

New Anti-Infective Preparations of Naphthyloxypropargylpiperidine Series

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Abstract

1-alkyl-4-(3-naphthyloxyprop-1-ynyl)piperidine-4-ols have been obtained by the condensation of 1-alkyl-piperidin-4-ones with 1- and 2-naphthoxypropines by the Favorsky method in absolute diethylether, in the presence of powered technical KOH, under atmospheric pressure. Acylation of tertiary naphthoxypropynyl piperidols by cyclopropanecarbonylchloride has been carried out in order to introduce a cyclopropanecarbonyl fragment into the structures of naphthoxypropargylpiperidines. The obtained esters of cyclopropanecarboxylic acid represent crystalline substances with the definite melting temperature, very soluble in water, ethanol, acetone. The composition and structure of the synthesized compounds have been confirmed by the data of elemental analysis, IR-spectroscopy, NMR-spectroscopy, the identity has been confirmed by thin-layer chromatography. The compounds under the code AIP (anti-infective preparation) have been studied for an antimicrobial activity in relation to museum microbial strains. The effects of these preparations have been assessed in vitro in relation to *Bacillus subtilis* ATCC 6633, *Escherichia coli* ATCC 25922, *Salmonella enterica* ATCC 14028 and *Staphylococcus aureus* ATCC 6538-P. It has been found that the compounds AIP-30 and AIP-31 possess an antimicrobial activity in relation to all strains of microorganisms, engaged in the experiment. AIP-30 and AIP-31 have antimicrobial effects to different extents, AIP-30 has displayed the highest activity in relation to the museum strain *Bacillus subtilis* ATCC 6633 in the concentration of 250 µg/ml. It has been established that AIP-32 displays a selective antimicrobial activity towards one type, and AIP-33 – towards two types of the museum strains, engaged in the experiment.

1. Introduction

One of the main directions of synthetic organic chemistry is still a purposeful search for and creation of highly efficient and innocuous medicinal preparations.

More than ten million individual substances have been created for almost two centuries history of organic chemistry. Synthesis of new organic compounds is steadily growing, which comes, first of all, from the necessity of widening the fundamental tasks. One of such tasks is the extension of the arsenal of available, reliable and efficient medicinal preparations for the prevention and treatment of human diseases.

An interest to the chemistry of saturated azacyclic compounds has been aroused by the fact, that they are included in the structure of many natural and synthetic medicinal preparations, often stipulating their pharmacological activity. Piperidine derivatives with different functional groups (carboxylic, hydroxylic, etc.), whose presence causes different biological effects, are of special interest. Herewith, a large attention is drawn to the interaction of a thin chemical structure of a substance with its activity, which is an important stage of the directed synthesis of physiologically active preparations.

A high pharmacological activity of nitrogenous heterocycles, whose component is 4-hydroxypiperidine, has given rise to a huge number of studies in

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synthesis of their homologues, analogs and various derivatives, as well as evaluation of their ability to influence the pharmacological properties of the molecule. The substituted piperidines are related to so-called "privileged structures", since they serve as a basis for the creation of medicines with different types of biological activity. The molecular design of the piperidine molecule provides the chemical scientists with an effective "tool" for the creation of valuable medicines, possessing a wide spectrum of pharmacological activities. More than 100 medicinal preparations, created on the basis of piperidine derivatives, have found a wide application in medicine.

A recent period of development of organic chemistry demonstrates not only the potential of organic synthesis, but also its importance for the development of chemistry as a whole, and many scientific and practical fields related thereto, in particular, the provision of the mankind with medicines. Due to a high physiological activity of azacycles, particularly, piperidine derivatives, these studies acquire the status of one of the topical tasks of modern chemistry, biology and medicine. The search for new compounds of antimicrobial and viricidal activities, including an ability to cause a reversion of drug susceptibility, is one of the highest priority directions in the sphere of development of anti-infective preparations. The substances, possessing an antimicrobial activity, are very valuable for medicine. Despite a big number of medicinal preparations the search for new antimicrobial preparations is a topical task, which is connected, first of all, with a high adaptability of pathogenic organisms to different antibiotics [1–3].

