Chemistry, Technology and Application of Substances
Vol. 4, No. 2, 2021

ФАРМАЦІЯ

N. Ya. Monka, L. R. Zhurakhivska, M. S. Kurka, H. B. Shyian, Yu. M. Semenchuk, V. I. Lubenets
Lviv Polytechnic National University,
Department of Technology of Biologically Active Substances, Pharmacy and Biotechnology
vlubenets@gmail.com

SYNTHESIS OF THIOSULPHONATE AND AMINO ACID DERIVATIVES OF BENZOCHINONE AND PREDICTED SCREENING OF THEIR BIOLOGICAL ACTIVITY

https://doi.org/10.23939/ctas2021.02.040

Quinoid derivatives are attractive not only as interesting synthons for synthesis, but also as potential biologically active substances, so it is important to modify the compounds of the quinone series with different pharmacoform fragments. In this work, the structural design of chlorine and bromanyl disulfur-containing fragments, namely thiosulfonate, and chloranyl – a fragment of 4-aminobutanoic acid. Methods of synthesis were developed and physicochemical characteristics of thiosulfonate and amino acid derivatives were studied: 2,5-bis (thiosulfonate) -3,6-halogen -1,4-benzoquinones and 2,5-bis (3-carboxypropylamino) -3,6 – dichlorobenzoquinone. The prospects for the design of chlorine and bromanyl thiosulfonate fragments and chloranyl fragment of 4-aminobutanoic acid are confirmed by the results of predicting the biological activity of 5 a, b, 6 a, b, 7 using the online resource PASS Online. In particular, the substance 6a obtained by us is promising in terms of research on Antiviral (Picornavirus). The obtained results of predicted cytotoxicity screening indicate the feasibility of conducting experimental studies by in vitro methods on anticancer activity against cancer cell lines of hematopoietic and lymphoid tissue, lungs, skin, ovaries, blood, breast, kidney, colon, brain.

Key words: benzoquinone, chloranyl, bromanyl, thiosulfonate, predicted activity, cytotoxicity.

Introduction

The priority of the research today is the use of quinones and their derivatives as organic reagents for the quantitative determination of medicinal substances [1, 2]. The scientific literature provides information on the use of quinone derivatives for quantitative analysis of cephalosporin [3–5] and β-lactam antibiotics [6], and describes the determination of antimigraine analgesics based on reactions with p-chloranil [7].

Quinoid derivatives are attractive not only as interesting synthons for synthesis, but also as potential biologically active substances, so the urgent task today is to create new effective substances with different spectrum of biological action, especially those whose structure includes other pharmacoform fragments. close to known biologically active substances. Modified quinone derivatives, in particular natural quinones and some synthetic derivatives, attract attention as insecticidal, anti-inflammatory and phytotoxic compounds [8-10]. Among the benzoquinone derivatives there are a number of compounds that exhibit high antimicrobial activity and a wide range of its action [11].

The results of studies of 1,4-benzoquinone derivatives indicate the prospects of studying their properties in order to create new effective substances as regulators of the activity of various enzymes. As a prooxidant, a strong antioxidant, a regulator of genetic expression and signal transduction, ubiquinone is able to affect the activity of a large number of enzymes that function in cells [12].

It is also known that some sulfur-containing quinonymines, namely N-arylthio-1,4-benzoquino-

nymines, can be used as reagents for the synthesis of important sulfur-containing compounds with a wide range of biological activity – thiosulfoester [13, 14], among which known compounds are effective regulators , and plant fungibactericides [15–20].

The aim of our research is the synthesis of some new benzoquinone derivatives, establishing the predicted structure-activity dependence and determining the priority areas of experimental studies of biological activity and the possibility of their practical application as promising biologically active substances for the development of drugs for various purposes.

Materials and methods of research

IR spectra were taken on aspectrophotometer SPECORD M 80 (KBr pellets); ^{1}H NMR spectra were recorded on a spectrometer Varian VXR-300, (^{1}H chemical shifts are expressed in δ–ascale relative to tetramethylsilane, solvent–DMSO-D6, and the integral intensitiescorrespond to the attributions that were made); purity of the synthesized compounds were monitored by TLC and elemental analysis performed on standard microanalysis equipment.

For the obtained compounds, computer prediction of biological activity was performed using the program PASS-online, which is based on the analysis of the dependence "structure-activity" [21, 22].

