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Synthesis and study of pesticidal activity of some N-arylthio-1,4-benzoquinone imines

Lyudmyla Kuz'menko [1], Anatoly Avdeenko [2], Svitlana Konovalova [2], Sofiya Vasylyuk [3], Olena Fedorova [3], Natalija Monka [3], Aelita Krychkovska [3], Vira Lubenets [3,*]

[1]Department of Biology and Fundamentals of Agriculture, Oleksandr Dovzhenko Hlukhiv National Pedagogical University, Tereshchenko Str., 47, Hlukhiv, Ukraine
[2]Donbass State Engineering Academy, Kramatorsk, 84313, Ukraine
[3]Department of Technology of Biologically Active Substances, Pharmacy & Biotechnology, Lviv National Polytechnic University, S. Bandery Str. 12, Lviv, Ukraine
*corresponding author e-mail address: ***kafbiol@i.ua; chimist@dgma.donetsk.ua; vlubenets@gmail.com***

ABSTRACT

Several N-arylthio-1,4-benzoquinone imines were synthesized.Using modern research methods their structures were investigated. A combinatorial library of perspective plant protection means, based on N-arylthio-1,4-benzoquinone imines, was created and their antimicrobial, insecticidal and acaricidal activities were studied. Certain dependencies of the antimicrobial activity of the synthesized compounds on their structure have been established. Using the online GUSAR service, the determination of acute toxicity of the synthesized N-arylthio-1,4-benzoquinone imines *in silico* for rats using four types of substance administration was carried out.

Keywords: *N-arylthio-1,4-benzoquinone imines, pesticides, antimicrobial activity, acaricidal activity, acute toxicity.*

1. INTRODUCTION

Some recent forecasts show that until 2050, the planet's population will increase to about 9 billion [1]. At the same time, world food production is not able to grow at a rate that would satisfy the needs of the fast-growing population. One of the most significant obstacles to sufficient quantities of food production are the diseases of agricultural plants [2]. The reduction in losses to pests, pathogens, and environmental stresses is equivalent to expanding the land and water resources for greater agricultural production [1]. Today pesticides are used worldwide to combat plant diseases [3,4]. The use of the latter has a significant positive effect on the increase in the quantity and the quality of agricultural products, but it is often short-term. The cause of this phenomenon may be the emergence of resistant pathogens as a result of the long-term use of pesticides [3].

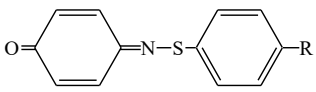
In this connection, the replenishment of the existing pesticide arsenal for successful pest control of agricultural and ornamental crops, the search for new effective plant protection means is an open and rather relevant issue of today. The screening of new compounds, primarily those with the structure close to the known biologically active substances, is aimed to address this issue. The latter compounds certainly include quinones, in particular, natural quinones and some synthetic derivatives, which attract attention as insecticidal, antifeedant and phytotoxic compounds [4-11].

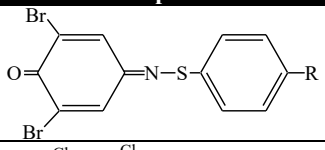
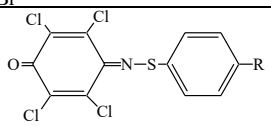
The nearest analogs of quinones are quinonimines, which are widely used as intermediates in the dyes manufacture, vulcanizing agents for rubber, gum, analytical reagents and reagents in color photography. Prospective is their application in optoelectronics and information registration. Among the quinonimines, some compounds exhibit antitumor, cytotoxic activity, and also inhibit the development of the human immunodeficiency virus [12].

Quinonimines in their structure contain a nitrogen atom and substituents near it, which influences the molecule symmetry and opens up wide possibilities for reactivity controlling. Therefore, the search for new herbicidal and fungicidal agents among the derivatives of quinonimines is prospective, as well as the possibility of the application of the latter for the synthesis of the compounds with better investigated pesticidal activity.

It is known that some sulfur-containing quinonimines, namely N-arylthio-1,4-benzoquinone imines, can be used as reagents for the synthesis of important sulfur-containing compounds with a wide spectrum of biological activity – thiosulfoesters [13], among which there are effective fungicides and plants protective compounds [14-23]. However, the pesticidal activity of N-arylthio-1,4-benzoquinone imines has still not been investigated. Therefore, the aim of this work is the synthesis of several N-arylthio-1,4-benzoquinone imines (the structure of compounds is given in Table 1) for the study of their antimicrobial, insecticidal and acaricidal activity, as well as the determination of the correlations between the structure of synthesized compounds and their pesticidal activity.