At the Laboratory of Chemistry of Synthetic and Natural Medicinal Preparations of A.B. Bekturov Institute of Chemical Sciences the most promising compounds-leaders have been revealed in the series of N-alkyl, N-alkoxyalkyl, N-phenylethyl derivatives of piperidine [4–9].

The present study is a continuation of the scientific research works for synthesis of piperidine-containing derivatives of cyclopropanecarboxylic acid [10–12]. The works in this direction are well substantiated, since the cyclopropane derivatives draw an ever increasing interest in the recent years due to their biological and pharmaceutical applications. The cyclopropane ring systems are widely spread by their nature, and are largely contained in natural products, insecticides and pharmaceutical preparations. The studies for the development of small molecules, which are bound with therapeutically

important biological targets with high affinity and selectivity, are topical in the recent years, being the main goal of the modern bioorganic and medicinal chemistry [13].

2. Experimental

2.1. Experimental chemical part

2.1.1. Methods and Instrumentation

IR spectra were taken on a «Nicolet 5700FT-IR» spectrometer as a thin film (ν in cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Jeol JNM-ECA-400 spectrometer, with ^1H and ^{13}C being observed at 400 and 100.8 MHz, respectively. Chemical shifts (in δ values or ppm) for ^1H and ^{13}C NMR spectra were taken in CDCl_3 downfield from TMS [$(\text{CH}_3)_4\text{Si}$], and coupling constants were reported as J in Hz. Thin layer chromatography was carried out on alumina of III activity. The reagents were used as received from commercial suppliers unless otherwise stated (Aldrich).

Hydrochloride of 1-methyl-4-[3-(naphth-1-yloxy)prop-1-in-1-yl]-4-cyclopropanecarbonyloxypiperidine (7). 1.36 ml (0.015 mol) of the solution of cyclopropanecarbonylchloride in absolute dioxane was added to the solution of 3 g (0.01 mol) of 1-methyl-4-[3-(naphth-1-yloxy)prop-1-in-1-yl]piperidine-4-ol (3) in absolute dioxane. The mixture was heated at about 60 °C for 15 min. Then the mixture was held for 24 h at the room temperature. The solvent excess was removed. The residue was re-crystallized from isopropanol.

3.4 g (82.0 % of the theoretical value) of hydrochloride of 1-methyl-4-[3-(naphth-1-yloxy)prop-1-in-1-yl]-4-cyclopropanecarbonyloxypiperidine (7) with the melting temperature of 173–175 °C, R_f 0.88 (Al_2O_3 , eluent – benzene:dioxane – 4:1) was obtained.

Elemental analysis found/calculated for $\text{C}_{23}\text{H}_{26}\text{NO}_3\text{Cl}$: C 68.69 (69.07); H 6.83 (H 6.55).

Hydrochloride of 1-methyl-4-[3-(naphth-2-yloxy)prop-1-in-1-yl]-4-cyclopropanecarbonyloxypiperidine (8). 0.3 ml (0.003 mol) of the solution of cyclopropanecarbonylchloride in absolute dioxane was added to the hot solution (60 °C) of 0.6 g (0.002 mol) of 1-methyl-4-[3-(naphth-2-yloxy)prop-1-in-1-yl]piperidine-4-ol (4) in absolute dioxane. Then the mixture was held for 24 h at the room temperature. The solvent excess was removed. The residue was re-crystallized from isopropanol.

0.45 g (56% of the theoretical value) of hydrochloride of 1-methyl-4-[3-(naphth-2-yloxy)prop-1-in-1-yl]-4-cyclopropanecarbonyloxypiperidine (8) with the melting temperature of 181–182 °C, R_f 0.77 (Al_2O_3 , eluent – diethyl ether: petroleum ether – 4:1) was obtained.

Elemental analysis found/calculated for $C_{23}H_{26}NO_3Cl$: C 68.55 (69.07); H 6.93 (H 6.55).

Hydrochloride of 1-propyl-4-[3-(naphth-1-yloxy)prop-1-in-1-yl]-4-cyclopropanecarbonyloxypiperidine (9). 0.4 ml (0.0045 mol) of the solution of cyclopropanecarbonylchloride in absolute dioxane was slowly dropped to the solution of 1 g (0.003 mol) of 1-propyl-4-[3-(naphth-1-yloxy)prop-1-in-1-yl]piperidine-4-ol (5) in absolute dioxane. The mixture was heated at 60 °C for about 15 min. Then the mixture was held for 24 h at the room temperature. The solvent excess was removed. The residue was re-crystallized from isopropanol.