The CLC-Pred method [23] based on a combination of QNA descriptors was used to model the predicted cytotoxicity.

2,5-bis- (4'-acetylaminobenzenesulphothioate) 3,6-dibromo-1,4-benzoquinone 5b.

To a solution of 0.5 g (0.001 mol) of bromanil in 60 ml of acetonitrile was gradually added at room temperature 1.19 g (0.004 mol) of sodium 4-acetylaminobenzene thiosulfonate. The reaction mass was heated to the boiling point of the solvent and kept for 7 hours. The precipitate was filtered off from the hot reaction mass and cooled, followed by isolation of the target product. The reaction was monitored by TLC.

IR (KBr, cm-1): 3336, 1634 (NH); 1684, 1648 (CO); 1602, 1588, 1576(C = C); 1332 γas,1144γs (SO_2); ^{1}H NMR (300 MHz, DMSO-d6): 2,23 (6H s, CH3), 7,38-8,18 (8H,m, Ar-H), 8,46 (2H, s, NH). mp: 101–102 °C; $C_{22}H_{16}Br_2N_2O_8S_4$ Calculated: C 36.46 H 2.20 N 3.86 S 17.67, Found: C 36.35, H 2.23, N 3.79, S 17.65. Yield 0,52g (62 %).

25-, bis- (4'-aminobenzenesulphothioate) 3,6-dibromo-1,4-benzoquinone 6b

To a solution of 0.5 g (0.001 mol) of bromanil in 60 ml of acetonitrile was gradually added at 20 °C. 0.99 g (0.004 mol) of sodium 4-aminobenzene thiosulfonate. The reaction mass was heated to the boiling point of the solvent and kept for 7 hours. The precipitate was filtered off from the hot reaction mass and cooled, followed by isolation of the product. The reaction was monitored by TLC.

IR (KBr, cm$^-$1): 3366, 3334 (NH2); 1682 (CO);1600, 1588, 1572(C = C); 1336 γas,1134γs (SO2); ^{1}H NMR (300 MHz, DMSO-d6): 6,32 (4H, s, NH2), 6,86 -7,84 (8H,m, Ar-H). mp: 141-142^{0}C; $C_{18}H_{12}Br_2N_2O_6S_4$ Calculated: C 33.75 H 1.87 N 4.37 S 20.00, Found: C 33.78, H 1.85, N 4.29, S 19.94. Yield 0,43g (58%).

2,5-bis- (4'-acetylaminobenzenesulphothioate) 3,6-dichloro-1,4-benzoquinone 5a

To a solution of 0.246 g (0.001 mol) of chloranil in 60 ml of acetonitrile was gradually added at room temperature 1.03 g (0.004 mol) of sodium 4-acetylaminobenzene thiosulfonate. The reaction mass was heated to the boiling point of the solvent and kept for 7 hours. The hot reaction mass was filtered off, the target product crystallized after cooling from the filtrate. The reaction was monitored by TLC.

IR (KBr, cm-1): 3346, 1638 (NH); 1686, 1646 (CO); 1600, 1584, 1572(C=C); 1328 γas,1140γs (SO_2); ^{1}H NMR (300 MHz, DMSO-d6): 2,29 (6H s, CH3), 7,28 -8,12 (8H,m, Ar-H), 8,36 (2H, s, NH). mp: 92-94 ^{0}C; $C_{22}H_{16}Cl_2N_2O_8S_4$ Calculated: C 41.57, H 2.52 , Cl 11.18, N 4.41, S 20.16, Found: C 41.47, H 2.50, Cl 11.18, N 3.69, S 20.09. Yield 0.54g (42%).

2,5-bis- (4'-aminobenzenesulphothioate) 3,6-dichloro-1,4-benzoquinone 6a

To a solution of 0.5 g (0.001 mol) of chloranil in 60 ml of acetonitrile was gradually added at 20 °C. 0.86 g (0.004 mol) of sodium 4-aminobenzene thiosulfonate. The reaction mass was heated to the boiling point of the solvent and kept for 7 hours. The precipitate was filtered off from the hot reaction mass and cooled, followed by isolation of the product. The reaction was monitored by TLC.