Table 1. Structures of compounds 1a-e, 2 a, d, e and 3 a, c, d.

Compound		R
1a		H
1b		OCH_3
1c		CH_3
1d		Cl
1e		NO_2

Compound		R
2a		H
2d		Cl
2e		NO_2
3a		H
3c		CH_3
3d		Cl

2. MATERIALS AND METHODS

General experimental details.

^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300spectrometer (^{13}C 300 MHz) in $CDCl_3$ solutions, the chemical shifts were measured relative to tetramethylsilane. The melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded on a "SPECORD M 80" spectrophotometer in tablets with KBr. Monitoring of the reactions and individuality of compounds were performed by TLC method on "Silufol UV 254" plates.

Synthesis of compounds.

Compounds 1a-e were obtained by the interaction in the equivalent ratio of N-chloro-p-quinone imine with the corresponding thiol and the corresponding amount of 10% sodium carbonate in tetrahydrofuran at - 5 to 0°C [24]. Yields of compounds 1a-e and their melting points correspond to the literature data [13, 24], and the spectral characteristics (^{1}Hand ^{13}C NMR spectra data) are consistent with data for the above-mentioned compounds reported in [27].

1,4-benzoquinone imines **2 a, d, e** were obtained using the method, similar to the method of obtaining the compounds **1a-e*2,6-dibromo-4-[(phenylsulfenyl)imino]cyclohexa-2,5-dien-1-one (2a)***64 %, mp: 171^{o}C;IR (KBr, cm^{-1}): 1586,1600 ($C=C_{ar}$), 1612 (C=N),1662 (C=O), ^{1}HNMR (300 MHz, $CDCl_3$) δ, pmm:7.89 d (1H, J = 2.4 Hz , H-5,), 7.35–7.58 m (5H, Ph),7.51 d (1H, J =2.4 Hz , H-3),^{13}CNMR (300 MHz, $CDCl_3$) δ, pmm: 126.63, 127.29, 130.04, 131.26, 134.76, 135.92, 145.28, 171.81, Anal. calcdfor$C_{12}H_7Br_2NOS$:C, 38.63; H, 1.89; N, 3.75; S, 8.59; found: C,38.75; H, 2.08; N, 3.70; S, 8.66.

2,6-dibromo-4-{[(4-chlorophenyl)sulfenyl]imino}cyclohexa-2,5-dien-1-one (2d)Yield72 %,mp: 195^{o}C;IR (KBr, cm^{-1}): 1582,1598 ($C=C_{ar}$), 1616 (C=N),1665 (C=O),^{1}HNMR (300 MHz, $CDCl_3$) δ, pmm:7.85 d (1H, J=2.4 Hz, H-5), 7.31–7.42 d.d (4H, J^O = 8.9 Hz, Ar,), 7.51 d (1H, J = 2.7 Hz, H-3), ^{13}CNMR (300 MHz, $CDCl_3$) δ, pmm:127.29,128.96,129.76,130.29, 130.96,134.76, 145.12,171.80, Anal. calcdfor$C_{12}H_6ClBr_2NOS$:C, 35.37; H, 1.48; Cl, 8.69; N, 3.44; S, 7.86; found:C, 34.97; H, 1.59;N, 3.38;S, 8.04.

2,6-dibromo-4-{[(4-nitrophenyl)sulfenyl]imino}cyclohexa-2,5-dien-1-one (2e)Yield58 %, mp: 212^{o}C;IR (KBr, cm^{-1}): 1528, 1347 (NO_2), 1588,1598 ($C=C_{ar}$), 1616 (C=N),1658 (C=O),^{1}HNMR (300 MHz, $CDCl_3$)7.79–8.33 d.d (4H, J^O = 9.0 Hz, Ar),7.89 d (1H, J 2.7 Hz, H-5), 7.56 d (1H, J 2.7 Hz, H-3), ^{13}CNMR (300 MHz, $CDCl_3$) δ, pmm:126.02, 129.18,130.98, 134.04,140.58, 144.92, 145.72,170.73, Anal. calcdfor$C_{12}H_6Br_2N_2O_3S$:C, 34.47; H, 1.44;N, 6.70;S, 7.66;found: C, 34.74; H, 1.56;N, 6.61;S, 7.66.

N-arylthio-1,4-benzoquinonine 3 a, c, d was obtained according to the method presented in the work[28].

