

## The synthesis and antimicrobial activity of new piperidine compounds

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**Abstract.** Year after year, we are seeing the increasing amount of scientific and patent data on the use of various piperidine-containing compounds as medicinal drugs. This indicates that such a group of synthons has good prospects for searching new biologically active compounds based on them [1, 2 and 3]. This paper contains the findings of synthesizing new piperidinous heterocyclic compounds for creating medicinal drugs due to their high biological activity. The structure and characteristics of synthesized compounds were analyzed using IR and NMR (<sup>1</sup>H and <sup>13</sup>C) spectroscopy. Nonpathogenic microbial strain tests detected new active substances with good prospects. These compounds can take part in additional tests on detecting antimicrobial activity in a wider range of microorganisms.

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**Keywords:** piperidine heterocycles, piperidone, Favorskii reaction, Mannich aminomethylation reaction, antimicrobial activity.

### Introduction

The Republic of Kazakhstan implements The State Program for Accelerated Industrial and Innovative Development (2010-2014) aimed at sustained and balanced growth of economy by means of diversification and competitive recovery [4]. The important line of this program is to develop the priority sectors of economy which promote its diversification and competitiveness. The pharmaceutical industry is one of such sectors. Its growth is possible on the basis of domestic demand. The government of the Republic of Kazakhstan adopted Resolution No. 791 (August 4, 2010) approving The Program for the Development of the Pharmaceutical Industry in the Republic of Kazakhstan (2010-2014) [5]. The positive results of this program include the increase in production of basic pharmaceutical goods in 2012 as compared to 2008 [6].

In order to make a significant and innovative breakthrough in the pharmaceutical sector of Kazakhstan, it is necessary to direct efforts to producing the output with higher added value and original medicines but not generics. ISPHC "Phytochimia" achieved serious success in this question. This company obtained scientific and practical results in working out a production technology for original medicines based on the herbal material of Kazakhstan [7].

The Bekturov Institute of Chemical Sciences also conducted the search and development of new domestic original medicines made from synthetic and

herbal material [8]. This article contains the findings of recent years in the synthesis and antimicrobial activity of new piperidinous compounds. The vexed problem of antibiotic resistance made for the urgency of this research [9]. The ratings of leading Anatomical Therapeutic Chemical Groups (ATC) show that antimicrobial drugs are the most called-for in Kazakhstan, both in drugstore market (the 1<sup>st</sup> place) and in hospital purchases (the 2<sup>nd</sup> place): their sales shares in 2012 made up 10% and 13%, respectively [10, 11].

### Materials and methods

The Scopus database was used for the analysis of publications by years, countries, branches, companies and authors with key words "piperidine" and "antimicrobial activity" [12].

New compounds were synthesized by means of fine organic synthesis. The IR spectra were fixed by tool Nicolet 5700 FT-IR in tablets KBr; the <sup>1</sup>H and <sup>13</sup>C spectra were fixed by tools BrukerDPX 400; JEOLJNM-ECA400 in CDCl<sub>3</sub> and DMSO, internal standard of HMDS and R<sub>f</sub> were found on the plates with silica gel "SilufolUV-254".

The synthesis conditions for 3-propyl-2.6-bis (2.5-dimethoxyphenyl) piperidine-4-one are given for example (1). Methyl-butylketone 1 g (0.01 mole), ammonium acetate 0.77 g (0.01 mole), 2.5-dimethoxybenzaldehyde 3.32 g (0.02 mole) and L-proline 0.025 g (0.0021 mole) are dissolved in 50 ml of ethanol and put in one-neck flask with magnetic stir bar and reflux condenser. The contents of the

flask are boiled during 4 hours in a water bath with stirring. Then ethanol (40 ml) is vaporized from the reaction mass using a rotary evaporator and left in freezer for a night. The rest of the ethanol is decanted, and the sediment is dissolved in 30 ml of ethyl acetate. When the ethyl acetate solution is flushed with hydrochloric acid, hydrochloride precipitates as white sediment which is filtered. In order to isolate the base, the obtained hydrochloride is dissolved in ethyl alcohol and alkalinized by the aqueous solution of sodium hydroxide. The white sediment is filtered and dried at room temperature. Now 1.54 g of base is obtained.

