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N-BENZYLBISPIDINE WITH METHOXYPHENETHYL AND IMIDAZOLEPROPYL PHARMACOPHORES: ASSESSMENT OF MYELOSTIMULATING AND GROWTH-STIMULATING ACTIVITY OF NOVEL DERIVATIVES β-CD COMPLEXES

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Abstract: *Introduction.* The search for new biologically active compounds remains one of the key goals in medicinal chemistry. *The goal of the present study* to synthesize two groups of compounds: derivatives of methoxyphenethylamine and imidazolpropylamine with a mandatory N-benzylbispidine backbone and evaluate their potential as plant growth regulators and myelostimulators. *Results and Discussion:* New series of 3,7-diazabicyclo[3.3.1]nonan-9-ones were synthesized using traditional methods. The structure of the obtained compounds was confirmed using nuclear magnetic resonance (NMR) spectroscopy, infrared spectroscopy, and elemental analysis. *Conclusion.* New bicyclic systems have been synthesized in order to identify compounds with high biological potential. The myelostimulating activity of the obtained compounds 5βCD, 6βCD was evaluated in laboratory white female rats and growth-stimulating activity in wheat and soy seeds. The results of the study of myelostimulating activity showed that an imidazole derivative, namely the complex 6βCD, at a dose of 5 mg/kg in a volume of 0.5 ml, exhibits moderate activity against leukocytopoiesis, erythrocytopoiesis and thrombocytopoiesis. The results of the study of growth-stimulating activity showed that the complex (5βCD, HZR-112) stimulates plant growth on soybean seed seedlings. However, the complex (6βCD, HZR-109) does not stimulate the growth of wheat and soybeans, but is an inhibitor. It turned out that the combination of the bispidin fragment with methoxyphenethyl or imidazolepropyl is very promising for the search for new biologically active substrates of various types of action.

Key words: 2-(3-methoxyphenyl)ethanamine, 3-(1*H*-imidazole-1-yl)propane-1-amine, bicycle, complex, β-cyclodextrin, myelostimulating and growth-stimulating effects.

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1. Introduction

One of the ways to create new and more effective drugs is to modify already known pharmacophore structures, which are known to have high biological activity. This method makes it possible to obtain compounds that selectively act on specific molecular targets. As a result, such molecules may have higher therapeutic activity and lower toxicity [1, 2]. One of such promising groups of compounds are 3,7-diazabicyclo[3.3.1]nonan-9-ones and their derivatives, as they are part of natural and synthetic biologically active compounds, possessing antispasmodic, anesthetic, antiarrhythmic and other biological properties [3-6]. And heterocyclic molecules, in turn, represent an important class of structures used in the development of new drugs [7]. Numerous scientific studies have shown that heterocyclic molecules containing the imidazole system have a wide range of biological activity [8, 9].

In the course of the study, for the above reasons, we decided to create two groups of compounds representing 3,7-diazabicyclo[3.3.1]nonan-9-ones. These compounds differ in their chemical structure and properties. The first group contains methoxyphenethyl, and the second group contains imidazole propyl fragments. We hoped to obtain new series of biologically active substances by reacting with these two groups of compounds. Both fragments are known to have antibacterial, antioxidant, antitumor, and antifungal properties [10-13].

2. Experimental part

2.1. The chemical part

The course of the reaction and the uniqueness of the compounds were controlled by TLC. The IR spectra were recorded on a Nicolet 5700 spectrometer in tablets with potassium bromide, which are sealed between potassium bromide plates. The ^{1}H and ^{13}C spectra of the studied chemicals dissolved in deuterated chloroform were recorded on a JEOL JNM-ECA400 spectrometer with an operating frequency of 400 MHz on hydrogen nuclei. The internal standard is GMDS.

