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The Search for Biologically Active Compounds in the Series of N-ethoxyethylpiperidine Derivatives

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Abstract

With the aim to introduce fragment of cyclopropane and fragments of *p-, m-, o*-fluorophenyls into the structures of N-ethoxyethylpiperidines, acylation of oxime and phenylacetylenic alcohol of 1-(2-ethoxyethyl)-4-ketopiperidine by cyclopropanecarbonylchloride was carried out; on the basis of 1-(2-ethoxyethyl)-4-ethynyl-4-hydroxypiperidine (cascaine alcohol), acylation by 4-fluoro-, 3-fluoro-, 2-fluorobenzoylchlorides was carried out with formation of the corresponding piperidine containing hydrochlorides of cyclopropanecarboxylic acid esters and para-, meta-, ortho-fluorobenzoic esters. Acylation reaction on the hydroxyl group of compounds is carried out in absolute dioxane, the acylating agents are cyclopropanecarbonylchloride, *p-, m-, o*-fluorobenzoyl chlorides taken in excess. The obtained esters of cyclopropanecarboxylic and para-, meta-, ortho-fluorobenzoic acids are crystalline substances with a clear melting point, well soluble in water, ethanol, acetone. *P*-fluorobenzoates are obtained with better yields, m-fluorobenzoates occupy an intermediate position, and o-fluorobenzoates are formed with the lowest yields. The best yields of fluorobenzoates are obtained using dioxane as a solvent. Para-, meta-, ortho-fluorobenzoic esters of 1-(2-ethoxyethyl)-4-ethynyl-4-hydroxypiperidine coded A-4 – A-6 were studied for the presence of antimicrobial activity, the actions of these preparations were evaluated *in vitro* in relation to strains of gram-positive bacteria *Staphylococcus aureus*, *Bacillus subtilis*, gram-negative strains of *Escherichia coli*, *Pseudomonas aeruginosa* and to yeast fungus *Candida albicans* by the diffusion method into agar (holes). Introduction of fluorine atom into the structure of cascaine lead to manifestation of antimicrobial activity.

1.Introduction

At present, despite of a great range of drugs being used and difficulties in creation of new preparations, the actuality of investigations aimed at the development of effective and qualitative biologically active substances is indisputable. The reasons encouraging us to deal with this problem are different: weakening of the human immune system, the rapid spread of dangerous viral infections, environmental degradation as well as resistance of dangerous microorganisms to the existing medicinal preparations.

In this regard, one of the priority tasks of synthetic organic chemistry is synthesis of new compounds with an original structure which have a complex of predicted properties. The search for new effective medicinal substances includes the techniques of modification of the existing substances with expressed pharmacological properties or creation of absolutely new classes of organic compounds. It should be noted that, among the

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medicinal substances being developed, special attention is paid to nitrogen heterocycles distinguished by a range of pronounced pharmacological properties and adaptability to streamlined production.

Introduction of an additional pharmacophoric group into the molecule of a potential medicinal substance can "graft" the necessary bioactivity onto it or even reduce such side effect as toxicity. In this regard, presented within the framework of this investigation new derivatives of piperidine with additionally introduced pharmacophoric group of cyclopropane and fluorine atoms are of interest as potential biologically active substances for creation of new medications on their basis.

The substances containing a fragment of cyclopropane are of great interest to both organic chemists and biochemists. A three-member saturated carbocycle is a structural element with an extensive synthetic potential conditioned by a high voltage energy (~27.5 kkal/mol) of the unusual type of carbon-carbon bonds called "banana" bonds. By nature, they are intermediate between σ- and π-bonds due to which cyclopropane derivatives undergo various cycle opening and extension reactions as well as cycle addition reactions [1, 2].

Many natural and synthetic compounds containing a cyclopropane fragment with simple functionality have a wide range of biological properties [3] beginning from inhibition of enzymes to insecticidal, antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumour [4] and antiviral, antiestrogenic, agonistic properties. The researches in the field of biosynthesis and metabolism of cyclopropane derivatives present information necessary for the development of new drugs [5]. Of special interest are heterocyclic compounds having a cyclopropyl group as a substituent [6–8].