Gross-formula:  $C_{24}H_{31}NO_5$

Molecular weight: 413.51 g/mole

Ultimate analysis:

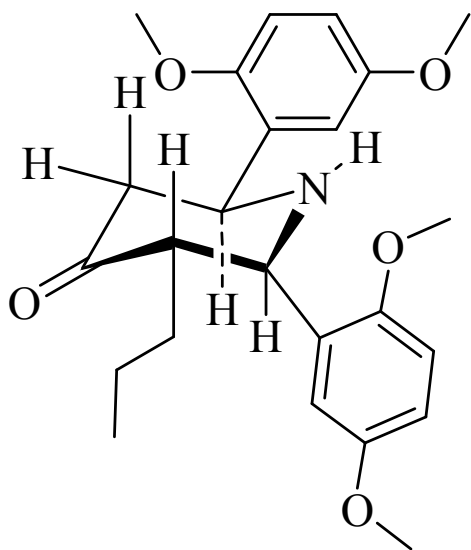
Computed: C, 69.71; H, 7.56; N, 3.39; O, 19.35

Found: C, 69.88; H, 7.37; N, 3.77; O, 18.98

Yield = 37,4 %

Melting temp. 127 °C, melting temp. Of hydrochloride 137 °C

**R<sub>f</sub> 0.62 (eluent – ethanol)**



IR absorption bands,  $cm^{-1}$ : 3307 (NH), 2836, 2961, 2995 (C-H), 1711 (C=O), 1648, 1589 and 1499 (C=C), 1440, 1280, 1210, 1100, 1048 и 1022 (Ar-O-CH<sub>3</sub>), 890, 800, 710.

NMR  $H^1$  in  $CDCl_3$ , [delta], ppm: 0.76 t (3H,  $CH_2CH_2CH_3$ ), 1.00 m (2H,  $CH_2CH_2CH_3$ ), 1.34 m and 1.67 m (2H,  $CH_2CH_2CH_3$ ), 2.43 with (1H, NH), 2.67 – 2.73 (3H,  $H-C^{3,5}$ -piperidone), 3.72 c and 3,78 with (12H,  $OCH_3$ ), 4.18 d and 4.38 t (2H,  $H-C^{2,6}$ -piperidone), 6.69 – 6.81 m and 7.06 – 7.10 m (6H,  $C_6H_3$ ).

NMR  $C^{13}$  in  $CDCl_3$ , [delta], ppm: 14.08 ( $CH_3CH_2CH_2$ ), 20.62 ( $CH_3CH_2CH_2$ ), 27.14

( $CH_3CH_2CH_2$ ), 43.08 ( $H-C^3$ -piperidone), 49.45 ( $H_2C^5$ -piperidone), 55.70 ( $OCH_3$ ), 55.92 ( $H-C^2$ Ar), 56.15 ( $H-C^6$ Ar), 111.30, 111.75, 112.83, 113.55 ( $C^{3,4,6}$ - $C_6H_3$ ), 130.96 and 131.78 ( $C-C_6H_3$ ), 150.66 and 151.38, 153.77 ( $C^{2,5}$ - $C_6H_3$ ), 210.19 ( $C=O$ ).