Synthesis of 3-(3-methoxyphenethyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonan-9-one (1). In a three-necked 250 ml flask equipped with a stirrer, a drip funnel, and a return refrigerator, 70.9 ml of methanol is deoxygenated under nitrogen current. After 30 min, a mixture of 9.79 g (0.065 mol) 2-(3-methoxyphenyl)ethanamine, 7.78 g (0.260 mol) paraform, 3.43 ml concentrated is added (in the ratio of N-benzyl-piperidine-4-one: 2-(3-methoxyphenyl)ethanamine: paraform 1:1:8) hydrochloric acid and 9.74 ml glacial acetic acid and stirred under nitrogen current for 15-20 min. A solution of

12.65 g (0.065 mol) of N-benzyl-piperidine-4-one and 9.74 ml of glacial acetic acid in 70.91 ml of methanol is added to the mixture for 30 min. After 10 h of heating at a temperature of 60-65 ^{0}C, another 7.78 g (0.260 mol) of paraform is added and maintained for another 10 h. The reaction is carried out in a nitrogen atmosphere. The solvent is evaporated on a water jet pump, the resulting light burgundy oil is dissolved in 103.4 ml of water and the neutral products are extracted with diethyl ether (it must be remembered that when extracting with diethyl ether, a bottom layer is needed). The aqueous layer is alkalized to a pH of 10.0–11.0. Next, the target product is extracted with chloroform. The combined chloroform extracts are dried over anhydrous magnesium sulfate. The desiccant is filtered out, the solvent is evaporated on a water jet pump. The resulting oil is isolated by column chromatography and 3-(3-methoxyphenethyl)-7-benzyl-3,7-diazabicyclo [3.3.1]nonane-9-one (1) is obtained. Yield 22.08 g (94 %), R_f = 0.675 (benzene : isopropanol 6:1), n_D^{20} = 1.561. Calculated, %: C 75.79; H 7.74; N 7.69. $C_{23}H_{28}N_2O_2$. Found, %: C 75.78; H 7.76; N 7.67. IR spectra, cm^{-1}: 1707 (C=O); 1455 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.42-2.46 (4H, dd, *J* = 11.9, 2.8 Hz, $CH_{2ax,\ 4ax,\ 6ax\ 8ax}$), 2.77-2.91 (4H, t, *J* = 2.7 Hz, $NCH_2CH_2CH_{ar}$), 3.06-3.11 (4H, dd, *J* = 12.7, 2.8 Hz, $CH_{2eq,\ 4eq,\ 6eq\ 8eq}$), 3.34-3.63 (2H, s, $CH_2C_6H_5$), 3.71-3.78 (3H, m, CH_3), 6.40-7.11, 7.12-7.36 (9H, m, *J* = 8.2, 2.8, 0.5 Hz, CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: 33.80 (C_{12}), 55.25 (C_{27}), 54.34 ($C_{4,6}$), 58.23 ($C_{1,5}$), 61.25 ($C_{2,8,11}$), 62.09 (C_{19}), 112.00 (C_{16}), 113.53 (C_{14}), 120.33 (C_{18}), 127.03 (C_{23}), 128.48-129.59 ($C_{17,21,22,24,25}$), 137.51 (C_{20}), 138.98 (C_{13}), 159.98 (C_{15}), 214.50 (C_9).

Synthesis of 3-(3-(1H-imidazole-1-yl)propyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonan-9-one (2) is carried out in a similar way. Yield 22.72 g (98 %), R_f = 0.636 (benzene:isopropanol 6:1), n_D^{20} = 1.560. Calculated, %: C 70.98; H 7.74; N 16.55; O 4,73. $C_{20}H_{26}N_4O$. Found, %: C 70.96; H 7.73; N 16.54. IR spectra, cm^{-1}: 1733 (C=O); 1451 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.74-1.90 (2H, quint, *J* = 2.7 Hz, $NCH_2CH_2CH_2N$), 2.16-2.28 (2H, t, *J* = 2.7 Hz, $NCH_2CH_2CH_2N$), 2.47-2.57 (2H, tt, *J* = 3.1, 2.5 Hz, CH_2CHCH_2), 2.65-2.81 (4H, dd, *J* = 11.8, 2.8 Hz, $CH_{2ax,\ 4ax,\ 6ax\ 8ax}$), 2.89-3.04 (4H, dd, *J* = 12.7, 2.8 Hz, $CH_{2eq,\ 4eq,\ 6eq\ 8eq}$), 3.46 – 3.55 (2H, s, $CH_2C_6H_5$), 3.89-3.98 (2H, t, *J* = 2.7 Hz, $NCH_2CH_2CH_2N$), 6.79-6.85, 6.93-7.02, 7.35-7.42 (3H, dd, *J* = 3.4, 1.9, 1.2 Hz, CH_{im}), 7.11-7.31 (5H, dd, *J* = 7.7, 1.8, 0.5 Hz, CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: 28.32 (C_{12}), 44.14 (C_{13}), 46.64 ($C_{1,5}$), 52.48 (C_{11}), 58.17 ($C_{2,8}$), 58.42 ($C_{4,6}$), 61.36 (C_{19}), 119.02 (C_{18}), 127.39 (C_{23}), 128.40 ($C_{22,24}$), 128.96 ($C_{21,25}$), 129.35 (C_{17}), 137.43 (C_{15}), 137.96 (C_{20}), 214.32 (C_9).

