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T7 Evaluation of antibacterial and antiviral activity of N-arylamides of 9-methyl- and 9-methoxyphenazine-1-carboxylic acids – inhibitors of the phage T7 model transctiption

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Aim. *Search for compounds with antibacterial and antiviral properties among N-arylamides of 9-substituted phenazine-1-carboxylic acids (PCA), inhibitors of the RNA synthesis.* ***Methods***. *Influence of N-arylamides on the RNA synthesis was tested in vitro in the model system of the DNA-dependent RNA polymerase of phage T7 (T7 RNAP). Antimicrobial activities of the N-arylamides against bacteria Erysipelothrix rhusiopathiae VR-2 var. IVM, Klebsiella spp. and Escherichia coli ATCC25922 were investigated by the method of two-fold dilution in a liquid medium. Antiviral effects against Bovine Viral Diarrhea Virus (BVDV) and cytotoxicity of the N-arylamides were evaluated using Madin-Darby bovine kidney (MDBK) cells.* ***Results***. *Twenty N-arylamides appeared to be efficacious inhibitors of the RNA synthesis at concentrations of 0.48–61 μM. The compound 16 proved to be the most effective inhibitor of T7 RNAP with the IC50 value being 0.48 μM. Fourteen N-arylamides demonstrated antibacterial properties against gram positive and gram negative bacteria at the 0.1–10 μg/ml concentrations. A number of the N-arylamides revealed a multiplicity of their antimic- robial actions: 7 compounds against two bacteria and two compounds, 2 and 3, against three bacteria investigated. N-arylamides 16 and 26 showed high inhibitory activity as to BVDV with the* IC_{50} *values 0.43 and 0.88 μg/ml and SI values 160 and 10 correspondingly.* ***Conclusions***. *The obtained data evidence that the most likely targets of the N-arylamides 9-substituted PCA in bacteria and viruses are their RNA synthesizing complexes.*

Keywords: N-arylamides 9-substituted PCA, model system of the DNA-dependent RNA-polymerase of phage T7, antibacterial activity, antiviral activity.

Introduction. At the end of the 20th century the occurrence and spreading of the agents of new dangerous infectious diseases (HIV, rotaviruses, Ebola virus and Marburg virus, Hantaviruses, SARS, avian influenza virus H5N1, etc.) [1, 2] as well as new strains of the known microorganisms and viruses, getting resistant to modern clinical preparations, triggered the search for new biologically active compounds – potential therapeutic agents.

From this standpoint the heteroaromatic tricycle compounds, especially their carboxylic acids and amids, attract pharmacologists and medical chemists who consider them as the promising basis to create the databases of biologically active compounds.