Being present in animals, plants and microorganisms or temporarily emerging during primary and secondary metabolism, they provide convenient biological probes for mechanistic investigations and allow to develop new preparations.

From the point of view of medical use it should be noted that eight of 200 best selling pharmaceutical drugs are compounds containing a cyclopropane fragment [3].

A piperidine ring is an omnipresent structural feature of many alkaloid natural products and drug candidates. Watson P.S. et al. [9] state that thousands of piperidine compounds were mentioned during the last 10-year period in clinical and preclinical researches.

The variety of functional and substituting structures detetected in piperidine targets is the basis of the common concept that biological concepts of piperidines greatly depend on the type and position of substituentson the heterocycle ring.

The chemistry of fluoroorganic compounds is of great theoretical and practical importance [10–14]. Numerous investigations verified a high biological activity of a whole number of fluorine containing organic compounds as a result of which such preparations as fluoroquinol antibiotics, risperidone, fluorophenazine, haloperidol, etc. were created and successfully used. The number of publications and especially patents in this field rapidly increases, most of them referring to aromatic and heterocyclic compounds with fluorine containing substituents [15].

This interest was caused by significant improvement of pharmacological properties of fluorinated compounds. Introduction of fluorine atom into molecules of organic compounds increases their bioavailability, metabolic stability, lipophilicity and improves the ability of these substances to interact with target proteins [16].

During many years in the laboratory of chemistry of synthetic and natural medicinal substances at Institute of chemical sciences named after A.B. Becturov the workers have been intensively searching for highly effective and safe medicinal preparations among piperidine derivatives. As a result, preparations with a wide range of pharmacological action have been found [17–26]. Excellent results are found in the series of N-alkoxyalkylsubstituted acetylene containing derivatives of piperidine which possess a wide range of pharmacological activity.

Introduction of ethynyl group into the molecule of piperidine derivatives results in extension of the range of a biological action and the decrease of toxicity. Among the synthesized substances there are preparations with high analgetic, local anaesthetic and other activities having significant advantages over the existing drugs of the similar type of action.

Of special interest for practical medicine including field medicine is preparation cascaine –1-(2-ethoxyethyl)-4-ethynyl-4-benzoyloxypiperidine hydrochloride [27, 28] created by joint efforts of scientists and specialists of the Institute of Chemical Sciences named after A.B. Bekturov, Kazakh National Medical University and Novokuznetsk Scientific – Research Chemico-Pharmaceutical Institute (NK SRCPI).

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 (υ 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 are taken in $CDCl_3$ downfield from TMS [$(CH_3)_4Si$], and coupling constants are 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).

1–(2-ethoxyethyl)-4-(cyclopropanecarbonyloxyimino) piperidine hydrochloride (5)

We placed 3.0 g (0.016 mol) of 1-(2-ethoxyethyl) piperidine-4-one oxime **(2)** dissolved in absolute dioxane into a round-bottom, three-neck flask provided with a mechanical stirrer, reflux cooler and dropping funnel and added dropwise 2.2 ml (0.024 mol) of cyclopropanecarbonylchloride solution in absolute dioxane. The reaction mixture being stirred is heated during one hour at a temperature of 60 °C and is left at room temperature for 24 h. Dioxane is vaporized to dryness on a rotary evaporator. The residue is washed out with diethyl ether, the crystalline product is filtered and recrystallized from isopropanol.

So, 3.6 g (78.5% from theoretical) of hydrochloride of 1-(2-ethoxyethyl)-piperidine-4-one oxime ester of cyclopropanecarbonic acid **(5)** was obtained in the form of light yellow crystals with the melting point 148–151 °C, R_f = 0.81(Al_2O_3 eluent – benzene: dioxane – 4:1).

Elemental analysis found/calculated for $C_{13}H_{23}N_2O_3Cl$: C 54.07(53.69); H 8.30 (H 7.97).