Synthesis of 3-(3-methoxyphenethyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane (3). To a mixture of 3 g (0.008 mol) 3-(3-methoxyphenethyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonan-9-one (1) and 1.31 g (0.041 mol) of hydrazine hydrate (99 % solution) in 23.92 ml of triethylene glycol at 60 ^{0}C add 5.69 g (0.102 mol) KOH. The reaction mixture is heated to 160-170 ^{0}C and stirred at this temperature for 5 h. At a temperature of 190-200 ^{0}C, water and excess hydrazine are distilled off. After cooling the reaction mixture to room temperature, 40.42 ml of distilled

water is added, extracted with diethyl ether, and dried over anhydrous $MgSO_4$. The solvent is evaporated, and the resulting product is purified using column chromatography and of 3-(3-methoxyphenethyl)-7-benzyl-3,7-diazabicyclo [3.3.1]nonane (3) is obtained. Yield 1.25 g (44 %), R_f=0.173 (benzene :isopropanol 7:1). n_D^{20} = 1.446. Calculated, %: C 78.82; H 8.63; N 7.99. $C_{23}H_{30}N_2O$. Found, %: C 78.80; H 8.65; N 7.98. IR spectra, cm^{-1}: 1071 (C-N). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.56 (2H, dt, *J* = 13.0, 2.7 Hz, $CHCH_2CH$), 2.11 (2H, ttt, J = 3.2, 2.7, 2.5 Hz, $CHCH_2CH$), 2.67 (2H, t, J = 2.7 Hz, $NCH_2CH_2CH_{ar}$), 2.87-3.03 (10H, 2.94 (dd, J = 10.6, 2.8 Hz, $CH_{2ax,4ax,\ 6ax,\ 8ax}$), 2.96 (dd, J = 10.3, 2.8 Hz, $CH_{2eq,\ 4eq,\ 6eq,\ 8eq}$), 2.98 (t, J = 2.7 Hz, $NCH_2CH_2CH_{ar}$)), 3.66 (2H, s, $CH_2C_6H_5$), 3.73 (3H, m, CH_3), 6.74-6.91, 7.20-7.45 (9H, m, *J* = 8.2, 7.7, 2.8, 1.8, 0.5 Hz, CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: 28.90 ($C_{1,5}$), 33.90 (C_{11}), 36.11 (C_9), 55.52 (C_{26}), 59.70-59.81 ($C_{2,4,6,8}$), 61.31 (C_{10}), 62.83 (C_{18}), 112.52 (C_{15}), 114.32 (C_{13}), 121.32 (C_{17}), 127.21 (C_{22}), 128.30 ($C_{20,24}$), 129.01 ($C_{21,23}$), 129.40 (C_{16}), 134.51 (C_{12}), 137.32 (C_{19}), 159.64 (C_{14}).