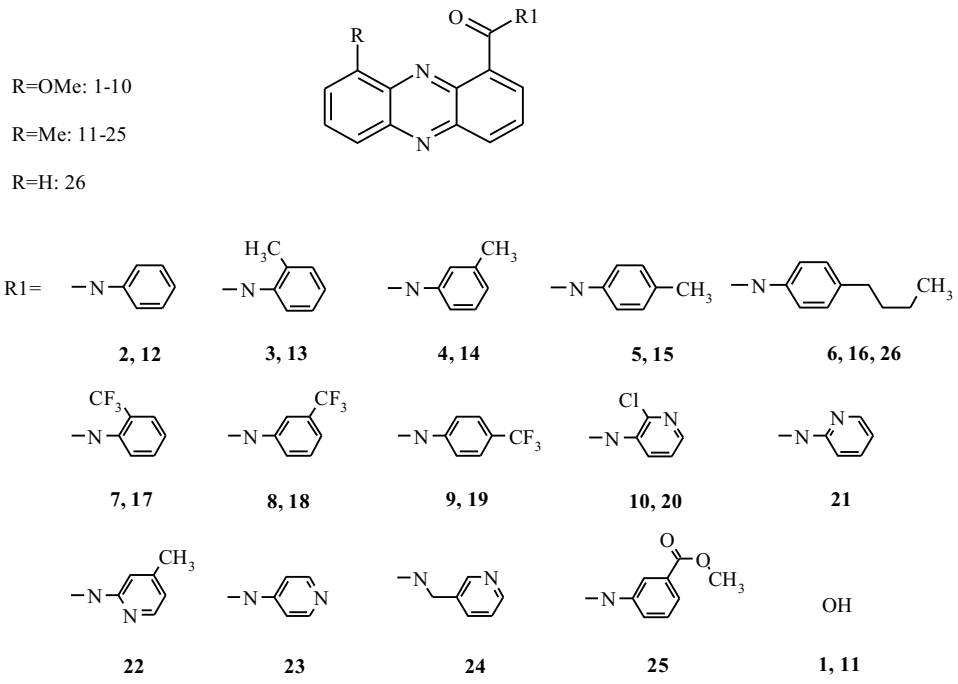

Fig. 1 The structures of investigated 9-substituted PCA-1 amides

In the previous work [3] we revealed a wide spectrum of antibacterial features of N-arylamides of phenazine-1-carboxylic acids (PCA-1). About 20 compounds demonstrated high antituberculosis activity towards museum and clinical strains of *Mycobacterium tuberculosis*. They included efficient inhibitors of a number of gram-positive bacteria, in particular – *Staphylococcus aureus*, *Bacillus cereus*, *Micrococcus* sp. and *Erysipelothrix rhusiopathiae* (the collection of the Institute of Veterinary Medicine, NAAS of Ukraine) [4].

It should be noted that the presence of carboxamide fragment conditions the potential conformational flexibility of N-arylamides of PCA-1. The conformational motility of these compounds promotes their efficient steric adjustment for the interaction with "homologous" enzymatic targets of the pathogenic agents and/or their resistant strains. This structural characteristic is important for the design of inhibitors with potential multiplex activity or inhibitors-agents, which are capable of fast mutating and acquiring resistance to clinical preparations. Noteworthy that the structural flexibility of non-nucleoside inhibitors of reverse transcriptase HIV *Delavirdine* and *Etravirine* [5–7] is the reason of preserving their antiviral activity regarding the resistant strains of HIV.

It is known that the substitution of "*peri*-position" of phenazine heterocycle (i.e. the position, adjoining the nitrogen atom) is vital for the biological activity of PCA-1 derivatives. For instance, lomofungin (the ether of multisubstituted PCA-1 with the hydroxyl group in position 9) is one of the preparations of wide antimicrobial activity [8]. The works [9, 10] show that the nature of the substitute in position 9 is highly relevant for N-alkylamides of monosubstituted PCA-1 as it impacts the level of their antitumor activity.

Taking into consideration the abovementioned promising characteristics of arylamides PCA-1 as well as the decisive significance of the substitution in the heterocycle for the biological activity of the compounds, we synthesized two new series of N-arylamides of 9-methyl and 9-methoxyphena-zine-1-carboxylic acids (Fig. 1) [11].

Phenazine antibiotics are remarkable for the multiplex mechanism of their biological activity. They easily penetrate the bacterial cell and join the oxidation-reduction processes [12, 13], transforming into relatively stable anions, which generate the formation of active oxygen forms (O_2, OH^- and H_2O_2). It inhibits the functioning of superoxide dismutase and causes the induction of oxidative stress and death of the microorganisms. In addition, the planar aromatic

derivatives of phenazine – antibiotics iodinine, muxin, pyocyanin – are capable of interacting with DNA/RNA [14]. It was also demonstrated that phenazine antibiotics inhibit DNA-dependent synthesis of RNA not only due to the blocking of the DNA-matrix via intercalation, but also due to the interaction with RNA-polymerase and/or ribonucleoside-3'-phosphates [15–17].

Therefore, we selected an easy-to-use and productive transcription system on the basis of DNA-dependent RNA-polymerase of phage T7 (RNAP T7) for the purpose of screening synthesized compounds and selecting RNA synthesis inhibitors. This model system was successfully used to reveal efficient inhibitors of transcription – antimicrobial and/or antiviral agents [18–20]. The preliminary testing of arylamides of 9-substituted PCA-1 in the abovementioned model system demonstrated reliable inhibition of RNA synthesis by a number of compounds at the concentration of 25 μg/ml (~80 μM) [11].