0.87 g (66 % of the theoretical value) of hydrochloride of 1-propyl-4-[3-(naphth-1-yloxy)prop-1-in-1-yl]-4-cyclopropanecarbonyloxypiperidine (9) with the melting temperature of 167–169 °C, R_f 0.87 (Al_2O_3 , eluent – benzene:dioxane – 4:1) was obtained.

Elemental analysis found/calculated for $C_{25}H_{30}NO_3Cl$: C 69.79 (70.16); H 6.71 (H 7.06).

Hydrochloride of 1-propyl-4-[3-(naphth-2-yloxy)prop-1-in-1-yl]-4-cyclopropanecarbonyloxypiperidine (10). 0.4 ml (0.0045 mol) of the solution of cyclopropanecarbonylchloride in absolute dioxane was slowly dropped with the help of a separation funnel, while stirring, to the solution of 1 g (0.003 mol) of 1-propyl-4-[3-(naphth-2-yloxy)prop-1-in-1-yl]piperidine-4-ol (6). The mixture was heated at 55 °C for 1 h. Then the reaction mixture was held at the room temperature. The reaction course was controlled by thin layer chromatography. The solvent excess was removed. The residue was re-crystallized from isopropanol.

0.86 g (65 % of the theoretical value) of hydrochloride of 1-propyl-4-[3-(naphth-2-yloxy)prop-1-in-1-yl]-4-cyclopropanecarbonyloxypiperidine (10) with the melting temperature of 152–154 °C, R_f 0.78 (Al_2O_3 , eluent – benzene:dioxane – 4:1) was obtained.

Elemental analysis found/calculated for $C_{25}H_{30}NO_3Cl$: C 69.87 (70.16); H 6.2 (H 7.6).

2.2. Experimental biological part

The compounds under the codes AIP-30, AIP-31, AIP-32, AIP-33 were studied for an antibac-

terial activity in relation to the museum strains of microorganisms, the effects of these preparations in vitro in relation to *Bacillus subtilis* ATCC 6633, *Escherichia coli* ATCC 25922, *Salmonella enterica* ATCC 14028 and *Staphylococcus aureus* ATCC 6538-P were studied.

2.3. Materials and methods of study

Nutrient medium and chemicals:

- Nutrient agar M001 (HiMedia), Müller-Hinton broth AM5072;
- Müller-Hinton agar AM5071 (Accumix);
- NaCl (Reaktiv OJSC), ethyl alcohol.

Reference strains of microorganisms:

- *Bacillus subtilis* ATCC 6633,
- *Escherichia coli* ATCC 25922,
- *Salmonella enterica* ATCC 14028,
- *Staphylococcus aureus* ATCC 6538-P.

The methods of study used:

- the Koch's method – determination of viability of the museum strains, engaged in the experiment;
- an evaluation of physiological and biochemical properties of the museum strains, engaged in the experiment;
- a macromethod of two-fold serial dilutions in the nutrient broth – determination of a minimum inhibitory concentration of the studied substance.

2.4. Justification of the chosen study flow chart

The study model includes a necessary minimum of tests with different extent of susceptibility, which may provide reliable and objective information on availability of antimicrobial properties of the compounds studied in vitro [14]. All selected tests are adequate from the viewpoint of the results, obtained in the course of their performance. Besides, the study flow chart is carried out in accordance with the methodical recommendations and normative documents effective in the territory of Kazakhstan, approved by the State Pharmacological Committees of Kazakhstan [15].

1. *Preparation of the museum strains for the study: reactivation, viability test and control of physiological and biochemical properties.*

Prior to the start of the experiment the microorganisms have been reactivated (resuscitated), followed by subcultivation. To determine viability of the microorganisms, engaged in the experiment, the Koch's method [16] has been used. It has been established that all cultures possess good viability, exceeding 10^{11} cfu/ml.