IR (KBr, cm-1): 3356, 3330 (NH_2); 1680 (CO);1604, 1590, 1548 (C=C); 1324 γas,1128γs (SO_2); ^{1}H NMR (300 MHz, DMSO-d6): 6,12 (4H, s, NH_2), 6,96 -7,88 (8H,m, Ar-H). mp: 128-130^{0}C; $C_{18}H_{12}Cl_2N_2O_6S_4$ Calculated: C 39.22, H 2.18, Cl 12.89, Cl 12.69, N 5.08, S 23.23, Found: C 39.18, H 2.09, N 4.98, S 23.15. Yield 0,42g (38%).

2,5-bis- (4'-aminobenzenesulphothioate) 3,6-dichloro-1,4-benzoquinone7

To 2.46 g (0.01 mol) of chloranil in 200 ml of ethyl alcohol was added a solution containing 2.06 g (0.02 mol) of 4-aminobutanoic acid, 2.24 g (0.04 mol) of potassium hydroxide in 100 ml of water. The reaction mixture was kept under stirring at 80 ° C for 1.5 hours. Cooled to 0 ° C and acidified with hydrochloric acid to pH = 5.0-6.0. Purple crystals were filtered.

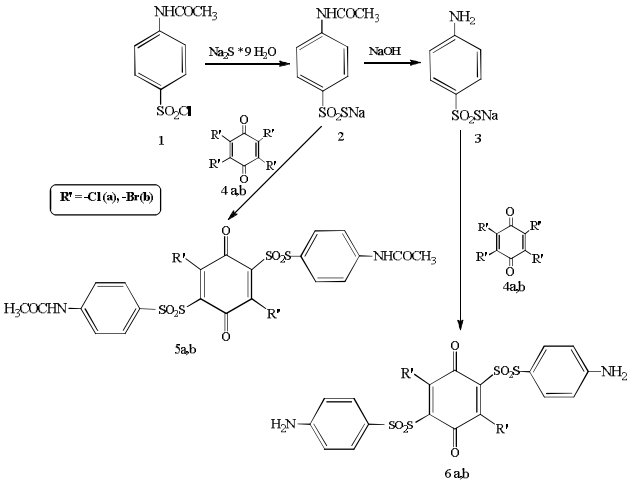
IR (KBr, cm^{-1}): 3340 (NH), 3036, 1720 (C = O,COOH), 1645 (C = O, quinoid.), 1625, 1608,1600 (C = C), 760 (C-Cl); ^{1}H NMR (300 MHz, DMSO-d6): 2.28-1.70 (m, 8H, CH2CH2), 2.32 (m,4H,CH2COOH), 4.02-3.86 (m, 4H,NCH2), 7.36 (s, 2H,NH). mp: 232 °C; $C_{14}H_{16}Cl_2N_2O_6$ Calculated: C 44.36 H 4.22 Cl 18.71, N 7.39 Found: C 44.51, H 3.98, Cl 19.02, N 7.05. Yield 2.58 g (68%).

Research results and their discussion

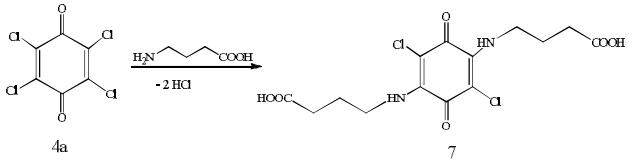
We investigated the interaction of halogen derivatives of 1,4-benzoquinone (bromo- and chloranyl) with salts of thiosulfonic acids and 4-aminobutanoic acid. Sodium-4-acetylaminobenzene and sodium 4-aminobenzene thiosulfonates are used as thiosulfonate reagents, as esters of these thiosulfonic acids are low-toxic compounds [24, 25].

The synthesized thiosulfoester derivatives with the benzoquinone moiety were obtained by nucleophilic substitution of halogen atoms of 2,3,5,6-tetrabromocyclohexa-2,5-diene1,4-dione (bromanyl, chloranyl) on the thiosulfonate fragment by the action of 4-acetylamino-, 4-acetylamino sodium solvents (methanol, propanol and acetonitrile) at different ratios of reagents at prolonged boiling according to the scheme of the following transformations:

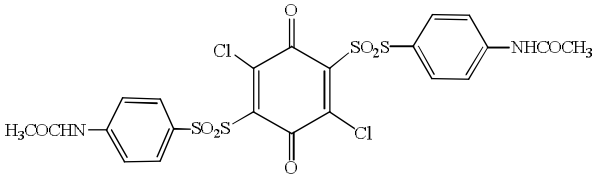
The best yields of the target products were obtained in acetonitrile with the formation of only from the products of disubstitution – 2,5-bisubstituted thiosulfonate derivatives of 3,6-dihalogen-1,4-benzoquinones **5 a.b, 6 a.b.**