The current work was aimed at thorough investigation of the concentration-dependent influence of 9-substituted PCA-1 carboxamides on RNA synthesis to detect the effective transcription inhibitors, to study their antimicrobial and antiviral properties and to determine the structure-activity relationship.

Materials and Methods. The investigated PCA-1 phenylamides were synthesized by the methods, described in [11]. All the calculations, including the optimization of ligand geometry, were *accomplished* using QXP/Flo$^+$ software package. The docking was performed using a flexible ligand and a stable receptor model [11].

The compounds for biological studies were dissolved in 100% DMSO up to the concentration of stock solutions of 100 μg/ml.

In vitro transcription assay. The influence of the synthesized compounds on RNA synthesis was tested in RNAP T7 system by the method [described in] [5], using the commercial reagents of *Fermentas* (Lithuania). The transcription was performed in 20 μl of the reaction mixture, containing 0.5 μg of the linearized plasmid DNA *pTZ19R*, 2 mM ribonucleoside triphosphates, 20 units of the active inhibitor of RNAses RiboLock^{TM} in the presence of the following substances (in mM): tris-HCl – 40, pH 7.9, $MgCl_2$ – 6, spermidine – 2, NaCl – 10, DTT – 10 and 12 units of active RNA-polymerase of phage T7. The studied substances were dissolved in DMSO (1 mg/ml) and added to the reaction mixture in the amount of 0.5 μl. DMSO concentration in the control and experiment samples was 2.5%. The reaction mixture was kept at 37°C for 45 min and the reaction was terminated by cooling (–20°C).

The reaction products were detected by gel-electrophoresis in 1.2% agarose with ethidium bromide included in the gel. RNA-transcripts were visualized on transilluminator in UV-light with subsequent photographing [of] the electrophoregrams with a digital camera.

The inhibiting activity of test-agents was determined by comparing the amount of the obtained RNA-product with the control (the amount of RNA-product without the inhibitor). The value of IC_{50} (the inhibitor concentration, required for the 50%-inhibition of the enzymatic activity) was determined via densitometry, evaluating the intensity of electrophoretic stripes using Scion Image for Windows, Release Beta 4.0.3 software.

Microbiological studies. The strains of microorganisms from the collection of the Institute of Veterinary Medicine, NAAS, *E. rhusiopathiae* VR2 var. IVM, *Klebsiella* spp. and *Escherichia coli* ATCC 25922 were used in the work. Pure test-cultures of bacteria were obtained by plating them on solid nutrient medium with further incubation for 24 h. After the microscopic control the colonies of microorganisms were suspended in the physiological solution until 0.5 turbidity level by McFarland standard.

The antimicrobial activity of 9-substituted PCA-1 phenylamides was studied by the method of two-fold dilution in a liquid medium of Muller-Hinton and BHI broth (*BioMeriex*, France), prepared following the manufacturer's instructions in 96-vial plates [21–23].

Previously prepared sterile plates (*Sarstedt*, Germany) were filled up with 140 μl of the medium with the addition of 50 μl of suspension of the test-microorganism in the final concentration of $1 \cdot 10^7$ of the colony-forming units (CFU) in one cubic centimeter, and 10 μl of test substances (in DMSO solvent) in corresponding concentrations; then the incubation was carried out for 18–24 h at 36.7 ± 0.3°C.

The vials with the corresponding liquid medium and microorganism culture but without the test-agent

served as a control.Only DMSO was added to some vials instead of the test-substance solution to control the toxicity. Two vials were used for all concentrations of each sample and control. The results were visually registered by the presence of evident growth of the bacterial culture.

The minimal inhibiting concentration (MIC) was determined as the least concentration of the antimicrobial agent, inhibiting the evident growth of the microorganism test-culture completely.