Upon the control of a physiological and biochemical activity [17] it has been proved, that the cultures correspond to the systematic position, they are standard and have not changed their properties while storing.

2. Determination of the minimum inhibitory concentration (MIC) of AIP

Evaluation of the minimum inhibitory concentration (MIC) in relation to the microorganisms, engaged in the experiment, has been carried out following the generally accepted method of two-fold serial dilutions in the Müller-Hinton [14, 18] broth. To prepare basic solutions of AIP-30, AIP-31, AIP-32 and AIP-33 in the concentration of 4000 µg/ml, a sample weight of 0.2 g has been diluted in 50 ml of 0.9% solution of sodium chloride. Then two-fold serial dilutions from 2000 µg/ml to 2 µg/ml (2000 µg/ml, 1000 µg/ml, 500 µg/ml, 250 µg/ml, 125 µg/ml, 63 µg/ml, 31 µg/ml, 16 µg/ml, 8 µg/ml, 4 µg/ml, 2 µg/ml) have been prepared. A freshly prepared suspension of microorganisms in the concentration of 10⁶ cfu/ml has been introduced into the prepared dilutions. A tube, containing the nutrient medium and the tested strain has been used for control. The cultures have been incubated at 37 °C for 18–24 h. On expiry of the incubation time plating into the Müller-Hinton broth has been carried out from each dilution. The Petri dishes with the cultures have been incubated at 37 °C for 18–24 h. MIC has been determined by the least concentration of AIP-30, AIP-31, AIP-32 and AIP-33, which has

suppressed the growth of the microorganism being tested. The study of an antimicrobial activity of the new compounds has been repeated twice. A heavy growth of the tested strains has been observed in the control tube.

3. Results and Discussion

Synthesis of the compounds with a potential antibacterial activity has been performed in three stages. At the first stage the initial 1- and 2-naphthoxypropines have been synthesized by the interaction of α - and β -naphthols with propargyl bromide in the acetone medium in the presence of potash.

1-alkyl-4-(3-naphthyloxyprop-1-ynyl)piperidine-4-ols (3-6) [19] have been obtained by the condensation of [1-methyl-, 1-propyl-]piperidine-4-ones (1,2) with 1- and 2-naphthoxypropines by the Favorsky method in absolute diethyl ether, in the presence of powered technical KOH, under atmospheric pressure.

Acylation of tertiary naphthoxypropynyl piperidols (3–6) by cyclopropanecarbonylchloride has been carried out in order to introduce a cyclopropanecarbonyl fragment into the structures of naphthoxypropargylpiperidines.

The reaction of acetylation of a hydroxyl group of the compounds (3–6) has been carried out in absolute dioxane upon heating, with cyclopropanecarbonylchloride, taken in excess as an acylating agent.