1-(2-ethoxyethyl)-4-phenylethynyl-4-cyclopropanecarbonyloxypiperidine hydrochloride (6)

Solution of 1.5 ml (0.016 mol) cyclopropanecarbonylchloride in absolute dioxane being stirred is slowly poured into the solution of 1.5 g (0.005 mol) 1-(2-ethoxyethyl)-4-phenylethynyl-4-hydroxypiperidine (3) in absolute dioxane. The reaction mixture is observed to be heated. The mixture is left to stand for 24 h at room temperature. The reaction course is controlled using thin layer chromatography. The solvent is distilled. The residue is washed out with diethyl ether and is recrystallized from isopropanol. So, 1.0 g (48.3% from theoretical) 1-(2-ethoxyethyl)-4-phenyl-ethynyl-4-cyclopropanecarbanyloxypiperidine hydrochloride **(6)** is obtained with the melting point 157–159 °C, R_f 0.91 (Al_2O_3, eluent – benzene: dioxane – 4:1).

Elemental analysis found/calculated for $C_{21}H_{28}NO_3Cl$: C67.07(66.74); H 7.42 (H 7.47).

1-(2-ethoxyethyl)-4-ethynyl-4-(p-fluorobenzoyloxy)piperidine hydrochloride (7)

2g (0.01 mol) of 1-(2-ethoxyethyl)-4-ethynyl-4-hydroxypiperidine **(4)** is dissolved in a small amount of absolute benzene, then the solution of 4.75 g (0.03 mol) *p*-fluorobenzoylchloride in absolute benzene is slowly poured dropwise into this solution being stirred. White sediment is observed to form. The reaction mixture is left to stand for 48 h at room temperature. The reaction course is controlled using thin layer chromatography. The reaction mixture is washed out with diethyl ether and the sediment is filtered out and recrystallized from isopropyl alcohol. 2.3 g (86% from theoretical) of 1-(2-ethoxyethyl)-4-ethynyl–4-(p-fluore) benzoyeloxypiperidine hydrochloride **(7)** is obtained with the melting point 106–107 °C, R_f 0.83 (Al_2O_3, eluent–benzene: dioxane – 4:1)

Elemental analysis found/calculated for $C_{18}H_{23}NO_3FCl$: C 61.14(60.76) ; H 6.77 (H 6.51).

1-(2-ethoxyethyl)-4-ethynyl-4-(m-fluorobenzoyloxy)piperidine hydrochloride (8)

At room temperature, solution of 3.64 ml (0.03 mol) 3-fluorobenzoylchloride in absolute dioxane is slowly added dropwise to the solution of 2 g (0.01 mol) 1-(2-ethoxyethyl)-4-ethynyl-4-hydroxypiperidine **(4)** being stirred. The reaction mixture is observed to be heated and a small amount of sediment is formed. The mixture is left to stand for 24 h at room temperature. The sediment is washed out with diethyl ether, the sediment is recrystallized from isopropanol. 1-(2-ethoxyethyl)-4-ethynyl -4-(m-fluoro) benzoyloxypiperidine hydrochloride **(8)** is obtained in the amount of 1.68 g (56% from theoretical) with the melting point 115–117 °C, R_f 0.79(Al_2O_3, eluent – benzene: dioxane – 4:1.

Elemental analysis found/calculated for $C_{18}H_{23}NO_3FCl$: C 61.11(60.76); H 6.65 (H 6.51).

1-(2-ethoxyethyl)-4-ethynyl-4-(m-fluorobenzoyloxy)piperidine hydrochloride (9)

The solution of 2 g (0.01 mol) 1-(2-ethoxyethyl)-4-ethynyl-4-hydroxypiperidine **(4)** in absolute dioxaneis mixed with the solution of 3.57 ml (0.03 mol) 2-fluorobenzoylchloride in absolute

dioxane at room temperature. The reaction mixture is observed to be insignificantly heated. The mixture is left for a night. The reaction course is controlled using thin layer chromatography. The solvent is evaporated, the residue is washed out with diethyl ether and recrystallized from isopropanol. So, 1.6 g (47% from theoretical) 1-(2-ethoxyethyl)-4-ethynyl-4-(o-fluoro)benzoyloxypiperidine hydrochloride **(9)** is obtained with the melting point 147–149 °C, R_f 0.77 (Al_2O_3, eluent – benzene: dioxane – 4:1).