Cytotoxicity test. The cytotoxicity (CC_{50}) was evaluated using the monolayer line of transplanted culture of Madin-Darby bovine kidney (MDBK) cells, previously tested by the method of polymerase chain reaction (PCR) for the micoplasm contamination. The cell culture was cultivated on the nutrient medium RPMI-1640 *Sigma-Aldrich* (USA) with 10% heat-inactivated fetal bovine serum (*Sigma-Aldrich*), penicillin and streptomycin (100 IU/ml [each) or kanamycin (50 IU/ml) in 96-vial plates of Nunc Company (Denmark) in the atmosphere with 5% CO_2. The monolayer of cells, formed in vials 24 h later, was washed and the supporting non-serum medium with the corresponding concentration of the investigated compound was added to the vials. The supporting medium with the solvent (DMSO) was added to the control vials.

The registration of results was performed daily for 120 h (*Leica DMIL* microscope, Germany), observing the monolayer of MDBK cell culture – the presence or absence of their degeneration, or the change in their morphology. The concentration was considered to be cytotoxic when the number of living cells decreased by 50%.

The antiviral activity of preparations was studied using the bovine viral diarrhea virus (BVDV) which is a typical surrogate model for the hepatitis C virus (HCV) while studying the impact of antiviral preparations, as its structural genes are similar to those of HCV and it can be reproduced *in vitro* [24]. To determine the efficient inhibiting concentration EC_{50} (the lowest concentration of the preparation, when 50% of infected cell samples had the infectious titer of the virus, reduced by 1.75–2.0 $lgID_{50}$), the test-virus in the dose of 100 TCD_{50}/0.1 ml was introduced into MDBK cell culture and incubated for 1 h at 37°C. After the adsorption of the virus on the cells for 1 h it was extracted and the cells were washed with the nutrient medium. Then the preparations in different concentrations were introduced into the supporting medium (RPMS-1640 + 2% fetal serum). The virus reproduction was determined by the special cytopathogenic activity and the infectious titer for each concentration of the preparation.

Results and Discussion. Our previous work presented detailed description of obtaining two series of new N-arylamides of 9-methyl and 9-methoxy-PCA-1 [11]. In total we synthesized 26 compounds for biological testing. The aryl fragments of both series of compounds were presented by aromatic systems with different exocyclic groups (CH_3, CF_3, $(CH_2)_3CH_3$, Cl and other substitutes) in certain ring positions.

DMSO is known for its vivid antimicrobial properties [25]. Taking this fact into consideration we determined the concentration dependence of the DMSO inhibitory activity with regard to the bacterial test-cultures for further objective evaluation of the antibacterial activity of the investigated compounds. It was established that DMSO in the concentration range of 5–10% demonstrates its toxic impact on all the test-cultures, while the concentration of 2.5% has no evident impact on the growth of the investigated bacteria compared to the control of culture growth.

Table 1 presents the results of the enzymatic and antimicrobial screening of the synthesized compounds. It is evident that 20 compounds efficiently inhibit the RNA synthesis in the transcriptional system for RNAP T7 in the range of 0.48–63 μM. *n*-butylphenylamide 9-methyl-PCA-1 (**16**) with IC_{50} = 0.48 μM proved to be the most efficient. High activity level was also demonstrated by pyridine (4-il)amide (**23**) and *м*-carbomethoxyphenylamide (**25**) of 9-methyl-substituted PCA-1 with IC_{50} value of 9.6 and 16.2 μM, respectively.