Synthesis of 3-(3-(1H-imidazole-1-yl)propyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane (4) is carried out in a similar way. Yield 3.20 g (56 %), R_f=0.21 (benzene :isopropanol 7:1). n_D^{20} = 1.483. Calculated, %: C 74.03; H 8.70; N 17.27; $C_{20}H_{28}N_4$. Found, %: C 74.01; H 8.73; N 17.26. IR spectra, cm^{-1}: 1070 (C-N),1510 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.52 (2H, dt, *J* = 13.0, 2.7 Hz, $CHCH_2CH$), 1.56 (2H, quint, *J* = 2.7 Hz, $NCH_2CH_2CH_2N$), 2.04 (2H, ttt, *J* = 3.2, 2.7, 2.5 Hz, CH_2CHCH_2), 2.15-2.37 (4H, dd, *J* = 10.6, 2.8 Hz, $CH_{2ax,4ax,\ 6ax,\ 8ax}$), 2.61-2.83 (4H, dd, *J* = 10.2, 2.8 Hz, $CH_{2eq,\ 4eq,\ 6eq,\ 8eq}$), 3.05-3.14 (2H, t, *J* = 2.7 Hz, $NCH_2CH_2CH_2N$), 3.35 (2H, s, $CH_2C_6H_5$), 3.85 (2H, t, *J* = 2.7 Hz, $NCH_2CH_2CH_2N$), 6.96 (1H, dd, *J* = 3.4, 1.9 Hz), 7.03 (1H, dd, *J* = 3.4, 1.1 Hz), 7.49 (1H, dd, *J* = 1.9, 1.1 Hz), 7.12-7.25 (5H, dd, *J* = 7.8, 1.84, 0.94 Hz, CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: 29.15 ($C_{1,5}$), 29.44 (C_{11}), 34.46 (C_9), 47.73 (C_{12}), 50.08 (C_{10}), 56.35 ($C_{4,6}$), 59.25 ($C_{2,8}$), 62.05 (C_{18}), 120.45 (C_{17}), 127.03 (C_{22}), 128.48 ($C_{21,23}$), 129.74 ($C_{20,24}$), 133.92 (C_{16}), 136.33 (C_{14}), 138.10 (C_{19}).

The complex of 3-(3-methoxyphenethyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane with β-cyclodextrin (5βCD). Hot solutions of 1.19 g (0.0034 mol) 3-(3-methoxyphenethyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane (3) are mixed in 25 ml of ethyl alcohol and 3.85 g (0.0034 mol) β-cyclodextrin in 40 ml of distilled water. The mixture is placed in a drying cabinet, ethanol and water are evaporated at 50-55 ^{0}C, and 3-(3-methoxyphenethyl) propyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane with β-cyclodextrin (5βCD) inclusion complex is obtained in the form of a white powder. Yield 4.25 g (84 %). Calculated, %: C 52.56; H 6.79; N 1.89. $C_{65}H_{100}N_2O_{36}$. Found, %: C 52.59; H 6.77; N 1.92.

The complex of 3-(3-(1H-imidazole-1-yl)propyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane with β-cyclodextrin (6βCD) is carried out in a similar way. Yield 5.95 g (88 %). Found, %: C 51.02; H 6.77; N 3.84. $C_{62}H_{98}N_4O_{35}$. Найдено, %: C 51.01; H 6.75; N 3.87.

2.2. The biological part

In the course of studies of myelostimulating activity, white female laboratory rats aged 12 to 16 weeks with a body weight of 210 to 280 grams were used. The blood test was performed on an Abacus junior vet hematology analyzer manufactured by Diatron, Denmark. The leukogram was monitored using Romanovsky-Giemse smear microscopy using a SA3300C microscope. The concentration of cells in the smear during immersion was 500 units. Myelosuppression was caused by the administration of cytostatic cyclophosphamide at a dose of 30 mg/kg of animal weight. Then, on the 6th, 8th and 10th days of follow-up, the rats were divided into 4 groups. Animals from group 1 were daily intramuscularly injected with the studied compound (6βCD) under the code BIV-277 at a dose of 5 mg / kg in a volume of 0.5 ml. Rats from group 2 were injected with reference compounds, namely the drug methyluracil, at a dose of 0.4 mg / kg and a volume of 0.5 ml, group 3 received a placebo (physical solution) in a volume of 0.5 ml, and group 4 remained intact. Statistical processing of the data was carried out using Student's confidence interval.