Elemental analysis found/calculated for $C_{18}H_{23}NO_3FCl$: C 60.98 (60.76) ; H 6.22 (H 6.51).

2.2. Experimental biological part

The compounds coded A-4–A-6 were studied for antibacterial activity in regard to museum strains of microorganisms, the actions of these preparations were evaluated in the experiment *in vitro.*

2.3. Materials and methods

The antimicrobial activity of samples A-4-A-6 was studied in relation to strains of gram-positive bacteria *Staphylococcus aureus*, *Bacillus subtilis*, gram-negative strains of *Escherichia coli*, *Pseudomonas aeruginosa* and to yeast fungus *Candida albicans* by the agar diffusion method [29]. The reference preparations are gentamicin for bacteria and nystatin for yeast fungus *Candida albicans*.

The cultures were grown on a liquid medium with pH 7.3+0.2 at a temperature from 30 to 35 °C during 18–20 h. The cultures were diluted 1:1000 in a sterile 0.9% isotonic solution of sodium chloride and placed into dishes (1 ml into each) with the corresponding elective, nutrient media for the test-strains being studied and sowed using the "solid lawn" method. After drying, holes of the size 6.0 mm were formed on the surface of agar into which the solution of the samples under study, gentamicin, nystatin was introduced. Ethyl alcohol in equivolume amounts was used as a reference. Thus, the samples under study were tested in the amount of 1 mg and the reference preparation – in the amount of 1 mg. The crops were inclubated at 37 °C, the growing cultures were counted every 24 h.

The antimicrobial activity of the samples was evaluated by the diameter of test-strain growth zones (mm). The diameter of growth zones less than 10 mm and solid growth in the dish were evaluated as the absence of antibacterial activity, 10–15 mm – weak activity, 15–20 mm – moderately pronounced activity, more than 20 mm – pronounced activity. Each sample was tested in three parallel experiments. Statistical processing was carried out by the method of parametric statistics with calculation of arithmetic and standard error.

3. Results and discussion

Within the framework of this investigation new derivatives of the series of N-ethoxyethylpiperidine with fragments of cyclopropane and para-, meta-, orthofluorophenyls were synthesized.

Oximes of carbonic compounds and their derivatives [30, 31] are well known as one of the main classes of organic substances which are promising for the search of new biologically active preparations of a wide range of action. Besides, oximes serve as convenient objects for the study of fundamental issues of modern organic chemistry, such as stereochemistry, conformational analysis as well as statement of relationship between the structure and properties of compounds.

Due to interaction of hydroxylamine hydrochloride with 1-(2-ethoxyethyl)-4-oxypiperidine **(1)** in the presence of alkali in ethanol the corresponding oxime **(2)** was obtained [32].

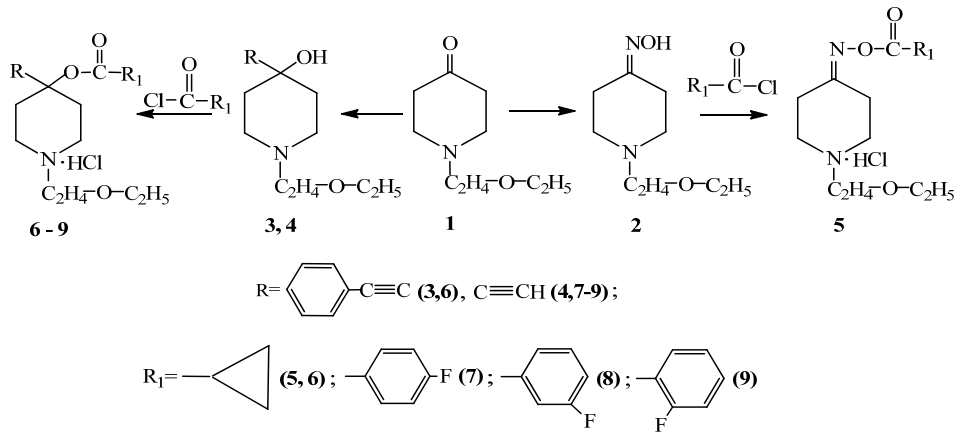
The literature data indicate the continuing interest of researchers to acetylene derivatives of piperidine. The presence of a triple bond in the molecule, as a rule, reduces toxicity, acetylene preparations often being more active than their saturated analogs [33, 34].