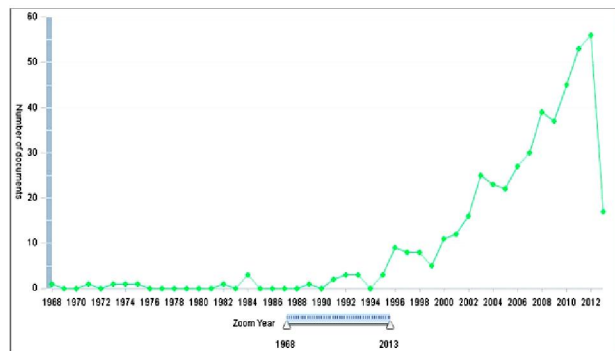
The antimicrobial activity was detected by agar diffusion towards the following testing cultures: gram-negative bacteria: *Escherichia coli*, *Salmonella gallinarum*, *Pasteurella multocida*, *Klebsiella pneumoniae* 444; gram-positive bacteria: *Mycobacterium B<sub>5</sub>*, *Staphylococcus aureus* 209p and the clinical isolate of *Staphylococcus aureus* 9; yeast-like fungi *Candida albicans*; microfungi *Aspergillus niger*.

The assessment of the minimum inhibitory concentration (MIC) was conducted towards the minimum set of museum microbial strains: *Bacillus subtilis* ATCC 6633, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 9027, *Salmonella enterica* ATCC 14028 and *Staphylococcus aureus* ATCC 6538-P. The authors used the conventional method of serial two-fold dilution in Mueller Hinton broth. In order to make a basic solution with concentration 4000 mcg/ml, a sample 0.2 g was dissolved in 50 ml of 0.9%-solution of sodium chloride. Then the serial two-fold dilutions from 2000 to 2 mcg/ml were made. The suspension of microorganism in concentration  $10^6$  CFU/ml was inoculated in prepared dilutions. The inoculations were incubated in thermostat at 37° C during 18-24 h. After incubation, the cultures from each dilution were plated in Mueller Hinton broth. The Petri dishes with cultures were incubated at 37° C during 18-24 h. The MIC was found by the minimum concentration which inhibited the visible growth of the microorganism under testing.

### Findings and discussion

The structural analysis of medicines for the treatment and prevention of infectious diseases showed that only one of 200 medicines contains a piperidine fragment. This is mefloquine – an antimalarial medicine from the group of remedies for protozoan infections [13].

At the same time, if we search for information in the Scopus database by the word “piperidine”, the database outputs 42494 sources. The last 5 years, 1800 publications appear every year. Figure 1 shows the results of search by key words “piperidine” and “antimicrobial activity”. These results indicate that beginning with 2000 one can see a five-fold growth (from 11 to 56) of publications about the antibacterial characteristics of piperidine compounds per year. Besides, one can notice a tendency that the number of publications doubles every 5 year.



Year	Documents
2013	17
2012	56
2011	53
2010	45
2009	37
2008	39
2007	30
2006	27
2005	22
2004	23
2003	25
2002	16
2001	12
2000	11

Figure 1. The number of publications about the piperidine compounds with antimicrobial activity

The analysis of publications by country showed that the most active research in this sphere takes place in India (total 150 articles). Among authors, S. Kabilan issued the largest number of articles. The most quoted article (42 references) is dedicated to the synthesis of some new benzoxazolinethoxypiperidones and their antimicrobial activity against *Streptococcus faecalis*, *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and antifungal activity against *Candida-6*, *Candida albicans*, *Aspergillus niger*, *Candida-51* and *Aspergillus flavus*.

Moreover, the authors conduct research on the synthesis of new piperidine compounds. The basic schemes of directed synthesis and chemical transformation are shown in Figure 2.

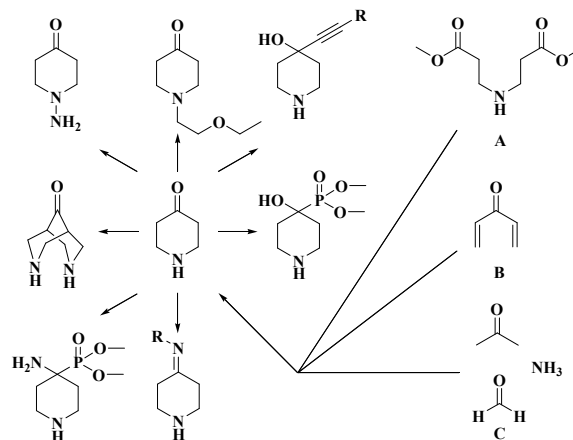


Figure 2. The methods of synthesis and the directed chemical modification of piperidine-4-ones

14 new compounds were synthesized with the help of the foregoing methods and schemes (Figure 3). It should be noted that the initial compounds 15-17 are given by the colleagues from the Favorsky Irkutsk Institute of Chemistry. Currently, the authors together with these scientists are conducting joint research on using them in the chemical transformation of diarylpiperidones.

