti-cancer [7], bactericidal, [8], fungicidal [9, 10], analgesic [11] and anti-viral properties [12]. Some have cardiovascular applications [13] while some derivatives have been synthesized and evaluated for inhibition of HIV-1 infectivity [14].

Benzimidazole carbamates are generally poorly soluble in water. For some useful applications of the compounds the poor water solubility of the benzimidazoles is a major obstacle. Therefore, there is an option to take the



suspension form of carbamate benzimidazoles [15]. We can say suspensions are those coarse dispersions in which internal phase i.e., coarse powder is dispersed into the external phase i.e., liquid vehicle. Internal phase that consists of solid particles that are uniformly suspended in sufficient amount of vehicle by the addition of individual or combined form of suspending agents. Vehicles in external phase are commonly aqueous in nature in oral preparation, on the other side organic and oily liquids are used for non-oral preparations. Nowadays, many suspensions are marketed in the form of powder which are suspended into specified amount of vehicle just before use because of stability considerations [16]. Insoluble particles must be uniformly dispersed in ideal suspensions. The solid particles are isolated from the liquid as sediments in a standing state. Usually, the volume of sediment should be re-dispersed evenly in the system while shaking. The settling rate can be enhanced with the help of agents which increase viscosity. For preparing elegant and smooth product suspended particles should be smaller in size and avoid gritty texture [17].

### Experimental

IR spectra were recorded on a System 2000 IR Fourier spectrometer in KBr tablets,  $^1\text{H}$  NMR spectra - on a Unity-400+ instrument (operating frequency 400 MHz, internal standard TMS,  $\delta$  scale) solvents -  $\text{CD}_3\text{OD}$ ,  $\text{CD}_3\text{COOD}$ ,  $\text{DMSO}-d_6$ . The purity of the products and the progress of the reaction were monitored by TLC on Silufol UV-254 in the system - chloroform: benzene: methanol - 5: 1.5: 1.

High resolution mass spectrum conditions (HR-EI-MS: GCT (Micromass)) are direct sample injection, ionization energy 70 eV and source temperature  $250^\circ\text{C}$ . Mass spectra were obtained on a Micromass LCT premier with a LockSpray direct injection source and a Q-TOF (Waters) LC-MS/MS instrument with an ESI source (3 kV,  $250^\circ\text{C}$ ). In all cases, acetonitrile was used as a solvent.

**Synthesis of 2-propionylaminobenzimidazole.** 10 g (0.052 mol) of methylbenzimidazol-2-yl carbamate was dissolved in 35 ml of propionic acid ( $d=0.99$  g/ml), the reaction mixture was heated in an oil bath at the boiling point of glacial propionic acid ( $141^\circ\text{C}$ ) for 8 hours. Then the acid was partially (40%) distilled off and the reaction mixture was left overnight at room temperature. The

precipitated crystals were filtered off, washed with alcohol, and dried. There was obtained 9.5 g (96%) 2-propionylaminobenzimidazole with mp  $259-261^\circ\text{C}$  (ethanol), Rf 0.65 (chloroform: benzene: methanol - 5:1.5:1)

$^1\text{H}$  NMR-spectrum ( $\delta$ , ppm, Hz,  $\text{DMSO}-d_6$ ): 9.03 (2H, br.s.,  $\text{NH}_2$ ), 7.07-7.09 (2H, AA'BB'-type, H-4,6), 6.84-6.86 (2H, AA'BB'-type, H-5,7), 2.15 (2H, q,  $J=7.53$ ,  $\text{CH}_2\text{-CO}$ ), 0.95 (3H, t,  $J=7.52$ ,  $\text{CH}_3$ ). IR-spectrum ( $\nu$ ,  $\text{cm}^{-1}$ ): 3451 ( $\text{NH}_2$ ), 1689 (C=O), 1632 (C=N), 1580 (C-N), 2851, 2918 ( $\text{CH}_2$ ,  $\text{CH}_3$ ), 1516 (C=C). MS (70 eV)  $m/z$  (%) = 189 (13)  $[\text{M}]^+$ , 133 (100), 106 (3.2), 105 (7.18), 80 (3.2) ESI-HRMS: calculated for  $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}$ : 189.0902, found 189.0904.

In this study, a 10% suspension form of 2-propionylaminobenzimidazole compound, which showed high biological activity against anthelmintics, was developed. To create a stable suspension form of the drug, it is necessary to minimize the particle size of the active substance. In addition, the minimum size of the active ingredients helps to ensure the best contact of the drug with the object of exposure. Therefore, the use of drugs in the suspension form in Veterinary medicine is widely proven to give positive results.