Acetylene containing derivatives of piperidine are of great interest for the search and creation of new highly effective and nontoxic drugs with different biological activity.

Participation of a triple bond of ethynyl containing piperidols in the chemical reaction lead to formation of a whole number of new derivatives possessing a high pharmacological activity.

Due to the above mentioned interaction of 1-(2-ethoxyethyl)-4-oxopiperidine **(1)** with phenylacetylene according to Favorsky method in absolute benzene in the presence of powdery technical KOH at atmospheric pressure, 1-(2-ethoxyethyl)-4-phenylethyl-4-hydroxypiperidine **(3)** [34] with the yield of 53.2% from theoretical was obtained.

To determine the effect of introducing a cyclopropanecarbonyl fragment on pharmacological activity of compounds by acylation of oxime (2) and phenylacetylene alcohol **(3)** with 1-(2-ethoxyethyl-4-ketopiperidine cyclopropanecarbonylchloride, hydrochlorides of cyclopropanecarbonic acid esters **(5,6)** were obtained (Scheme).



Scheme. Synthesis of cyclopropanecarboxylic and para-, meta-, ortho-fluorobenzoic acid esters of N-ethoxyethylpiperidine

The acylation reaction was carried out in absolute dioxane at room temperature and when heating, the acylating agent was taken in excess.

The obtained corresponding hydrochlorides of esters **(5,6)** are white crystalline substances with a clear melting point (Table 1). The structure of the compounds synthesized was confirmed by IR and ^{1}H and ^{13}C NMR spectroscopy.

In IR-spectra of cyclopropanecarbonic acid esters **(5,6)** there are intensive adsorption bands at 1740–1764 cm^{-1} characteristic of stretching vibrations of ester carbonyls, besides, in the spectra there are adsorption bands of C=N group (1640 cm^{-1}) for compound (5), phenyl group at 696–760 cm^{-1} for compound (6). Also, in IR-spectra there are adsorption bands of stretching vibrations of ether bond of N-ethoxyethyl substituent at 1111 cm^{-1}, 1144 cm^{-1}.

When continuing investigations, in the series of acetylene derivatives of piperidine with the aim to introduce fluorine atom into the molecule of cascaine [27, 28] on the basis of acetylene (cascaine) alcohol **(4)**, acylation was carried out with 4-fluoro-, 3-fluro-, 2-fluorobenzoylchlorides with formation of the corresponding esters of para-, meta-, ortho-fluorobenzoic acids (**7-9**) (Scheme). The reaction was carried out in benzene, dioxane by the action of excess of acid chlorides on the initial piperidol.

The obtained *p-, m-, o*-fluorobenzoates (7-9) are crystalline substances well soluble in water, ethanol, acetone. Hydrochlorides of para-, meta-, ortho-fluorobenzoic acid esters **(7-9)** are characterized by intensive adsorption bands of ester carbonyls at 1724–1731 cm^{-1} in IR-spectra, there are also characteristic adsorption bands corresponding to stretching vibrations of the triple bond at 3210–3325 cm^{-1} and adsorption bands of ether bond of N-substituent at 1109–1119 cm^{-1}.

The yield, physic-chemical characteristics and data on elemental analysis of compounds **(5-9)** are presented in Table 1.

Table 1

Yields, physical and chemical characteristics of esters **(5-9)**

Compound	Yield, %	R_f	m.p, °C	Calculated found, %		IR, cm^{-1}	
				C	H	C=N	C=O
5	78.5	0.81	148-151	54.16 53.69	8.30 7.97	1640	1764
6	48.3	0.91	157-159	67.25 66.74	7.42 7.47	-	1740
7	86.0	0.83	106-107	61.14 60.76	6.77 6.51	-	1726
8	56.0	0.79	115-117	61.21 60.76	6.65 6.51	-	1731
9	61.0	0.77	147-149	60.98 60.76	6.22 6.51	-	1724