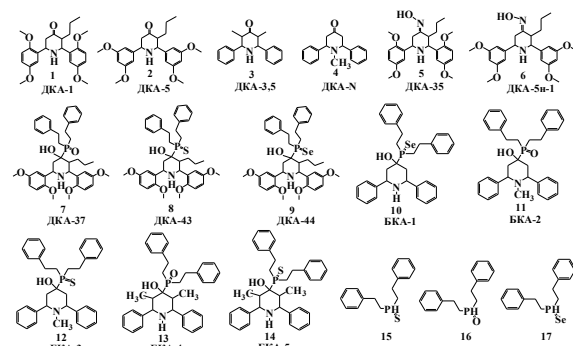


Figure 3. New piperidones and their derivatives

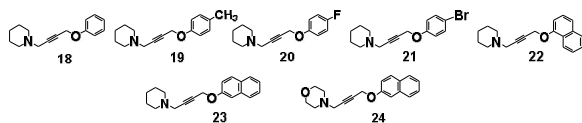
The data on the antimicrobial activity of the compounds shown in Figure 3 are presented in Table 1.

During the antimicrobial tests, 3 compounds with high activity against *Mycobacterium B5*, *Staphylococcus aureus* 9 and *Candida albicans* were isolated. [15, 16].

The Mannich reaction is another available method of building the C-N-bond and introducing piperidine fragment. The authors synthesized various phenyloxybutenyl piperidines. Their structures are shown in Figure 4.

**Table 1. The MIC data for new 2,6-diarylpiperidine-4-one and their derivatives**

Chemical compounds	The minimum inhibitory concentration (MIC), mcg/ml								
	<i>Escherichia coli</i>	<i>Staphylococcus aureus</i>	<i>Klebsiella pneumoniae</i> 444	<i>Staphylococcus aureus</i> 209p	<i>Staphylococcus aureus</i> 9	<i>Candida albicans</i>	<i>Aspergillus niger</i>	<i>Penicillium multiseptatum</i>	<i>Mycobacterium F5</i>
1 DKA1-HCL	0	5000	0	0	0	4500	0	0	0
2 DKA-5	0	0	0	0	0	0	0	0	5000
3 DKA-3,5	2500	2500	2500	2500	2500	0	2500	0	10
4 DKA-N	2500	2500	2500	2500	2500	0	0	2500	2500
5 DKA-35	0	5000	5000	0	0	4000	0	0	0
6 DKA-5n-1	0	5000	500	0	50	800	0	4000	500
7 DKA-37	5000	5000	0	4000	5000	5000	0	0	0
8 DKA-43	0	0	0	0	5000	0	0	0	0
9 DKA-44	0	0	500	5000	45	3	5000	800	0
10 BKA-1	1000	2500	2500	2500	2500	2500	0	2500	2500
11 BKA-2	1000	2500	2500	2500	2500	2500	0	1500	2500
12 BKA-3	2500	2500	2500	2500	2500	0	0	1000	2500
13 BKA-4	2500	2500	2500	2500	0	0	0	0	2500
14 BKA-5	2500	2500	2500	2500	2500	2500	0	1000	0
15 sulphide	2500	2500	2500	2500	2500	2500	0	2500	2500
16 oxide	2500	2500	2500	2500	2500	0	0	2500	2500
17 selenide	2500	2500	2500	2500	2500	1000	0	2500	2500

**Figure 4. Phenyloxybutynil piperidines**

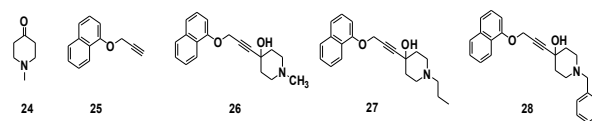
The results of tests on antimicrobial activity are presented in Table 2.