The impact of the substitute in position 9 of phenazine heterocycle on the ability of inhibiting RNA synthesis may be traced by comparing the activity of compounds with the same arylamide fragments. For instance, it was established that 9-methyl-phenazines with methyl and trifluoromethyl substitutes in different positions of phenylamides are much more active compared to analogous 9-methoxy substitutes. Regardless of the nature of the substitute, the compounds with substitutes

Table 1
The results of enzymatic and antimicrobial screening of PCA-1 phenylamides

No. of compound	*E. rhusiopathiae* VR-2 var. IVM		*Klebsiella spp*.		*E. coli* ATCC25922		РНКП Т7
	100 μg/ml	MIC, μg/ml	100 μg/ml	MIC, μg/ml	100 μg/ml	MIC, μg/ml	IC_{50}, μM (μg/ml)
1	+	0,1	–	–	–	–	>100 (>25)
2	+	1	+	10	+	10	30,4 (10)
3	+	0,1	+	1	+	10	45 (15)
4	+	–	–	–	–	–	> 80 (> 25)
5	+	1	+	1	–	–	> 80 (> 25)
6	–	–	+	10	+	10	31,2 (12)
7	+	1	–	–	+	0,1	63 (25)
8	–	–	+	1	–	–	25,2 (10)
9	–	–	–	–	+	–	> 80 (> 25)
10	–	–	–	–	–	–	55 (20)
11	+	1	+	1	+	100	37,8 (9)
12	+	100	+	1	–	–	38,3 (12)
13	+	1	+	1	–	–	32,1 (10,5)
14	+	1	+	100	–	–	26 (8,5)
15	–	–	–	–	–	–	> 80 (> 25)
16	–	–	–	–	–	–	0,48 (0,17)
17	–	–	–	–	–	–	36,7 (14)
18	–	–	–	–	–	–	28,9 (11)
19	–	–	–	–	–	–	32,8 (12,5)
20	–	–	+	1	+	10	57,4 (20)
21	–	–	–	–	–	–	28,7 (9)
22	+	100	+	10	+	1	61 (20)
23	–	–	–	–	+	100	9,6 (3)
24	–	–	–	–	+	100	> 80 (> 25)
25	–	–	+	100	+	–	16,2 (6)
26	–	–	–	–	–	100	33,8 (12)

in *ortho*-position of the phenylamide fragment demonstrated their ability of inhibiting RNA synthesis. Instead, the activity of *meta*- and *para*-substituted compounds was greatly depen- dent on both the nature of the substitute in the aryl- amide fragment and the substitute in position 9 of phe- nazine.

The initial screening of the antibacterial activity was performed at the concentration of 100 μg/ml. The obtained active compounds were tested in the range of 100–01 μg/ml with consecutive 10-fold dilution.

Gram-positive bacteria *E. rhusiopathiae* VR-2 var. IVM appeared to be sensitive to 12 investigated

Table 2
The results of studies on antiviral activity of PCA-1 para-butylphenylamides

No. of compound	BVDV/MDBK cell culture		*SI*	RNAP T7
	IC_{50}, μM	CC_{50}, μM		EC_{50}, μM
6	64,9	–	–	31,2
16	67,2	0,42	160	0,48
26	8,8	0,88	10	33,8

compounds at 100 μg/ml. The highest activity against bacteria of this strain was demonstrated by 9-methoxy-PCA-1 (1) and its *ortho*-tolyl amide (3). At 0.1 μg/ml they were capable of almost complete inhibition of the microorganism growth. Seven compounds, namely, phenylamide (2) *para*-tolyl amide (5) and *ortho*-trifluoromethyl phenylamide (7) out of the series of 9-methoxy-substituted PCA-1, initial acid (11) and three tolyl amides (13–15) out of the series of 9-methyl-PCA-1 turned out to be active at 1 μg/ml (Table 1).

A considerable number of the investigated test-agents proved to be efficient inhibitors of gram-negative bacteria. For instance, in the abovementioned concentration range 10 phenylamides of 9-substituted PCA-1 were efficient inhibitors of the growth of bacteria *Klebsiella* spp., and six phenylamides inhibited the growth of bacteria *E. coli* ATCC25922. Here phenylamide (2), *ortho*-tolyl amide (3) and *para*-butylphenylamide (6) of 9-methoxy-PCA-1 inhibited the growth of both gramnegative bacteria. According to the results obtained, the most promising investigated compounds are phenylamide (2) and *ortho*-tolyl amide (3) of 9-methoxy-PCA-1, efficiently blocking the growth of all the test cultures, used by us.