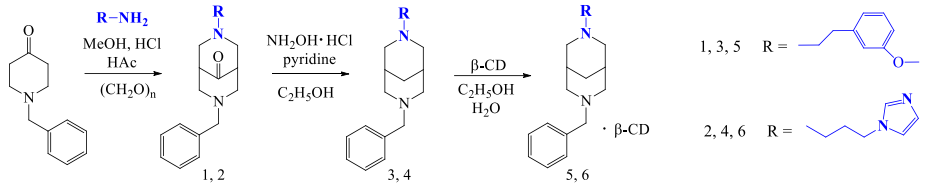
All experiments were conducted taking into account chronobiological principles and in full compliance with ethical standards for working with laboratory animals.

The study examined the effect of two substances (5βCD, 6βCD) — HZR-109 and HZR-112 — on stimulating the growth of seeds of spring wheat of the Kazakhstanskaya 10 variety and soybeans of the Zhansaya variety. The experiments were conducted in a laboratory setting. The seeds were germinated in moist chambers, after which they were planted in moistened soil. Germination was determined in four stages using 10 seeds in each repeat.

3. Results and discussion

In order to search for and isolate potentially biologically active substances, new bicyclic systems based on 2-(3-methoxyphenyl)ethanamine and 3-(1*H*-imidazole-1-yl)propane-1-amine were synthesized (Scheme 1). 3-(3-Methoxyphenyl)- and 3-(3-(1*H*-imidazole-1-yl)propyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane-9-ones 1, 2 were obtained from N-benzyl-4-oxopiperidine using a paraform and a corresponding primary amine in an acetic-methanol medium. The yield of products was 94-98 %. As a result of the reduction of the reaction products 1, 2 by the Kizhner-Wolf method using hydrazine hydrate in the presence of alkali in triethylene glycol, the corresponding bispidins (3, 4, with yields of 44-56 %) were synthesized. The resulting compounds are insoluble in water. To study their biological properties, complexes of these compounds with β-cyclodextrin were isolated. The complex of 3-(3-methoxyphenyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane with β-cyclodextrin (5βCD) was synthesized in 84 % yield. At the same time, the complex of 3-(3-(1*H*-imidazole-1-yl) propyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane with β-cyclodextrin (6βCD) was obtained in 88 % yield. The synthesis of these complexes was accompanied by the dissolution of

substances in a mixture of water and ethanol, prolonged heating in a sand bath, and subsequent ultrasound treatment. After all the procedures and drying, powdered products were obtained.



Scheme 1 - Synthesis of new bicyclic systems

In the IR spectra of 3,7-diazabicyclo[3.3.1]nonane-9-ones 1, 2 there are absorption bands of the carbonyl group at 1707 cm^{-1} and 1733 cm^{-1}. In the ^{13}C NMR spectrum of compounds (**1, 2**), the signals with the lowest chemical shift values at 214.32 ppm and 214.50 ppm were attributed to ketone carbon atoms (C-9), respectively. In the spectra, carbon atoms C-1 and C-5, as well as C-2, C-4, C-6 and C-8, which are marked in red, appeared at 54.32-58.17 and 58.42-61.25 ppm, respectively, and confirm the formation of target bispidinones. In the spectrum of the 2nd compound, it can be seen that the manifestations of imidazole carbon atoms that resonated at 119.02 ppm, 129.35 ppm and 137.43 ppm. Carbon atoms of the phenyl fragment were recorded at 112.00-159.98 and 127.03-137.96 ppm, respectively.

In the ^{1}H NMR spectrum of compounds 1, 2, imidazole protons appeared as single-proton doublets at 6.79-6.85, 6.93-7.02, and 7.35-7.42 ppm. Aromatic protons of the phenyl ring appeared as single-proton doublets in the region at 7.11-7.31 ppm and 6.40-7.11, 7.12-7.35 ppm. Methylene protons H-2ax,8ax,4ax,6ax and H-2eq, 8eq,4eq, and 6eq manifested as two four-proton multiplets at 2.42-2.81 and 2.89-3.11 ppm, respectively.