2,3,5,6-Tetrachloro-1,4-benzoquinone (chloranyl) **4a** also reacts with 4-aminobutanoic acid, by nucleophilic substitution of chlorine atoms at positions 2 and 5 for amino acid residue according to the following scheme:



To determine the priority areas of experimental studies of the biological activity of our synthesized substances **5 a, b, 6 a, b, 7,** studies were conducted in the following areas: prediction by computer program PASS, prediction of cytotoxicity by program CLC-Pred. The results of computer screening of predicted biological activity according to the program *PASS – online* ***5a****:*



0,841 Cl-transporting ATPase inhibitor

0,684 Phospholipid-translocating ATPase inhibitor

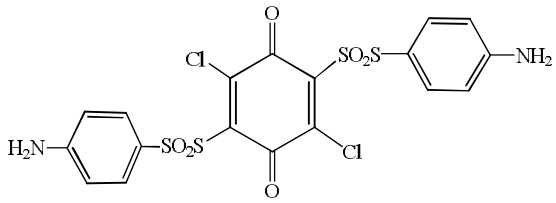
0,591–0,503 Ubiquinol-cytochrome-c reductase inhibitor, Thioredoxin inhibitor, Chloride peroxidase inhibitor, CYP3A1 substrate, IgA-specific serine endopeptidase inhibitor, N-acylmannosamine kinase inhibitor

Table 1

Cytotoxicity of compound 5a

Affected organ	Cancer cell line name / code	Pa	Pi
Breast	Carcinoma Breast MCF7	0.752	0.014

Results of computer screening of predicted biological activity according to the *PASS-online 6a* program:



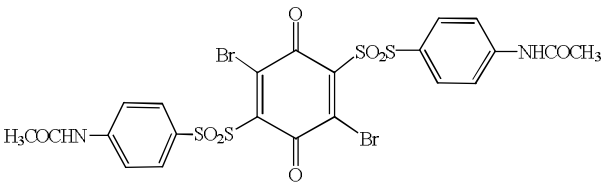
0,793 –0,751 NADPH peroxidase inhibitor, Phospholipid-translocating ATPase inhibitor; *0,694 -0,619* Glycosylphosphatidylinositol phospholipase D inhibitor, Myeloblastin inhibitor, Complement factor D inhibitor, Chloride peroxidase inhibitor, Cl--transporting ATPase inhibitor, Arylsulfate sulfotransferase inhibitor, Thioredoxin inhibitor, Phthalate 4,5-dioxygenase inhibitor, Glutamyl endopeptidase II inhibitor, Lysase inhibitor *0,597–0,511* Thiol oxidase inhibitor, Sulfite oxidase inhibitor, CDP-4-dehydro-6-deoxyglucose reductase inhibitor, Antiviral (Picornavirus), L-glutamate oxidase inhibitor, Linoleoyl-CoA desaturase inhibitor, Spermidine dehydrogenase inhibitor, Omptin inhibitor, CYP2J substrate, CYP3A1 substrate, Para amino benzoic acid antagonist, Cholestanetriol 26-monooxygenase inhibitor, CYP2J2 substrate, Platelet aggregation stimulant, Arylacetonitrilase inhibitor, 3-Hydroxybenzoate 6-monooxygenase inhibitor, 5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor, Alopecia treatment.

Table 2

Cytotoxicity of compound 6a

Affected organ	Cancer cell line name / code	Pa	Pi
Haematopoietic and lymphoid tissue	Adult immunoblastic lymphoma SR	0.582	0.011
Colon	Colon carcinoma/RCO	0.523	0.005
Breast	Carcinoma Breast MCF7	0.841	0.008

The results of computer screening of predicted biological activity by the program *PASS-online* ***5b*****:**



0,771 Aspulvinone dimethylallyltransferase inhibitor; *0,651 – 0,629* Thioredoxin inhibitor, NADPH peroxidase inhibitor, Phospholipid-translocating ATPase inhibitor; *0,590- 0,503* Prolyl aminopeptidase inhibitor; Feruloyl esterase inhibitor; Myeloblastin inhibitor; Glutamyl endopeptidase II inhibitor; Phosphatidylserine decarboxylase inhibitor; Linoleoyl-CoA desaturase inhibitor; Lysase inhibitor; Para amino benzoic acid antagonist; Alanine-tRNA ligase inhibitor; Cholestanetriol 26-monooxygenase inhibitor; Platelet aggregation stimulant; Arylacetonitrilase inhibitor; Alopecia treatment; Chloride peroxidase inhibitor; Omptin inhibitor; GST A substrate; Complement factor D inhibitor.