The fact of inhibiting the growth of microbial agents by one and the same substance may be explained by acting on the functionally identical cellular targets. This assumption is based on the fact that 3D structures of different DNA and RNA-polymerases are highly homologous, contain the same structural domains and conservative motives, required for the elongation of the nucleic acid chain [26, 27]. Therefore, one may anticipate that a substance, binding to the conservative elements of the corresponding enzyme complex and blocking its functional activity, is capable of inhibiting the work of other representatives of this superfamily of enzymes, but the degree of inhibition is likely to vary. Although there was not found a direct correlation between the inhibitory activity of substances in the model enzymatic and bacterial systems (because of individual peculiarities of bacterial transcriptional complexes and some other factors), the reliable inhibition of RNA synthesis, established by us in the model system RNAP T7 by the compounds, actively inhibiting the growth of bacteria, allows the assumption that RNA-synthesizing complex is a probable cell target.

It is possible to predict the antiviral activity of the compounds of this series, at least due to their ability of inhibiting the viral enzyme – RNA-polymerase of phage T7, as the bacteriophages are viruses of bacteria [28], and phage T7 is considered to be a surrogate model of DNA viruses without a supercapside [29].

There were two reasons of our selection of BVDV model to test the antiviral activity of phenylamides. Firstly, BVD is one of most common veterinary infections, causing serious health problems for animals and leading to considerable economic losses [30]. Secondly, the virus belongs to the pestiviruses of *Flaviviridae* family and its cellular model is used as a surrogate model of HCV [31] for the selection of compounds, inhibiting its reproduction.

To evaluate antiviral properties and to establish the connection between the functional activity and the structure of phenylamides the testing required three *para*-butylphenylamides – compounds 6, 16 and 26, as the work [19] demonstrated that the introduction of the butyl substitute into the benzol fragment of the molecule of 3-oxo-1,2,4-[5,6-*b*][1,4]-benzothiazine leads to reliable enhancement of the ability of this compound to inhibit RNA synthesis in the T7 RNAP transcription system compared to trifluoromethyl-substituted derivative.

The antiviral properties of phenylamides 6, 16, and 26 were evaluated, analyzing the level of their impact on the eukaryotic cells in MDBK culture. The results of the investigations are presented in Table 2. It was

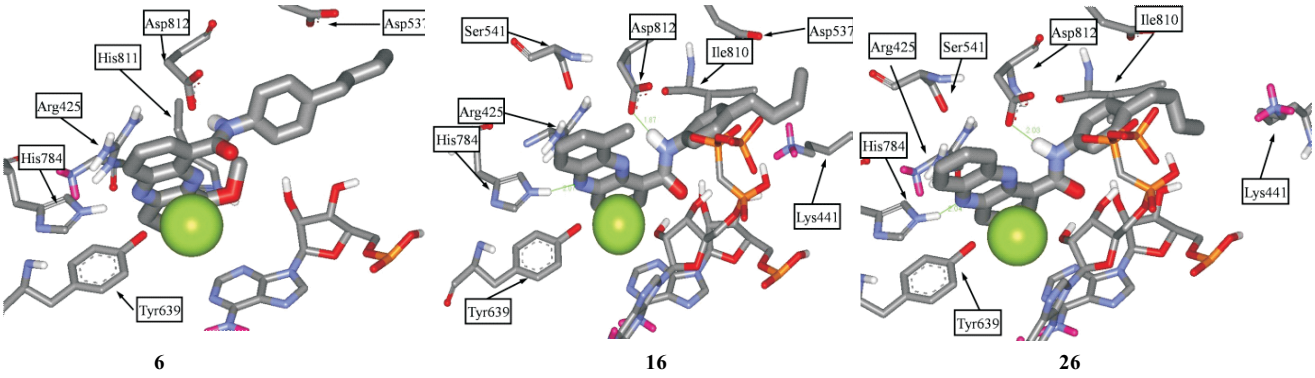

Fig. 2 The location of compounds **6**, **16** and **26** in the model of the active site of RNAP T7 (the data, obtained by the molecular docking [11])