10 g of glycerol, 2.25 g of ethyl alcohol and 10. g of 2-propionylaminobenzimidazole were stirred with a overhead stirrer for 60 minutes. until a pale yellow homogeneous mass is obtained. Then, 80.0 g ml of a 2.0% pre-prepared CMC solution was added with continuous stirring. To the resulting suspension was added 3.0 g of a 5% pre-prepared solution of sodium benzoate to obtain a stabilized suspension of 2-propionylaminobenzimidazole (10%) with a pH of 5.8.

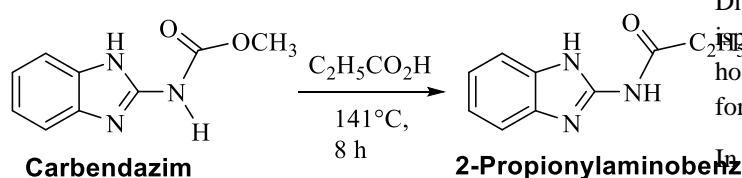
The toxicological properties of 2-propionylaminobenzimidazole in laboratory animals were determined in white mice, guinea pigs and rabbits in the helminthology laboratory vivarium of the Veterinary Scientific Research Institute, and the anthelmintic and toxicological properties of the drug were determined in sheep spontaneously infected with various helminthoses using physiological, clinical, hematological and helminthocoprological (fuelborne and rewashing) methods.

### Results and discussion



Recently we revealed that reactions of methylbenzimidazol-2-ylcarbamate (Carbendazim) with aliphatic carboxylic acids of normal and iso-structure, as well as benzoic acid, proceeds by re-acylation; thus, new 2-acetamides are formed. It was shown that with an increase in the size of the alkyl group and the reaction temperature, due to the possible thermal decomposition of the reaction product forming the reaction, the yield of the target acyl products sharply decreases [18].

Continuing research in this direction, in current work we studied interaction of methylbenzimidazol-2-ylcarbamate with propionic acid. The reaction with propionic acid was carried out by boiling (141°C) of carbamate in excess acid for eight hours:



It should be emphasized that the reaction in propionic acid, in contrast to acetic acid, proceeds with the formation of a product at the exocyclic. 2-Propionylaminobenzimidazole yield of products is quantitative (96%). The structure of the obtained compound was proved by IR, <sup>1</sup>H NMR-spectroscopy and mass spectra. It can be noted that the reaction of carbamate with propionic acid due to influencing of temperature and a ratio of substances are formed of acetyl compound [18].

A suspension was obtained by dispersion method based on synthesized 2- interaction. Grinding of solid substances of AD is carried out by crushing, abrasion, crushing, splitting mechanically using crushers, mortars and mills of various designs (ball, vibration, jet), ultrasound, as well as electrical methods [19, 20].

In this work, we used a dispersion method for obtaining a stable suspension of 2-propionylaminobenzimidazole. For suspensions as a heterogeneous system, sedimentation stability (stability) is very important.

Surfactants and stabilizers are used to increase sedimentation stability in the preparation of suspensions. In the scientific propionylaminobenzimidazole. The dispersion method for obtaining suspensions is based on grinding particles of the active substance. Dis-persion

methods require energy to overcome the forces of intermolecular literature, Tween-80 and xanthan gum, liquid paraffin, agar-agar, propylene glycol, etc. are most often used as stabilizers [21].

In this work, as a stabilizer and surfactant, we used sodium carboxymethylcellulose, which is produced in the Republic of Uzbekistan and is quite affordable and inexpensive drug.

Obviously, the size and shape of particles in suspensions depend on the intensity and duration of mixing of the mixture of components, as well as on the type of stirrers in the device. We used a laboratory overhead stirrer in our work.

Dispersion was carried out by intensive stirring in a dispersive alcohol-glycerol medium until a visually homogeneous dispersion in the form of a white mass was formed.

In this study, a 2-propionylaminobenzimidazole compound, which showed high biological activity against helminthological, was developed. To create a stable suspension form of the drug, it is necessary to minimize the particle size of the active substance. In addition, the minimum size of the active ingredients helps to ensure the best contact of the drug with the object of exposure. Therefore, the use of drugs in the suspension form in veterinary medicine is widely proven to give positive results.

In our research, we studied the toxicological and helminthological properties of 2-propionylaminobenzimidazole powder.