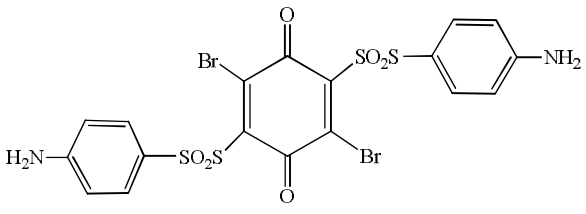
Table 3

Cytotoxicity of compound 5b

Affected organ	Cancer cell line name / code	Pa	Pi
Haematopoietic and lymphoid tissue	Adult immunoblastic lymphoma SR	0.981	0.002
Lung	Lung carcinoma A549	0.917	0.005
	Non-small cell lung carcinoma HOP-92	0.927	0.004
	Non-small cell lung carcinoma NCI-H522	0.930	0.003
Ovarium	Ovarian adeno-carcinoma /IGROV-1	0.736	0.005
Blood	Acute T-lymphoblastic leukemia MOLT-4	0.767	0.005
Skin	Melanoma/ SK-MEL-5	0.907	0.005
	Melanoma/ UACC-257	0,802	0.004
Colon	Colon adeno-carcinoma HCC 2998	0.799	0.004

Results of computer screening of predicted biological activity by *PASS-online* ***6b***

:



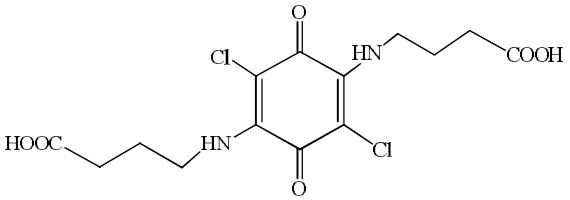
0,649–0,612 Aspulvinone dimethyl-allyltransferase inhibitor; Gluconate 2-dehydrogenase (acceptor) inhibitor; *0,577–0,511* Proteasome ATPase inhibitor; Mucomembranous protector, GST A substrate.

Table 4

Cytotoxicity of compound 6b

Affected organ	Cancer cell line name / code	Pa	Pi
Haematopoietic and lymphoid tissue	Adult immunoblastic lymphoma SR	0.991	0.001
Lung	Lung carcinoma A549	0.976	0.004
	Non-small cell lung carcinoma NCI-H522	0.957	0.002
	Non-small cell lung carcinoma/ HOP-92	0.959	0.003
Skin	Melanoma/ SK-MEL-5	0.942	0.003
	Melanoma/ UACC-257	0,838	
Colon	Colon adenocarcinoma/ HCC 2998	0.895	0,004
Ovarium	Ovarian adenocarcinoma/ IGROV-1	0.895	0.004
Blood	Acute T-lymphoblastic leukemia/ MOLT-4	0.856	0.004

Results of computer screening of predicted biological activity according to the *PASS-online 7* program:



0,908 – Phobic disorders treatment; *0,893–0,859* CYP2J2 substrate, CYP2J substrate,Gluconate 2-dehydrogenase (acceptor) inhibitor; *0,798–0,702* Acylcarnitine hydrolase inhibitor, Mucomembranous protector, Glycosylphosphatidylinositol phospholipase D inhibitor, Membrane permeability inhibitor, Phthalate 4,5-dioxygenase inhibitor, Fructose 5-dehydrogenase inhibitor, Mucositis treatment, 2-Hydroxyquinoline 8-monooxygenase inhibitor, Acrocylindropepsin inhibitor, Saccharopepsin inhibitor, Chymosin inhibitor, Chlordecone reductase inhibitor, NADPH peroxidase inhibitor, Methylamine-glutamate N-methyltransferase inhibitor, Arylsulfate sulfotransferase inhibitor, Exoribonuclease II inhibitor, 3-Phytase inhibitor, Arginine 2-monooxygenase inhibitor, GST A substrate, Beta-adrenergic receptor kinase inhibitor, G-protein-coupled receptor kinase inhibitor.