Note – Al_2O_3, eluent: benzene:dioxane 4:1

Table 2
Chemical shifts of carbons (δ, ppm) (**7-10**) in $CDCl_3$

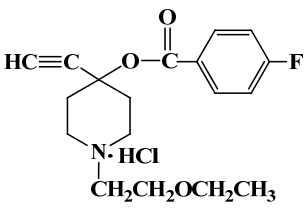
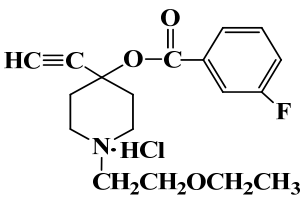
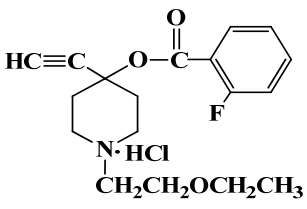
Compound	Chemical shifts ($CDCl_3$), δ, ppm								
	$C_{3,5}$	$C_{2,6}$	C_4	R_1	C=O	C≡C	C_4-C=C	Ph	N-$CH_2CH_2OCH_2CH_3$
5	27.24; 23.24	50.39; 51.39	161.27	9.13; 11.07 **cyclopropane**	175.53	-	-	-	55.55; 63.21; 66.81; 13.99
6	32.93; 33.48	48.10; 49.95	71.54	8.81; 13.17 **cyclopropane**	175.80	84.67	86.33	120.67; 131.80; 128.67; 129.64	55.58; 63.15; 66.79; 13.97
7	33.30	47.90	72.37	164.65; 116.28; 133.01; 128.94 **4-F-phenyl**	163.43	98.49	97.54	-	55.20; 64.75; 66.14; 15.29
8	33.26	47.78	70.15	163.17; 116.33; 133.25; 131.35; 126.25 **3-F-phenyl**	161.25	78.37	84.00	-	57.02; 64.77; 66.12; 15.39
9	33.22	49.65	72.59	163.08; 117.59; 118.50; 132.71; 136.35; 125.27 **2-F-phenyl**	161.84	78.44	82.38	-	55.21; 64.64; 66.15; 15.38

Most informative for the structure of ester hydrochlorides proved to be ^{13}C NMR spectra (Table 2).

The signal of carbonyl carbon in the low field indicates formation of esters, in ^{13}C NMR spectra (Table 2) of cyclopropanecarbonyloxy derivatives **(5, 6)** and *p-, m-, o*-fluorobenzoyloxy derivatives **(7-9)** there are singlet signals of ester carbonyl carbon at 161.25–175.8 ppm, a singlet signal of C_4 carbon atom of ketoxime ester of compound 5 resonates in the low field 161.27 ppm, and singlet signals of C_4 carbon atoms of the rest compounds **(6-9)** resonate in the field of values 70.15–72.59 ppm, carbon atom of compounds **(6-9)** in a triple bond C≡C is manifested in the region of 78.37 ppm, also, a carbon atom of compounds **(6-9)** in a triple bond and C_4 carbon atom C_4-C≡C is manifested in the region of 82.38–97.54 ppm. Besides, signals of carbon atoms of benzene nuclei and cyclopropyl fragment system are observed. A different position of fluorine atom of compounds **(7-9)** confirms the shift of the corresponding aromatic carbon signal to the low field (163–164 ppm). Carbon atoms of piperidine cycle and nitrogen atom substituents are manifested in the expected region.

The presence of signals in ^{13}C NMR Spectra of carbon atoms of nitrogen substituents as well as substituents in the 4-position completely confirms the attributed structure of the synthesized esters.

Table 3
Fluorobenzoic esters studied for antimicrobial activity in the experiment *in vitro*

Code	A-4	A-5	A-6
Compound			

3.1. The study of biological activity

Para-, meta-, ortho-fluorobenzoic ethers 1-(2-ethoxyethyl)-4-ethynyl-4-hydroxypiperidine (7-9) coded A-4 – A-6 were studied for the presence of antimicrobial activity (Table 3).

The study on the antimicrobial activity of the above mentioned samples was carried out in relation to the strain of gram-positive bacteria *Staphylococcus aureus*, *Bacillus subtilis*, gram-negative stains of *Escherichia Coli*, *Candida Albicans* by the diffusion method into agar (holes) [29]. The reference preparations are gentamicin for bacteria and nystatin for yeast fungus C*andida Albicans*.