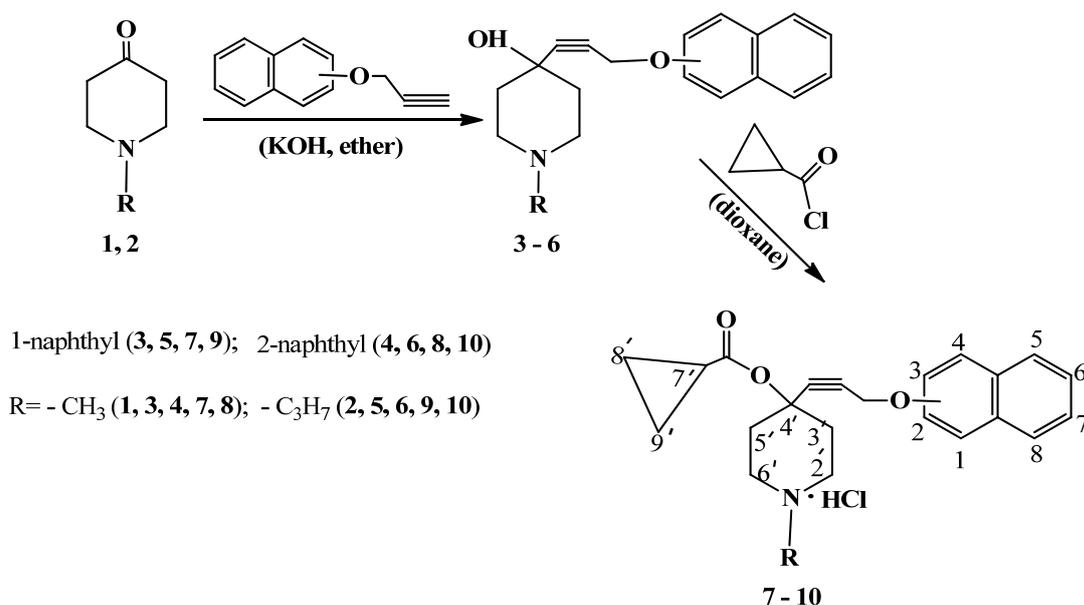


Table 1
Yields, physical and chemical characteristics of esters (7–10)

Compound	Yield, %	R _f	Calculated Found, %		IR, cm ⁻¹	
			C	H	OH	C=O
7	82	0.88	<u>68.69</u> 69.07	<u>6.83</u> 6.55	-	1732
8	56	0.77	<u>68.55</u> 69.07	<u>6.93</u> 6.55	-	1740
9	66	0.87	<u>69.79</u> 70.16	<u>6.71</u> 7.06	-	1742
10	65	0.78	<u>69.87</u> 70.16	<u>6.82</u> 7.06	-	1735

Note – Al₂O₃, eluent: benzene:dioxane 4:1

Table 2
Chemical shifts of carbons (δ, ppm) (7–10) in CDCl₃

Compound	C _{3',5'}	C _{2',6'}	C _{4'}	C _{7'}	C _{8',9'}	N-R	C=O	≡C-	-C≡	OCH ₂	naphtyl - C ₁	naphtyl - C ₂
7	33.6	49.9	82.3	13.3	8.9	42.5	165.1	84.2	85.5	56.7	153.1	106.5
8	29.8	47.4	81.4	13.6	8.9	51.9	173.6	81.6	86.3	60.1	107.7	155.4
9	33.9	47.5	82.3	12.7	8.4	13.3 17.2 57.1	172.6	78.3	91.5	56.7	153.0	106.9
10	32.9	42.7	71.2	12.1	9.1	12.1 19.2 59.8	165.1	79.9	90.6	47.3	107.3	163.5

The obtained esters of cyclopropanecarboxylic acid (7–10) represent crystalline substances with the definite melting temperature, very soluble in water, ethanol, acetone.

The composition and structure of the synthesized compounds (7–10) have been confirmed by the data of elemental analysis, IR-spectroscopy, NMR-spectroscopy, the identity has been confirmed by thin-layer chromatography.

The yields, physical and chemical characteristics and elemental analysis data are presented in Table 1.

In the IR-spectra of esters (7–10) (Table 1) absorption bands, which are stipulated by the oscillations of C=O bond of the ester group and confirm the presence of ester groupings in the structures of these compounds, are observed at 1732–1742 cm⁻¹.

In the upfield region of the PMR-spectrum (δ = 0.83–0.87 ppm) signals of a cyclopropyl fragment are observed, and in the lowest down field region of the spectrum, protons of a naphthalenic radical are observed at 6.98–8.10 ppm in the form

of multiplets, oxymethylene protons appear as singlets in the field of 3.27–5.09 ppm, protons of the piperidine cycle resonate at 1.81–2.54 ppm as unresolved multiplets. Protons of alkyl substituents at nitrogen are also observed in the spectrum.

In the ¹³C NMR-spectra (Table 2) of cyclopropanecarboxyloxy-derivatives (7–10) singlet signals of carbon of ester carbonyls are observed in the region of 165.1–173.6 ppm, a singlet signal of C₄ atoms of carbon of these compounds resonates in the region of 71.2–82.3 ppm, a carbon atom of the methyl group of the compounds 7 and 9 with triple bond ≡C-CH₂ is observed as a triplet in the region of 56.7 ppm, and in the compounds 8, 10 – in the region of 60.1 ppm and 47.3 ppm, respectively. Besides, signals of carbon atoms of the system of condensed benzene nuclei and a cyclopropyl fragment are observed.

The presence of signals of the ¹³C NMR-spectra of carbon atoms of substituents at nitrogen, as well as substituents in position 4 fully confirms the assigned structure of the synthesized esters.