In the IR spectra of compounds 3, 4, the absorption bands of the C=O group are removed and absorption bands of the CH_2 bond appear, proving the formation of the corresponding bicyclic nonans. The absorption bands C-N and C=N groups are observed at 1510 cm^{-1} and 1070-1071 cm^{-1}. The ^{13}C NMR spectra of nonanes 3, 4 showed resonances for C-9 at 34.46 and 36.11 ppm, respectively. The signals of the carbon atoms of the bispidin framework appeared at 28.90-29.15 and 56.35-59.81 ppm. The carbon atom of the methoxyl fragment appeared at 55.52 ppm. The carbon atoms of the imidazole ring resonated in the range of 120.45-136.33 ppm, and the carbon atoms of the phenyl fragment in the range of 112.52-159.64 and 127.03-138.10 ppm.

The reaction products 3, 4 were viscous oils, soluble only in organic solvents. Complexes 5βCD, 6βCD with β-CD were obtained as solids and used to study the biological properties of the synthesized compounds.

The complex 6βCD was studied for myelostimulating activity, which includes stimulation of erythropoiesis, leukopoiesis and thrombocytopoiesis. The study was conducted under the code BIV-277 (see Table 1).

Compound 6βCD BIV-277 demonstrated moderate activity against leukocytopoiesis, erythrocytopoiesis and thrombocytopoiesis.

Table 1 - Peripheral blood parameters

Blood counts*	BIV-277 (6βCD)	The control group	The placebo group	The intact group
RBC, 10^{12}/l	8.09±0.52	6.06 ± 0.06	3.59 ± 0.20	7.02 ± 0.23
HGB, g/l	125±15.21	125 ± 4.00	96 ± 2.67	147 ± 6.00
HCT, %	37.37±4.21	23.35 ± 0.70	20.75 ± 0.30	37.3 ± 0.27
MCV, fl	46±4.58	54.45 ± 0.43	41.8 ± 0.07	82.6 ± 0.23
PLT, 10^9/l	133±5.55	521 ± 135.33	422 ± 41.33	690 ± 166.33
PCT, %	0.08±0.00	0.2815 ± 0.07	0.23 ± 0.02	0.372 ± 0.08
MPV, fl	6.2±0.01	6.1 ± 0.47	5.5 ± 0.13	7.4 ± 0.30
PDWS, %	9±0.05	12.25 ± 0.57	11.25 ± 0.23	11.4 ± 0.43

*RBC – total erythrocyte count; HGB – hemoglobin; HCT – hematocrit; MCV- average volume of red blood cells; PLT – total platelet count; PCT – the amount of thrombocrit; MPV – average platelet volume; PDWS – platelet distribution index

The red blood cell level increased from (3.59±0.2) 10^{12}/l of blood to (8.09±0.52) 10^{12}/l of blood by 2.25 times, and the hemoglobin level recovered 1.3 times from (96.0 ±2.67) g/l of blood to (125±15.21) g/l. The average volume of red blood cells increased from (41.8±0.07) fl to (46±4.58) fl. Platelet mass and thrombocrit also showed a decrease in the number of platelets by 3.17 and 2.88 times to (133±5.55)·10^9 /l of blood and (0.08±0.00) %, respectively. The average platelet volume increased by 1.13 times and amounted to (6.2±0.01) fl.

The complexes of compounds 5βCD, 6βCD under the codes HZR-109 and HZR-112 were studied in the laboratory for their stimulating effect on plant growth. The following indicators were determined during the study: germination energy, laboratory germination and germination intensity of seeds of Kazakhstanskaya 10 wheat and Zhansaya soybean (Table 2, Fig. 1).