2,3,5,6-tetrachloro-4-[(phenylsulfenyl)imino]cyclohexa-2,5-dien-1-one (3a)Yield68 %, mp: 232^{o}C;IR (KBr, cm^{-1}): 1586,1598 ($C=C_{ar}$), 1616 (C=N), 1665 (C=O), ^{1}HNMR (300 MHz, $CDCl_3$) δ, pmm:7.04–7.48 m (5H, Ph), ^{13}CNMR (300 MHz, $CDCl_3$) δ, pmm: 127.29, 127.39, 128.27, 130.42, 135.67, 140.98, 144.89, 168.17, Anal. calcdfor$C_{12}H_5Cl_4NOS$: C, 40.82; H, 1.42; Cl, 40.16;N, 3.97;S, 9.08; found: C, 41.06; H, 1.35; Cl, 40.10;N, 3.92; S, 9.22.

2,3,5,6-tetrachloro-4-{[(4-methylphenyl)sulfenyl]imino}cyclohexa-2,5-dien-1-one (3c)Yield70 %, mp: 240^{o}C;IR (KBr, cm^{-1}): 1584,1598 ($C=C_{ar}$), 1614 (C=N), 1650 (C=O),^{1}HNMR (300 MHz, $CDCl_3$) δ, pmm:7.21 –7.47 d.d (4H, J^O = 8.6 Hz, Ar,), 2.27 s (3H, CH_3), ^{13}CNMR (300 MHz, $CDCl_3$) δ, pmm: 21.57, 125.91, 128.01, 131.06, 135.67, 137.41, 140.97, 144.88, 168.16.Anal.calcdfor$C_{13}H_7Cl_4NOS$: C, 42.53; H, 1.92; Cl, 38.63;N, 3.82;S, 8.73; found: C,42.90; H, 2.02; Cl, 39.04; N, 3.75; S, 8.42.

2,3,5,6-tetrachloro-4-{[(4-chlorophenyl)sulfenyl]imino}cyclohexa-2,5-dien-1-one (3d)Yield66 %, mp: 236^{o}C; IR (KBr, cm^{-1}): 1588,1592 ($C=C_{ar}$), 1616 (C=N),1665 (C=O),^{1}HNMR (300 MHz, $CDCl_3$) δ, pmm:7.33 –7.49 d.d (4H, J^O = 8.6 Hz, Ar,),^{13}CNMR (300 MHz, $CDCl_3$) δ, pmm: 128.79, 128.89, 128.97, 130.31, 135.67, 140.98, 144.89, 169.16. Anal.calcdfor$C_{12}H_4Cl_5NOS$: C, 37.19; H, 1.04; Cl, 45.70; N, 3.61;S, 8.27; found:C, 37.18; H, 1.26; Cl, 45.78; N, 3.53; S, 8.76.

Biologogical studies.

Determination of fungicidal activity *in vitro.*

The acetone solution of the test substance was introduced into a flask with the sterile warmed to 40-50^{0}C potato-dextrose agarized nutrient medium to obtain the concentration of test substance 0,003%in the medium. The medium after mixing was poured into Petri dishes. 24 hours later, after evaporation of acetone, the inoculation with fungal spores of *Fusarium moniliforme* ATCC 60846, *Verticillium dahliae* KlebanATCC MYA-4575, *Venturia inaequalis*(Cooke) Winter, *Botrytis cinerea* ATCC 46522, *Aspergillus niger*van. Tiegh.BKM F-412, *Sphacelotheca panicimiliacei*(Pers.) Bub., *Phytophthora infestans* (Mont.) de Bary(capacity 10^5 spores/ml) was carried out. The Petri dishes were placed for incubation in a thermostat at 22-25^{0}C.

The calculation was made after 72 hours by determining the percentage of growth of fungal colonies in comparison with control. The experiment was conducted in triplicates.

Determination of fungicidal activity in green plants *in vivo*.

2-3-week-old green plants (tomatoes, cucumbers) were treated with 0,05% water-acetone solutions of the tested substances until the liquid run off from the leaves. After the drying of drip-liquid moisture,the plants were infected with the pathogen (*Phythophtora infestans,Erysiphegraminis).* After that, the plants were placed in a humid camera at a temperature of 16-18° C.After 24 hours in humid camera the plants were transferred to the greenhouse. The experiment was conducted in triplicates.