Table 3
Data on an antimicrobial activity of AIP-30, AIP-31, AIP-32 and AIP-33

Strain/ Code of the compound	MIC, µg/ml			
	<i>Bacillus subtilis</i> ATCC 6633	<i>Escherichia coli</i> ATCC 25922	<i>Staphylococcus aureus</i> ATCC 6538-P	<i>Salmonella enterica</i> ATCC 14028
AIP-30	250	250	1000	500
AIP-31	250	500	1000	1000
AIP-32	1000	-	-	-
AIP-33	500	2000	-	-

Note: “-” - “no activity”

3.1. Study of biological activity

Hydrochloride of 1-methyl-4-[3-(naphth-1-yloxy)prop-1-in-1-yl]-4-cyclopropanecarbonyloxypiperidine (compound 7, code AIP-30), hydrochloride of 1-methyl-4-[3-(naphth-2-yloxy)prop-1-in-1-yl]-4-cyclopropanecarbonyloxypiperidine (compound 8, code AIP-31), hydrochloride of 1-propyl-4-[3-(naphth-1-yloxy)prop-1-in-1-yl]-4-cyclopropanecarbonyloxypiperidine (compounds 9, code AIP-32), hydrochloride of 1-propyl-4-[3-(naphth-2-yloxy)prop-1-in-1-yl]-4-cyclopropanecarbonyloxypiperidine (compound 10, code AIP-33) have been studied for an antimicrobial activity at the Laboratory of Microbiology of Scientific Center of Anti-Infective Drugs JSC [20–23]. The results of the twice repeated biological tests are presented in Table 3.

It is seen from the data provided in Table 3 that the compounds AIP-30 and AIP-31 possess an antimicrobial activity in relation to all strains of the microorganisms, engaged in the experiment. AIP-30 and AIP-31 have antibacterial effects to different extents. AIP-30 has displayed the highest activity in relation to the museum strain *Bacillus subtilis* ATCC 6633 in the concentration of 250 µg/ml. Streptomycin is active in relation to the gram-negative strains of microorganisms (*Escherichia coli*, *Staphylococcus aureus*, *Salmonella enterica*), and its efficiency towards *Bacillus subtilis* makes up only 50–60%.

The compound AIP-32 possesses an antimicrobial activity in relation to the museum strain of *Bacillus subtilis* ATCC 6633 in the concentration of 1000 µg/ml.

AIP-33 possesses an antimicrobial activity in relation to the museum strain of *Bacillus subtilis* ATCC 6633 in the concentration of 500 µg/ml, in relation to collibacillus this compound displays an

activity in the high concentration of 2000 µg/ml.

Thus, it has been established that AIP-32 displays a selective antimicrobial activity towards one type, and AIP-33 – towards two types of the museum strains, engaged in the experiment.

According to the Guidance for experimental (pre-clinical) study of new pharmacological substances the tested compounds may be used in the additional studies for revealing a specific antimicrobial activity within a wider range of microorganisms, as well as for the study of toxicity on models *in vitro* and *in vivo*.

4. Conclusions

1-alkyl-4-(3-naphthyloxyprop-1-ynyl)piperidine-4-ols have been obtained by the condensation of 1-methyl-, 1-propylpiperidine-4-ones with 1- and 2-naphthoxypropines by the Favorsky method in absolute diethyl ether, in the presence of powdered technical KOH, under atmospheric pressure. With the purpose to synthesize the preparations with a potential antimicrobial activity acylation of tertiary naphthoxypropynyl piperidols has been carried out by cyclopropanecarbonylchloride, with the formation of the corresponding hydrochlorides of esters. The structure of the synthesized compounds has been confirmed by the data of IR- and NMR-spectroscopy.

The compounds under the codes AIP-30, AIP-31, AIP-32, AIP-33 have been studied for an antimicrobial activity in the experiments *in vitro* in relation to *Bacillus subtilis* ATCC 6633, *Escherichia coli* ATCC 25922, *Salmonella enterica* ATCC 14028 and *Staphylococcus aureus* ATCC 6538-P. AIP-30 has displayed the widest specter of an antimicrobial activity in relation to all museum strains, involved in the experiment in the concentration of from 250 µg/ml up to 2000 µg/ml.