The antimicrobial activity of the samples was evaluated by the diameter of test-strain growth zones (mm). The diameter of growth zones less than 10 mm and solid growth in the dish were evaluated as the absence of antibacterial activity, 10–15 mm – weak activity, 15–20 mm – moderately pronounced activity, more than 20 mm – pronounced activity. Each sample was tested in three parallel experiments.

According to the investigation (Table 4) it is stated that meta- and othofluorobenzoic esters of cascaine alcohol coded A-5, A-6 possess antimicrobial activity. They showed moderately pronounced antimicrobial activity in regard to gram-positive test-strain of *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonaaeruginosa*. Sample A-6 has a weak antimicrobial activity in relation to yeast fungus *Candida Albicans*.

It can be supposed that introduction of fluorine atom, the presence of ethoxyethyl radical of nitrogen atom and a triple bond in the forth position cause antimicrobial activity. However, flurobenzoic ester with fluorine atom in para-position did not manifest this activity. Fluorobenzoic ester with fluorine atom in ortho-position showed antimicrobial activity not only in relation to *Staphylococcus aureus, Pseudomonas aeruginosa* but also in relation to yeast fungus *Candida albicans*.

4. Conclusions

Interaction of hydroxylamine hydrochloride with 1-(2-ethoxydyl)-4-oxopiperidine in the presence of alkali in ethanol resulted in formation of the corresponding oxime, interaction of the same aminoketone with phenylacetylene according to Favorsky method in absolute benzene in the presence of technical KOH at atmospheric pressure yielded 1-(2-ethoxyethyl)-4-phenylethynyl-4-hydroxypiperidine. With the aim to introduce cyclopropanecarbonyl fragment and fragments of *p-,m-,o*-fluorophenyls into the structures of N-ethoxyethylpiperidines, acylation of oxime and phenylacetylenic alcohol of 1-(2-ethoxyethyl)-4-ketopiperidine by cyclopropanecarbonylchloride was carried out; on the basis of acetylene (cascaine) alcohol, acylation by 4-fluoro-, 3-fluoro-, 2-fluorobenzoylchlorides was carried out with formation of the corresponding piperidine containing hydrochlorides of cyclopropanecarboxylic acid esters and para-, meta-, ortho-fluorobenzoic esters.

The composition and structure of the synthesized compounds were confirmed by the data of elemental analysis, IR spectroscopy, NMR spectroscopy and individuality-by thin-layer chromatography.

Para-, meta-, ortho-fluorobenzoic esters of 1-(2-ethoxyethyl)-4-ethynyl-4-hydroxypiperidine coded A-4 – A-6 were studied for the presence of antimicrobial activity, the actions of these preparations were evaluated *in vitro* in relation to strains of gram-positive bacteria S*taphylococcus aureus*, *Bacillus subtilis*, gram-negative strains of *Escherichia coli*, *Pseudomonas aeruginosa* and to yeast fungus *Candida albicans* by the diffusion method into agar (holes).

Table 4
The investigation results on antimicrobial activity of samples A-4 – A-6

	Substance name	*Staphylococcus aureus*	*Bacillus subtilis*	*Escherichia Coli*	*Pseudomonas aeruginosa*	*Candida albicans*
1	A-4	-	-	-	-	-
2	A-5	-	16±0.1	-	-	-
3	A-6	18±0.1	-	-	12±0.1	15±0.1
Gentamicin		24 ± 0.1	21 ± 0.2	26 ± 0.1	27±0.1	-
Nystatin		-	-	-	-	21 ± 0.2

Introduction of fluorine atom into the structure of cascaine lead to manifestation of antimicrobial activity, fluorine atom in orthoposition proved to be optimal, hydrochloride of 1-(2-ethoxyethyl)-4-ethynyl-4-hydroxypiperidine *o*-fluorobenzoate showed a wider range of antimicrobial activity in relation to *Staphylococcus aureus*, *Pseudomonas aeruginosa*, yeast fungus *Candida albicans.*

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