Table 5

Cytotoxicity of compound 7

Affected organ	Cancer cell line name / code	Pa	Pi
Haematopoietic and lymphoid tissue	Promyeloblast leukemia/ HL-60	0.516	0.025

Compound **7** obtained by us with a 90 % probability will show Phobic disorders treatment, and compound **5a** can act with 80 % probability Cl–transporting ATPase inhibitor. It would also be advisable to test Compound **5b** for Antiviral (Picornavirus).

When analyzing the results of the predicted cytotoxicity, it was found that all compounds were predicted to have activity against immunoblastic lymphoma of adult SR and non-small cell lung cancer cell line NCI-H522. According to the results of the CLC-Pred program, the widest range of cytotoxicity is found in compounds **5b, 6a, b,** which can be further tested for different lines of cancer cells of hematopoietic and lymphoid tissue, lungs, skin, ovaries, blood, breast, kidney, colon, main brain.

Conclusions

Methods of synthesis were developed and physicochemical characteristics of thiosulfonate and amino acid derivatives were studied: 2,5-bis (thiosulfonate)-3,6-halogen-1,4-benzoquinones and 2,5-bis(3-carboxypropylamino)-3,6-dichlorobenzoquinone.

Prospects for the design of chloro- and bromanyl thiosulfonate fragments and chloranyl fragment of 4-aminobutanoic acid are confirmed by the results of predicting biological activity **5 a, b, 6 a, b, 7** using the online resource *PASS Online*. In

particular, we obtained substance **6a** is promising in terms of research of Antiviral (Picornavirus).

The results of predicted cytotoxicity screening indicate the feasibility of conducting experimental in vitro studies on anticancer activity against cancer cells of hematopoietic and lymphoid tissue, lungs, skin, ovaries, blood, breast, kidney, colon, brain.

References

1. K. P. Medvedeva, A. O. Donchenko, S. O. Vasyuk. (2019). Zastosuvannya pohidnih hinonu dlya spektrofotometrichnogo viznachennya likars'kih zasobiv. *Aktual'ni pitannya farmacevtichnoi i medichnoi nauki ta praktiki*. T. 12, No3(31), 250–255 DOI: 10.14739/2409-2932.2019.3.184173 [Ukraine]

2. Donchenko A. O., Vasyuk S. O., Portna K. P. (2015). Vikoristannya 2,3-dihlor-1,4-naftohinonu dlya spektrofotometrichnogo viznachennya acetilcisteïnu v likars'kih preparatah. *Aktual'ni pitannya farmacevtichnoï i medichnoï nauki ta praktiki*. No 1. C. 36-39. **https://doi.org/10.14739/2409-2932.2015.1.41374** [Ukraine]

3. Rani M. E. (2014). Spectrophotometric determination of cefadroxil with 2,3 – dichloro-5,6 dicyano-1, 4-benzoquinone. *World Journal of Pharmaceutical Research*. Vol. 3. Issue 9. P. 1196-1200

4. Sheikh R., Amin A., Gouda A., Zahran D. (2017). Validated spectrophotometric methods for determination of cefdinir in pure and dosage forms through charge transfer complexation using alizarin derivatives. *International Journal of Research in Pharmacy and Pharmaceutical Sciences*. Vol. 2. Issue 6. P. 11-18

5. Ali Ahmed S., Elbashir A., Aboul-Enein H. (2015). New spectrophotometric method for determination of cephalosporins in pharmaceutical formulations. *Arabian Journal Of Chemistry*. Vol. 8. Issue 2. P. 233-239. doi: 10.1016/j.arabjc.2011.08.012

6. Kumari N. A., Vasundhara A. (2016). A noval method development for spectrophotometric determination of ertapenem in bulk and injection formulations by NQS. *International Journal of Science Technology and Management*. Vol. 5. Is. 1. P. 1–9.

7. Omar M., Hammad M., Eltoukhi W. (2017). Spectrophotometric Determination of Certain Antimigraine Drugs in Pharmaceutical Formulations Using p-Chloranil Reagent; *Application to Content Uniformity Testing. Analytical Chemistry Letters*. Vol. 7. Issue 5. P. 611–622.