established that the nature of 9-substitute has significant impact on both the toxicity and the antiviral properties of the abovementioned compounds. For instance, *para*-butylphenylamide **26** demonstrated a high activity with EC_{50} = 0.88 μM. The introduction of a hydrophobic methyl group into position 9 of the phenazine heterocycle caused the increase in the activity of *para*-butylphenylamide **16** which demonstrated the highest activity with EC_{50} = 0.42 μM. Instead, the substitution of the methyl group by the methoxy-group in position 9 leads to practically complete loss of the antiviral activity of the corresponding *para*-butylphenylamide 6.

The chemotherapeutic index, or selectivity index (*XTI* = *SI*), is calculated as CC_{50} to EC_{50} ratio. The compounds with *XTI* (*SI*) = 4 or more are considered to be active. It is noteworthy, that the higher *SI*, the safer and more efficient the investigated test-agent.

High antiviral impact of amides **16** and **26** correlates with the results [11], which demonstrate that conformationally labile butyl "tail" of these compounds is capable of stabilizing the transcriptional complex RNAP T7 [11], filling in the residual volume of the catalytic socket, restricted by the residues of aminoacids Lys441 and Ile810 (Fig. 2), while 9-methyl group of phenylamide **16** is fixed in the narrow hydrophobic socket, common for many DNA-dependent RNA-polymerases [32].

The interaction of the ligand and the amino acid environment of this socket may have considerable impact on the functioning of the enzyme and govern the level of inhibitory properties of the ligand. The configuration of the location of *para*-butylphenylamide 6 is realized in the transcriptional complex RNAP T7, "reversed" due to the configuration of phenylamides 16 and 26 (Fig. 2), which may be related to the excessive volume and polarity of 9-methoxy-group of compound 6. The realization of the important hydrogen bond between the amide proton and the carbonyl group of Asp812 requires evident exit of the amide bond of compound 6 from the plane of the basic phenazine heterocycle, compared to the compounds 16 and 26, which is accompanied by the decrease in conjugation in the structure.

These differences in the structure of model complexes of the RNAP T7 catalytic socket with compounds 6, 16 and 26 are likely to condition the difference in their antiviral properties.

Therefore, taking the abovementioned into consideration, phenylamides 16 and 26, with *XTI* values of 160 and 10, respectively, appear to be quite promising inhibitors of BVDV.

It is noteworthy that compound 16 demonstrated the most efficient inhibitory activity regarding both RNA synthesis in the model system of RNAP T7 transcription, and in BVDV model.

These results are promising for further study of the investigated compounds activity against other viral infections, including HCV on both cellular and animal models.

Conclusions. It was shown that N-arylamides of 9-substituted PCA-1 are a promising class for the elaboration of efficient antimicrobial preparations.

The study of their biological activity *in vitro* revealed a number of antibacterial compounds with rather a high activity regarding gram-positive and gram-

negative bacteria with MIC values in the range of 0.1–10 μg/ml. The multiple activity against bacterial test-systems was established for some compounds. Two arylamides (**16** and **26**) demonstrated efficient activity against BVDV (IC_{50} = 0.42 and 0.88 μM) with high *XTI* values (160 and 10, respectively). It should be noted that all the arylamides with antibacterial and antiviral properties are blocking RNA synthesis reliably in the model system of RNAP T7 transcription, which was generally more sensitive to arylamides of 9-methyl PCA-1. The activity of compounds also depends on the nature and position of the substitute in the arylamide fragment.

The data obtained are one more confirmation of the reasonable application of the abovementioned model system for the primary selection of RNA synthesis inhibitors – potential antibacterial and antiviral agents.