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References

- [1]. L. Bryan, Antimicrobial drug resistance. / L. Bryan. – Orlando: Academic press, 1984. – 450 p.
- [2]. G. Regev-Yochay, M. Raz, R. Dagan, H. Roizin, B. Morag, Sh. Hetman, S. Ringel, N. Ben-Israel, M. Varon, E. Somekh, E. Rubinstein, *Clinical Infectious Diseases* 3 (1) (2011) 33–41. DOI: 10.1093/cid/cir272
- [3]. Antimicrobial resistance surveillance in Europe 2012. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). European Centre for Disease Prevention and Control.: – Introduced 2013, Stockholm, 208 p. DOI: 10.2900/93403
- [4]. K.D. Praliyev. C- and N- substituted mono- and bicyclic piperidines: synthesis, stereochemistry, transformations and properties. *Materialy Pervoj Mezhdunarodnoj konferencii "Himija i biologicheskaja aktivnost' azotistyh geterociklov i alkaloidov"* [Materials of the First International Conference "Chemistry and Biological Activity of Nitrous Heterocycles and Alkaloids"]. Moscow, 2001, p. 130–138 (in Russian).
- [5]. K.D. Praliyev, V.K. Yu, I.A. Poplavskaya. The directed synthesis of new pharmacologically active substances in the series of 4-ethinyl-4-hydroxypiperidine derivatives. *Materialy Pervoj Mezhdunarodnoj konferencii "Himija i biologicheskaja aktivnost' azotistyh geterociklov i alkaloidov"* [Materials of the First International Conference "Chemistry and Biological Activity of Nitrous Heterocycles and Alkaloids"]. Moscow, 2001, p. 484–489 (in Russian).
- [6]. E.A. Babayan. "Procidol" – an organic domestic synthetic analgesic of central action. *Novye lekarstvennye preparaty* [New drugs] 7 (2006) 3–6 (in Russian).
- [7]. G.S. Akhmetova, V.K. Yu, K.D. Praliyev, N.M. Pominova, Ye.A. Severova. Synthesis and pharmacological activity of some N-aryl-ethyl-4,4-disubstituted piperidines. *Izvestija ministerstva obrazovanija i nauki Respubliki Kazahstan (serija khimicheskaja)* [Proceedings of the Ministry of Education and Science of the Republic of Kazakhstan (chemical series)] 3 (2001) 53–65 (in Russian).
- [8]. G.S. Akhmetova, A.K. Amantayeva, V.K. Yu, K.D. Praliyev, L.M. Moissejeva, M.S. Lukyanova, A.A. Koltunova, Ye.I. Voronina. Synthesis and pharmacological properties of the new homolog of the native original analgesic drug prosidol. *Izvestija Tomskogo politehnicheskogo universiteta* [Proceedings of Tomsk Polytechnic University] 3 (317) (2010) 140–143. (in Russian).
- [9]. V. Yu, K. Praliyev, A. Nagimova, A. Zazybin, *Tetrahedron Lett.* 56 (2015) 1631–1634. DOI: 10.1016/j.tetlet.2015.02.001
- [10]. V.I. Kozlovskiy, K.D. Praliyev, V.V. Goncharuk, L.B. Zavodnik, G.S. Akhmetova, T.K. Iskakova, V.K. Yu, Analgesic activity of the original substances of the piperidine series: an experimental study on the model of thermal stimulation, *Zhurnal Grodnenskogo gosudarstvennogo medicinskogo universiteta* [Journal of Grodno State Medical University, Belarus] 3 (2014) 38–41. (in Russian).
- [11]. G.S. Akhmetova, F.M. Sadyrbayeva, V.K. Yu, K.D. Praliyev, O.T. Zhilkibayev, G.M. Pichkhadze, S.R. Nassyrova, Sh.O. Imashova, M.K. Amirkulova. Piperidine-containing cyclopropanecarboxylic acid derivatives – potential PEAs, *Khimicheskij zhurnal Kazahstana* [Chemical Journal of Kazakhstan], 1 (2012) 118–127 (in Russian).
- [12]. F.M. Sadyrbayeva, S.I. Ospanova, U.B. Issayeva, G.S. Akhmetova, V.K. Yu, K.D. Praliyev. Amides of cyclopropanecarboxylic acid – potential biologically active substances, *Klaster konferencij po organicheskoy khimii OrgHim-2013* [Cluster of conferences on organic chemistry OrgChim-2013] St. Petersburg, Repino, 2013, June 17–21, p. 248–249 (in Russian).
- [13]. K. Ajar Kumar, *International Journal of Pharmacy and Pharmaceutical Sciences* 5 (1) (2013) 467–472.
- [14]. Guidance for experimental (pre-clinical) study of new pharmacological substances, the RF Ministry of Health», «IIA Remedium», Moscow, 2000, 679 p. (in Russian).
- [15]. Pre-clinic tests of medicinal preparations (Methodological recommendations). The Republic of Kazakhstan State Pharm. Committee, Almaty, 1997, 22 p. (in Russian).
- [16]. N.S. Yegorov. *Rukovodstvo k prakticheskim zanjatijam po mikrobiologii* [A guide to practical lessons in microbiology Guidance for practical training in microbiology]. 3rd edition, M.: Moscow State University, 1995, p. 224. (in Russian).
- [17]. J. Jolt, N. Crieg, P. Smith, J. Staily, S. Williams. *Opredelitel' bakterij Berdshi* [The Berji bacteria determinant] In 2 volumes. v.1: Translated from English. M.: Mir, 1997. – p. 432.