**Table 2. The diameter of retardation zones, mm.**

No.	Code	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Candida albicans</i>
18	M3PGH	0	0	24	0
19	M3PMGH	0	0	24	0
20	M3PFGH	0	0	20	0
21	M3PBGH	0	0	26	0
22	M1PGH	0	0	20	0
23	M2PGH	0	0	25	0
24	M2MGH	0	0	27	0

It was ascertained that compounds 18-24 display a pronounced antimicrobial activity only against *Pseudomonas aeruginosa*. It is interesting to note that derivatives [beta]-substituted in naphthalene ring are more active in bacteria growth inhibition as compared with [alpha]-substituted derivatives.

More than 100 years passed since A.E. Favorsky discovered the reaction of potassium hydroxide ethylation of ketones. Today this reaction is the most popular method for synthesizing tertiary acetylenic alcohols. The authors synthesized piperidine alcohols on the basis of 1-methyl-, 1-propyl-, 1-benzyl-piperidine-4-ones. The structural formulae of initial and synthesized substances are shown in Figure 5.

**Figure 5. The structural formulae of 1-R-4-(3-naphthoxyprop-1-ynyl)piperidine-4-ols**

The assessment of antimicrobial activity of new potential antibacterial substances was conducted towards the minimum set of museum strains of microorganisms. The results are presented in Table 3.

**Table 3. The MIC values of naphthoxypropargyl piperidols**

Test strains	The minimum inhibitory concentration, mcg/ml				
	24	25	26	27	28
<i>Bacillus cereus</i> ATCC 11778	-	-	-	-	63
<i>Bacillus cereus</i> ATCC 10702	-	-	-	-	-
<i>Bacillus cereus</i> ATCC 6633	-	-	500	250	63
<i>Bacillus cereus</i> ATCC 6051	-	-	500	500	-
<i>Escherichia coli</i> ATCC 25922	-	500	500	-	250
<i>Pseudomonas fluorescens</i> ATCC 948	1	250	8	0.031	0.008
<i>Staphylococcus aureus</i> ATCC 6538-P	-	-	-	-	125

It should be noted that the initial 1-methylpiperidine-4-one and 1-(prop-2-ynyl)naphthalene display the activity against only 2 strains. The largest number of strains is inhibited by compound 5 with benzyl radical and with a nitrogen atom in piperidine ring.

#### Acknowledgements

In conclusion, the authors express their special thanks to the staff of the Scientific Center of Antiinfectives – A.B. Dzhumagazieva and N.V. Leonova, the Asfendiyarov Kazakh National Medical University – S.S. Shakiyev and B.A. Ramazanova, the Institute of Microbiology and Virology – I.A. Ratnikova for the conducted tests of antibacterial activity of new piperidine compounds.

#### Findings

The rating of leading ATC-groups shows that antimicrobial drugs are the most called-for medicines in Kazakhstan, both in drugstore market (the 1<sup>st</sup> place) and in hospital purchases (the 2<sup>nd</sup> place).

The structural analysis of antimicrobial medicines showed that piperidine fragment enters into the composition of only 1 antimalarial medicine mefloquine. At the same time, since 2000 we see a five-fold growth (from 11 to 56) of publications about the antibacterial characteristics of piperidine compounds per year.

The Bekturov Institute of Chemical Sciences synthesized new piperidine compounds in a row of 2,6-diarylpiperidine-4-ones, acetylenic piperidines and piperidols, oxy-, tio-, selenophosphonate piperidols. The tests on a wide range of pathogenic

strains detected new substances with good prospects. They display activity at the level of 3-125 mcg/ml. These compounds can take part in additional research on the antimicrobial activity on a wider range of microorganisms.

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