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Оцінка протибактерійної та противірусної активності N-ариламідів 9-заміщених феназин-1-карбонових кислот – інгібіторів модельної транскрипції фага

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Мета. *Пошук серед N-ариламідів 9-заміщених феназин-1-карбонових кислот (ФКК-1) – інгібіторів синтезу РНК – сполук з антибактерійними та антивірусними властивостями.* ***Методи***. *Вплив N-ариламідів на синтез РНК in vitro визначали із застосуванням модельної системи ДНК-залежної РНК-полімерази бактеріофага Т7; антимікробну активність N-ариламідів – методом дворазових розведень у рідкому середовищі проти бактерій Erysipelothrix rhusiopathiae VR-2 var. IVM, Klebsiella spp. та Escherichia coli ATCC25922. Антивірусну дію щодо вірусу бичачої вірусної діареї (ВБВД) і цитотоксичність N-арил- амідів оцінювали на перещеплюваній лінії культури клітин нирки теляти.* ***Результати***. *Двадцять N- ариламідів виявилися ефективними інгібіторами синтезу РНК у межах концентрацій 0,48–63 мкМ. Най- вищу активність продемонструвала сполука* ***16****, IC_{50} якої становить 0,48 мкМ. Антибактерійні власти- вості стосовно грампозитивних і грамнегативних бактерій проявили 14 N-ариламідів при концентраціях 0,1– 10 мкг/мл. Для низки N-ариламідів встановлено множинний характер антибактерійної дії: сім сполук проти двох і дві (2 і 3) – проти трьох досліджуваних бактерій. N-ариламіди* ***16*** *і* ***26*** *виявили високу інгібіторну здатність проти ВБВД з показниками IC_{50} 0,43 і 0,88 мкМ і SI > 160 і 10 відповідно.* ***Висновки***. *Отримані результати дають підставу вважати, що вірогідними мішенями для N-ариламідів 9-заміщених ФКК-1 у бактерій і вірусіможуть бути є їхні РНК-синтезувальні комплекси.*

Ключові слова: N-ариламіди 9-заміщених ФКК-1, модельна система транскрипції фага Т7, антибактерійна активність, антивірусна активність.

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Оценка антибактериальной и антивирусной активности N-ариламидов 9-замещенных ФКК-1 – ингибиторов модельной транскрипции фага Т7

Цель. *Поиск среди 9-замещенных N-ариламидов феназин-1-карбоновой кислоты (ФКК-1) – ингибиторов синтеза РНК – соединений с антибактериальными и антивирусными свойствами.* ***Методы***. *Влияние N-ариламидов на синтез РНК in vitro определяли с использованием модельной системы ДНК-зависимой РНК-полимеразы бактериофага Т7; антимикробную активность N-ариламидов – методом двукратных розведений в жидкой среде против бактерий Erysipelothrix rhusiopathiae VR-2 var. IVM, Klebsiella spp. и Escherichia coli ATCC25922. Антивирусное действие по отношению к вирусу бычьей вирусной диареи (ВБВД) и цитотоксичность N-ариламидов оценивали на перевиваемой линии культуры клеток почки теленка.* ***Результаты***. *Двадцать N-ариламидов оказались эффективными ингибиторами синтеза РНК в диапазоне концентраций 0,48–63 мкМ. Наивысшую активность продемонстрировало соединение* ***16****, IC_{50} которого составляет 0,48 мкМ. Антибактериальные свойства относительно грампозитивных и грамнегативных бактерий проявили 14 N-ариламидов в концентрациях 0,1–10 мкг/мл. Для ряда N-ариламидов установлен множественный характер антибактериального действия: семь соединений против двух, а два (****2*** *и* ***3****) – против трех исследуемых бак- терий. N-ариламиды* ***16*** *и* ***26*** *выявили высокий ингибиторный потенциал против ВБВД с показателями IC_{50} 0,43 и 0,88 мкМ и SI > 160 и 10 соответственно.* ***Выводы***. *Полученные результаты да- ют основание полагать, что возможными мишенями для N-арил- амидов 9-замещенных ФКК-1 у бактерий и вирусов могут быть их РНК-синтезирующие комплексы.*

Ключевые слова: N-ариламиды 9-замещенных ФКК-1, модельная система транскрипции фага Т7, антибактериальная активность, антивирусная активность.

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