The counts were made after 8-10 days, depending on the leaves affection by five-point scale:

0 - the leaf is healthy

1 point - 10-15% of leaf is affected

2 points - 10 - 25% of the leaf is affected

3 points - 25 - 50% of the leaf is affected

4 points - 50 - 75% of the leaf is affected

5 points - 75 - 100% of the leaf is affected

Then the average percentage of the disease affection was calculated. The conclusion of the efficacy of the compounds was made based on the disease inhibition degree compared with the control.

Determination of insecticidal and nematocidal activity.

The insecticidal activity of the compounds was determined according to the methods given in the recommendations [29], the nematocidal activity was determined according to the method presented in [30].

Determination of acaricidal activity.

20-30 female spider mites (Tetranychus urticae Koch) were transferred onto the standard cuttings of beans leaves. Then the cuttings were sprayed with 0,1% water-acetone solution of the tested compound at a flow rate of the working fluid 35 ml/m2. After drying of drip-liquid moisture, cuttings were placed in a humid camera for 2 days at +20°C. The experiment was conducted in duplicates. The commercially available acaricide “Keltan” was used as a standard. Control was the option of the experiment with a pure water-acetone solution as a sprayed agent.

Conclusions on the activity of the tested substances were made based on the percentage of the mortality of mites after 48 hours of the treatment.

3. RESULTS

In general, N-arylthio-1,4-benzoquinone imines are produced by the following methods:

• interaction of N-chloro-1,4-benzoquinone imines with thiophenols (method A) [24-26];

• reaction of N-chloro-2,6-dihalogeno-1,4-benzoquinone imines with disulfides (method B) [31];

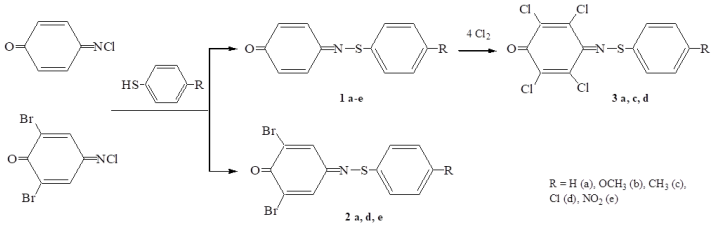
• oxidation of N-arylthio-1,4-aminophenols (method C) [32];

• interaction of p-aminophenols with arylsulphonyl chloride (method D) [23].

• interaction of thionitrates with 1,4-aminophenols (method E) [34].

For the synthesis of the compounds presented in this work, the method A was used, and the methods, optimized by the authors and described in [24,30], were reproduced. The process can be represented by the following scheme1:

Scheme 1. Synthesis of N-arylthio-1,4-benzoquinone imines



It should be noted that to obtain compounds **2**, method B was mainly used. Thus, in the above-mentioned method, 2,6-dibromo-4 - [(phenylsulfanyl) imino] cyclohexa-2,5-dien-1-one (2a) was obtained with a 84,4% yield [31]. It was shown that the method A is also sufficiently suitable for the synthesis of N-arylthio-2,6-dibromo-1,4-benzoquinone imines, and the target quinonimines 2 a, d, e were obtained with 58-72% yields.

The structures, determined in the studies of N-arylthio-1,4-benzoquinone imines, have been confirmed using modern methods of investigation (^{1}H and ^{13}C NMR spectroscopy).

Pesticidal activity.

An important part of the most widespread plant diseases are diseases caused by microorganisms. In general, from two to thirteen species of microbial phytopathogens parasitize on one type of plant. The present paper presents the results of the study of antimicrobial activity concerning phytopathogenic bacterium *Xanthomonas malvacearum* and fungi *Fusarium moniliforme, Verticillium dahliae, Venturia inaequalis, Botrytis cinerea, Aspergillus niger, Sphacelotheca panicimiliacei, Phytophthora infestans, Erysiphe graminis, Erysiphe cichoracearum* (Table 2).

As an example of the diseases caused by the above-mentioned microorganisms, several diseases can be mentioned, namely:black rust of cotton –causative agent *Xanthomonas malvacearum*; corn pink mold, stem elongation disease of rice - *Fusarium moniliforme*; powdery mildew of wheat, rye, barley, wild poaceae - the causative agent *Erysiphe graminis*; powdery mildew of melon, cucumber, pumpkin and zucchini - causative agent *Erysiphe cichoracearum*; head smut– causative agent *Sphacelotheca panicimiliacei*; late blight, a disease that affects potatoes, tomatoes and other kinds of passover - causative agent *Phytophthora infestans*; apple scab – causative agent *Venturia inaequalis* [35-38].