Table 2 - The effect of the studied substances on germination, growth and development of wheat seed seedlings (Kazakhstanskaya 10) and soybeans (Zhansaya) in laboratory conditions

Variety	Options	Control	HZR-109 (5βCD)	HZR-112 (6βCD)
Kazakhstanskaya 10	Germination, %	90	100	100
	Seed germination energy, %	82.5	95.0	85.0
	Average height of plants, cm	9.5	8.0	8.0
Zhansaya	Germination, %	50	40	60
	Seed germination energy, %	45.0	35.0	50.0

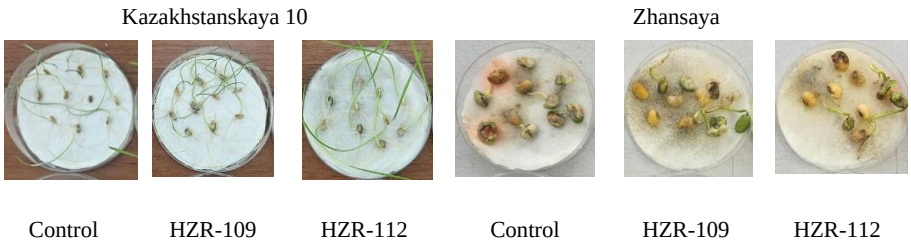


Figure 1 - Effect of XZR-109 and XZR-112 on germination, growth and development of wheat and soybean seedlings in laboratory conditions on day 7 of germination

During the study, it was found that the best results were obtained when using the complex (5βCD, HZR-112) for both types of wheat and soybean seedlings. The use of HZR-109 and HZR-112 preparations led to an increase in the germination energy of Kazakhstanskaya-10 wheat seeds by 85 and 95 %, respectively. When using HZR-109 and HZR-112, the average height of wheat plants of this variety was significantly lower than in the control group (treated with water) by 1.19 times. The germination rate and germination energy of soybean seeds of the Zhansaya variety treated with the HZR-109 preparation were lower compared with the control group. At the same time, when using the drug HZR-112, these indicators were 60 and 50 %, respectively.

4. Conclusion

As a result of the research, new bipidine-type systems based on 2-(3-methoxyphenyl)ethanamine and 3-(1*H*-imidazole-1-yl)propane-1-amine were synthesized. Then, the complexes of 3-(3-methoxyphenyl)- and 3-(3-(1*H*-imidazole-1-yl)propyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonans were obtained to study the biological activity with β-cyclodextrin. A study on myelostimulating activity showed that the complex (6βCD, BIV-277) reduces the number of platelet cells, while an increase in the level of erythrocyte cells, hemoglobin, and average platelet volumes was observed. This may indicate a moderate activity of the complex in relation to leukocytopoiesis, erythrocytopoiesis and thrombocytopoiesis. Biological screening conducted to determine the growth-stimulating activity showed that the complex (5βCD, HZR-112) stimulates plant growth on soybean seed seedlings. At the same time, the complex (6βCD, HZR-109) demonstrates inhibitory properties for all seed varieties.

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МЕТОКСИФЕНЭТИЛ ЖӘНЕ ИМИДАЗОЛПРОПИЛ ФАРМАКОФОРЛЫ N-БЕНЗИЛБИСПИДИН: β-CD ЖАҢА ТУЫНДЫ КЕШЕНДЕРІНІҢ МИЕЛОЫНТАЛАНДЫРУШЫ ЖӘНЕ ӨСУДІ ЫНТАЛАНДЫРАТЫН БЕЛСЕНДІЛІГІН БАҒАЛАУ