- [18]. CLSI M07-A9 Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. Approved Standard – Ninth Edition. - 2012.- v.32.- No.2.- p.88.
- [19]. M.T. Omirzak, R.Sh. Erkassov, B.G. Sukhov, T.V. Ganyenko. “Synthesis, structure, and growth-promoting activity of 1-alkyl-4-(3-naphthyloxyprop-1-ynyl)piperidine-4-ols”, Russian Chem. Bull., Int. Edition, 62 (11) (2013) 2442–2444.
- [20]. K.D. Praliyev, M.Ye. Kulmanov, A.I. Ilyin, F.M. Sadyrbayeva, G.S. Akhmetova, V.K. Yu, U.B. Issayeva, N.V. Leonova et al. [Hydrochloride of 1-methyl-4-[3-(naphth-1-yloxy)prop-1-in-1-yl]-4-cyclopropanecarbonyloxypiperidine (AIP-30), possessing an antimicrobial activity]. RK Innovative Patent No. 29020. Published in Bulletin No.10, dated 15.10.14. (in Russian).
- [21]. K.D. Praliyev, M.Ye. Kulmanov, A.I. Ilyin, F.M. Sadyrbayeva, G.S. Akhmetova, V.K. Yu, U.B. Issayeva., N.V. Leonova et al. Hydrochloride of 1-methyl-4-[3-(naphth-2-yloxy)prop-1-in-1-yl]-4-cyclopropanecarbonyloxypiperidine (AIP-31), possessing an antimicrobial activity. RK Innovative Patent No.29021. Published in Bulletin No.10, dated 15.10.14. (in Russian).
- [22]. K.D. Praliyev, M.Ye. Kulmanov, A.I. Ilyin, F.M. Sadyrbayeva, G.S. Akhmetova, V.K. Yu, U.B. Issayeva, N.V. Leonova et al. Hydrochloride of 1-propyl-4-[3-(naphth-1-yloxy)prop-1-in-1-yl]-4-cyclopropanecarbonyloxypiperidine (AIP-32), possessing an antimicrobial activity. RK Innovative Patent No.29022. Published in Bulletin No.10, dated 15.10.14. (in Russian).
- [23]. K.D. Praliyev, M.Ye. Kulmanov, A.I. Ilyin, F.M. Sadyrbayeva, G.S. Akhmetova, V.K. Yu, U.B. Issayeva, N.V. Leonova et al. Hydrochloride of 1-propyl-4-[3-(naphth-2-yloxy)prop-1-in-1-yl]-4-cyclopropanecarbonyloxypiperidine (AIP-33), possessing an antimicrobial activity. RK Innovative Patent No.29023. Published in Bulletin No.10, dated 15.10.14. (in Russian).