The harmful effects of some fungus are not limited to one particular plant or plant species. For instance, *Verticillium dahliae* has a large range of hosts, consisting of more than 350 plant species, mainly root plants [38,39]. *Botrytis cinerea* causes diseases of grapes, pasterns, onions, citrus fruits, as well as beats, flax, gladioluses, greenhouse crops, peas, and salad. It is the causative agent of the clamp rot and gray rot of strawberries [38].

The study of the fungicidal activity of N-arylthio-1,4-benzoquinone imines was carried out by the method of estimating the percent of growth inhibition of pathogens. The results are presented in Table 2.

Table 2. Antimicrobial activity of N-arylthio-1,4-benzoquinone imines.

No.	Growth inhibition, %								
	Bacteria	Fungi							
	Xanthomonas malvacearum	*Fusarium moniliforme*	*Verticillium dahliae*	*Venturia inaequalis*	*Botrytis cinerea*	*Aspergillus niger*	*Sphacelotheca panicimiliacei*	*Phytophthora infestans*	Diseases of plants caused by *Erysiphegraminis*
1a	7	19	31	40	30	25	12	1	56
1b	21	4	21	5	30	25	20	12	23
1c	16	2	9	15	0	15	39	0	100[a]
1d	0	11	7	25	40	13	73	67	0
1e	25	11	15	40	35	35	31	12	0
2a	14	28	36	30	42	15	13	14	38
2d	11	50	36	30	42	15	13	14	49[a]
2e	0	5	10	0	0	12	15	8	51
3a	0	0	5	20	0	25	22	2	52
3c	-	-	-	-	-	-	-	-	77[a]
3d	31	25	14	30	26	45	55	67	3[a]

Note: [a] Data are given in relation to *Erysiphecichoracearum*

The above data indicate that the studied N-arylthio-1,4-benzoquinone imines 1a-e, 2a, d, e and 3a, c, d are characterized by mild antimicrobial activity. The best results were observed for compounds 1a, c, 3a, c with respect to the fungi *Erysiphe graminis, Erysiphe cichoracearum* and compounds 1d, 3d in relation to *Sphacelotheca panicimiliacei, Phytophthora infestans*, which creates the prospects for the search for the agents for the protection of plants belonging to the Cucurbitaceae, Solanaceae and Gramineae families among the specified class of compounds.

The analysis of the results indicates the selectivity of the action of benzoquinone imines to various microorganisms. In particular, the compound (1d), which was active against the fungi *Sphacelotheca panicimiliacei, Phytophthora infestans* (growth inhibition are 73 and 67 % respectively), turned out to be completely ineffective to *Erysiphe graminis* (growth inhibition – 0%).

Also, the results of the studies have shown that the antimicrobial activity is influenced by the nature of the substituents in the arylthio group of N-arylthio-1,4-benzoquinone imines. For example, the introduction of chlorine atom into the arylthiol group of the compounds 3 increased their antimicrobial activity. Growth inhibition of microorganisms by benzoquinonine with phenyl group 3a was within 0-25%, while compounds with 4-chlorophenyl group 3d –14-67%. Similarly, the presence of chlorine atom in the arylthio group of the structure 1 contributed to an increase in the activity of the compound to *Sphacelotheca panicimiliacei, Phytophthora infestans* compared with benzoquinone imines 1, containing other substituents in the same position.

To create a combinatorial library of perspectivecompoundsfor plant protection based on N-arylthio-1,4-benzoquinone imines, a study of the insecticidal, nematocidal and acaricidal activity of the compounds 1a-e, 2a, d, e, and 3a, c, d was also conducted. Results of the research presented in Table 3.

Table 3. Insecticidal, nematocidal and acaricidal activity of N-arylthio-1,4-benzoquinone imines.

No. of comp.	Pest death rate, %				
	Housefly *Musca domestica*	Rice weevil *Sitophilus oryzae*	Black bean aphid *Aphis fabae* Scop.	Red spider mite *Tetranychus urticae Koch*	Root-knot nematodes *Meloidogyne*
1a	7,7	51,3	5,0	42,5	0
1b	2,5	29,7	2,5	32,5	39
1c	27,7	0	40	52,5	56
1d	0	20	12,5	15	35,7
1e	2,5	0	22,5	25	62,3
2a	2,5	29,7	42,5	32,5	-
2d	17,5	13,5	40,0	47,5	0
2e	0	7,5	25	0	10
3a	0	10	32,5	5,5	0
3c	8	15	12,6	100	36
3d	10	0	47,5	100	41

The results reveal that the highest efficacy of the studied substances was shown in the control of the red spider mite Tetranychus urticae Koch. Among them, N-arylthio-1,4-benzoquinone imines 1c (pest death rate was 52,5%), 3c (pest death rate – 100%) and 3d (pest death rate – 100%) turned out to be especially active. As for other investigated pests, the results obtained for the compound 1e demonstrate the death rate of the root-knot nematode Meloidogyne of 62,3%.