### Results of tests conducted to study the anthelmintic properties of 2-propionylaminobenzimidazole.

The anthelmintic properties of powder and suspension forms of 2-propionylaminobenzimidazole were studied. For this purpose, sheep were examined by fluoborne and re-infection methods of helminthovoscopy, and sheep infected with marshallagiosis, nematodirois, and other gastro-intestinal strongylatosis were detected spontaneously [22-24].

In the studies, attention was paid to the extent and intensity of helminthiasis present in affected sheep.

As can be seen in Table 1, 4 sheep infected with marshallagiosis, nematodirois, other gastrointestinal strongylatosis and fasciolosis were given the powder



form of 2-propynylaminobenzimidazole in the amount of 200 mg per 1 kg of live weight of sheep, and after 5 days repeated helminthoovoscopic examination.

**Test results of powder form of 2-propynylaminobenzimidazole against sheep helminthiasis (using helminthoovoscopy methods)**

**Table 1**

Number of sheep	Powder form (200mg per 1kg live weight)									
	Before administering the medicine					After administering the medicine				
	Marshallagiosis	Nematodirosis	Other strongylatoses	Phasiolosis	General damage(%)	Marshallagiosis	Nematodirosis	Other strongylatoses	Phasiolosis	General damage(%)
4	36	5	42	98	100	1	-	-	-	25
	45	20	17	2	100	1	-	-	-	25
	35	90	25	-	75	-	-	-	-	-
	17	15	17	50	100	-	-	-	-	-

Before the powder form of 2-propynylaminobenzimidazole was given to sheep, all 4 sheep were infected with marshallagiosis, nematodirosis, other gastro-intestinal strongylatosis and fasciolosis to varying degrees, and 5 days after the administration of the drug, the sheep were 100% free from other gastro-intestinal strongylatosis, nematodirosis and fasciolosis. was determined. It was also found that the powder form of this amount of the drug is 75% effective against marshalliasis.

We also studied the anthelmintic properties of the suspension form of this drug. For this, 4 sheep infected with spontaneous helminths were identified.

4 of these sheep were infected with fasciolosis and 3 with marshallagiosis, nematodirosis, and other gastro-intestinal strongylatosis. To study the anthelmintic properties of these sheep

From the suspension form of 2-propynylaminobenzimidazole, 2 ml per 10 kg of live weight was applied.

**Sheep of the suspension form of 2-propynylaminobenzimidazole results of testing against helminthiasis (using helminthoovoscopy methods)**

**Table 2**

Number and group of sheep	Suspension form (2 ml per 10 kg of live weight)	
	Before administering the medicine	After administering the medicine



	Marshallagiosis	Nematodirosis	Other strongylatoses	Phasiolosis	General damage(%)	Marshallagiosis	Nematodirosis	Other strongylatoses	Phasiolosis	General damage(%)
2-group 4 sheep	5	9	7	5	100	-	-	-	-	-
	-	-	1	11	50	-	-	-	-	-
	27	5	28	4	100	-	-	-	-	-
	3	2	-	1	75	-	-	-	-	-

As can be seen from the table, when 2 ml of the suspension form of 2-propynylaminobenzimidazole was given per 10 kg live weight of sheep, all 4 sheep infected with fasciolosis to varying degrees and 3 sheep infected with marshallagiosis, nematodirosis, other gastrointestinal strongylatosis were completely freed from helminths.

### Conclusions

It was found for the first time that the reaction of methylbenzimidazol-2-yl carbamate with propionic acid proceeds by transacylation, in this case, new 2-propionylaminobenzimidazole derivative. Thus, we obtained an effective stable 10% suspension form of 2-propionylaminobenzimidazole, which meets all the requirements for suspension preparations.

The results of the reasearch show that the powder form of 2-propynylaminobenzimidazole has 100% anthelmintic efficacy against nematodirosis, other gastrointestinal strongyliatosis and fasciolosis and 75% against marshalliasis when applied at 200 mg per 1 kg of live weight against sheep helminthiasis.

The suspension form of 2-propynylaminobenzimidazole was used against sheep helminthiasis in the amount of 2 ml per 10 kg of live weight, and when the anthelmintic property was studied, it was found that it has 100% anthelmintic efficiency against nematodirosis, marshallagiosis, other gastrointestinal strongylatosis and fasciolosis of sheep.

Considering that the suspension form of 2-propynylaminobenzimidazole against nematodirosis, marshallagiosis, other gastrointestinal strongylatosis, and fasciolosis, which are the main gastrointestinal helminthosis of sheep, taking into account that its

anthelmintic properties are higher than its powder form, we consider that it is appropriate to use the suspension form of 2-propynylaminobenzimidazole against the above-mentioned helminthic diseases of sheep in the future.

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