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Аңдатпа: *Кіріспе.* Жаңа биологиялық белсенді қосылыстарды іздеу дәрілік химияның негізгі мақсаттарының бірі болып қала береді. Осы *зерттеудің мақсаты* - қосылыстардың екі тобын - N-бензилбиспидин қаңқалы метоксифенетиламин және имидазолпропиламин туындыларын синтездеу және олардың өсімдіктердің өсуін реттеуші және миелоынталандырушы ретіндегі әлеуетін бағалау. *Нәтижелер және талқылау.* Дәстүрлі әдістерді қолдана отырып, 3,7-диазабицикло[3.3.1]нонан-9-ондардың жаңа сериялары синтезделді. Алынған қосылыстардың құрылымы ядролық магниттік-резонанстық спектроскопия (ЯМР), инфрақызыл спектроскопия және элементтік талдау арқылы расталды. *Қорытынды.* Биологиялық әлеуеті жоғары қосылыстарды анықтау мақсатында жаңа бициклді жүйелер синтезделді. Әрі қарай, алынған қосылыстардың 5βCD, 6βCD белсенділігін бағалау үшін зертханалық ақ аналық егеуқұйрықтарға миелоынталантырушылық және бидай мен соя тұқымына өсуді ынталандыру белсенділіктері жүргізілді. Миелоынталантырушы белсенділікті зерттеу нәтижелері бойынша имидазол туындысы, атап айтқанда 3-(3-(1*H*-имидазол-1-ил)пропил)-7-бензил-3,7-диазабицикло[3.3.1]нонанның β-циклодекстринмен кешені 6βCD 0,5 мл көлемінде 5 мг/кг дозада лейкоцитопоэзге, эритроцитопоэзге және тромбоцитопоэзге қатысты орташа белсенділікті көрсетті. Өсуді ынталандыратын белсенділікті зерттеу нәтижелері бойынша кешеннің (5βCD, ХЗР-112) соя тұқымының көшеттеріндегі өсімдіктердің өсуін ынталандыратынын көрсетті. Биспидин фрагментінің метоксифенэтилмен немесе имидазолпропилмен үйлесуі әр түрлі типтегі жаңа биологиялық белсенді субстраттарды іздеуде өте мақсатты болып табылды.

Түйін сөздер: 2-(3-метоксифенил)этанамин, 3-(1*H*-имидазол-1-ил)пропан-1-амин, бицикл, кешен, β-циклодекстрин, миелоынталантырушылық және өсуді ынталандырушы әсер.

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N-БЕНЗИЛБИСПИДИН С МЕТОКСИФЕНЭТИЛОВЫМИ И ИМИДАЗОЛПРОПИЛОВЫМИ ФАРМАКОФОРАМИ: ОЦЕНКА МИЕЛОСТИМУЛИРУЮЩЕЙ И РОСТСТИМУЛИРУЮЩЕЙ АКТИВНОСТИ НОВЫХ ПРОИЗВОДНЫХ КОМПЛЕКСОВ β –CD

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Аннотация: *Введение.* Поиск новых биологически активных соединений остается одной из ключевых задач медицинской химии. *Цель настоящего исследования* - синтезировать две группы соединений: производные метоксифенэтиламина и имидазолпропиламина с обязательным N-бензилбиспидиновым остовом и оценить их потенциал в качестве регуляторов роста растений и миелостимуляторов. *Результаты и обсуждение.* Были синтезированы новые серии 3,7-диазабицикло[3.3.1]нонан-9-онов с использованием традиционных методов. Структура полученных соединений была подтверждена с помощью спектроскопии ядерного магнитного резонанса (ЯМР), инфракрасной спектроскопии и элементного анализа. *Заключение.* Синтезированы новые бициклические системы с целью выявления соединений с высоким биологическим потенциалом. Была проведена оценка миелостимулирующей на лабораторных белых крысах-самках и ростстимулирующей на семянах пшеницы и сои активности полученных соединений 5βCD, 6βCD. Результаты исследования миелостимулирующей активности показали, что производное имидазола, а именно комплекс 3-(3-(1*H*-имидазол-1-ил)пропил)-7-бензил-3,7-диазабицикло[3.3.1]нонана с β-циклодекстрином 6βCD, в дозе 5 мг/кг в объёме 0,5 мл проявляет умеренную активность в отношении лейкоцитопоэза, эритроцитопоэза и тромбоцитопоэза. Результаты исследования ростстимулирующей активности показали, что комплекс (5βCD, ХЗР-112) стимулирует рост растений на проростках семян сои. Оказалось, что комбинация биспидинового фрагмента с метоксифенэтилом или имидазолпропилом весьма перспективна для поиска новых биологически активнх субстратов разнообразного типа действия.

Ключевые слова: 2-(3-метоксифенил)этанамин, 3-(1*H*-имидазол-1-ил)пропан-1-амин, бицикл, комплекс, β-циклодекстрин, миелостимулирующее и ростстимулирующее действие.

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