The assessment of the toxicity of compounds is an important aspect of research and development of new pesticides since it helps to prevent damage to human health and the environment. Such studies are mostly carried out on rodents, are quite expensive and constantly criticized for ethical reasons. The European Community Guidelines for Chemicals and Safe Use (REACH) provide the development of computational methods for analyzing "structure-activity" interactions and the study of toxic effects.

Nowadays there is a large amount of literature data of LD50 for various compounds on rats, which allows evaluating LD50 in silico using various SAR and QSAR techniques [40]. A method for simulating acute toxicity of rodent QSAR, implemented in the GUSAR software [40] was used to evaluate the toxicity of the studied compounds.

Results of the acute toxicity predictionmake it possible to assert that the synthesized N-arylthio-1,4-benzoquinone imines can be attributed to low-toxic compounds (4, 5class of toxicity) (Table 4). Such results are a good argument for the feasibility of further experimental biological research of the above-mentioned compounds to find new effective pesticides.

Table 4. Predicted acute toxicity for rats.

No.	Intraperitoneal administration		Intravenousadministration		Oral administration		Subcutaneous administration	
	LD_{50} (mg/kg)	Classification of substances toxicity*	LD_{50} (mg/kg)	Classification of substances toxicity*	LD_{50} (mg/kg)	Classification of substances toxicity*	LD_{50} (mg/kg)	Classification of substances toxicity*
1a	522.6	Class 5	60.68	Class 4	2324.0	Class 5	649.8	Class 4
1b	561.2	Class 5	100.4	Class 4	1637.0	Class 4	1402.0	Class 5
1c	487.5	Class 4	73.3	Class 4	2022.0	Class 5	1093.0	Class 5
1d	521.3	Class 5	68.85	Class 4	1399.0	Class 4	1085.0	Class 5
1e	265.6	Class 4	99.56	Class 4	1814.0	Class 4	191.0	Class 4
2a	540.3	Class 5	115.8	Class 4	1561.0	Class 4	1374.0	Class 5
2d	759.1	Class 5	161.5	Class 4	1356.0	Class 4	1083.0	Class 5
2e	302.5	Class 4	84.25	Class 4	1803.0	Class 4	233.4	Class 4
3a	458.5	Class 4	78.75	Class 4	1066.0	Class 4	1071.0	Class 5
3c	163.0	Class 4	82.34	Class 4	1582.0	Class 4	1203.0	Class 5
3d	768.5	Class 5	102.5	Class 4	1944.0	Class 4	981.8	Class 4

**acute toxicity classification for rodents according to the OECD standard project (organization of economic cooperation and development)*

4. CONCLUSIONS

Thus, in the course of thestudies, a combinatorial library of perspectivecompoundsfor plant protectionbased on N-arylthio-1,4-benzoquinone imines was created. In this case, methods of the synthesis of several N-arylthio-1,4-benzoquinone imines have been reproduced and the compounds' structures were determined using modern research methods (^{13}C and ^{1}H NMR spectroscopy).

Antimicrobial, insecticidal and acaricidal activity of synthesized N-arylthio-1,4-benzoquinone imines was studied and some correlations of synthesized compounds' structure and their antimicrobial activity was revealed.

The effectiveness of some N-arylthio-1,4-benzoquinone imines to fungus*Erysiphe graminis, Erysiphe cichoracearum, Sphacelotheca panicimiliacei, Phytophthora infestans*was shown, which opens the prospects for the search among this class of compounds for the plant protection products for the plants from the Cucurbitaceae, Solanaceae and Gramineae families.

Among the N-arylthio-2,3,5,6-tetrachloro-1,4-benzoquinone imines, two highly active compounds for the control of spider mite (*Tetranychus urticae* Koch) were identified, suggesting the feasibility of the further search for effective acaricides in this series.

The prospect of finding new effective pesticides among N-arylthio-1,4-benzoquinone imines *in silico* was confirmed by studying their acute toxicity in rats using the GUSAR software.

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