8 Sotirova A, Avramova T, Stoitsova S, Lazarkevich I, Lubenets V, Karpenko E, Galabova D. (2012). The importance of rhamnolipid-biosurfactant-induced changes in bacterial membrane lipids of Bacillus subtilis for the antimicrobial activity of thiosulfonates. *Curr. Microbiol*. № 65(5): 534–541

9. E. Mochizuki, H. Nakazawa. (1995). Sulfur Components of Garlic and Garlic Preparations and their Biological Activities. Foods & Food Ingredients Journal of Japan. No. 164. P. 36–45.

10. M. J. Peinado, R. Ruiz, A. Echavarri, and L. A. Rubio. (2012). Garlic derivative propyl propane thiosulfonate is effective against broiler enteropathogens in vivo. *Poultry S*cience. Vol. 91. P. 2148–2157

11. A. Mital, V. S. Negi and U. Ramachandran. (2008). Synthesis and Biological Evaluation of Naphthalene-1,4-dione Derivatives as Potent Antimycobacterial Agents. *Medicinal Chemistry*. № 4, 492–497.

12. V. Dziuba, O. Kuchmenko. (2017). Suchasni uiavlennia pro rol ubikhinonu v protsesakh metabolizmu klityny. *Visnyk Lvivskoho universytetu. Seriia biolohichna*. V. 75. C. 3–13 [Ukraine]

13. Kolesnikov V. T. Vid L. V. Kuzmenko L. O. (1982**)**. 1-benzenesulfonylsulfany-l-4 nitrobenzene *Hurnal organicheskoy khimii* 18.2163. (in Russian).

14. L. Kuz'menko, A. Avdeenko, S. Konovalova, S. Vasylyuk, O. Fedorova, N. Monka, A. Krychkovska,V. Lubenets. (2019). Synthesis and study of pesticidal activity of some N-arylthio-1,4-benzoquinone imines. *Biointerface Research in Applied Chemistry*. Vol. 9, Is. 5, 4232–4238. **https://doi.org/10.33263/BRIAC95.232238**

15. Vasylyuk, S.; Komarovska-Porokhnyavets, O.; Novikov, V.; Lubenets, V. (2018). Modification of Alkyl Esters of 4- Aminobenzenethiosulfonic Acid by s-Triazine Fragment and Investigation of their Growth-Regulative Activity. *Chemistry and Chemical Technology* 12, 24, **https://doi.org/10.23939/chcht12.01.024**.

16. Lubenets, V.; Vasylyuk, S.; Monka, N.; Bolibrukh, K.; Komarovska-Porokhnyavets, O.; Baranovych, D.; Musyanovych, R.;. Zaczynska, E.; Czarny, A.; Nawrot, U.; Novikov, V. (2017). Synthesis and antimicrobial properties of 4-acylaminobenzenethiosulfoacid S-esters. *Saudi Pharmaceutical Journal* 25, 266, **https://doi.org/10.1016/j.jsps.2016.06.007**.

17. Núñez L. C., Arjona A.B., A.E. Guillamón, López A. V., Ma (2018). Concepción Navarro Moll, Ana Sanz Rus Use of propyl propane thiosulfinate and propyl propane thiosulfonate for the prevention and reduction of parasites in aquatic animals Patent No.: US 2018/0014538 A1, Date of Patent: Jan. 18,

18. Santos dos, Edson dos A. Goncalves F. Prado P.C. Sasaki D. Y. Lima D.P.; M. L. (2012). Rodrigues Synthesis method for thiosulfonate and report of its insecticidal activity in Anagasta kuehniella (Lepidoptera: Pyralidae) *International Journal of Molecular Sciences*. 13, 15241

19. Lubenets V. I., Havryliak V. V., Pylypets A. Z., Nakonechna A. V. (2018). Changes in the spectrum of proteins and phospholipids in tissues of rats exposed to thiosulfanilates. *Regulatory mechanisms in biosystems* 9,4,52

20. Pylypets A. Z., Iskra R. Ya, Havryliak V. V, Nakonechna A. V, Novikov V. P, Lubenets V. I. (2017). Effects of thiosulfonates on the lipid composition of rat tissues. *Ukr. Biochem J.* 89,6,56.

21. T. A. Gloriozova, D. A. Filimonov, A. A. Lagunin, V. V. Poroykov (1998) Testirovaniye komp'yuternoy sistemy dlya predskazaniya biologicheskoy aktivnosti PASS na vyborke novykh khimicheskikh soyedineniy. *Khim.-farm. zhurnal*. 32(12), 32–39. [in Russian]

22. A. Lagunin, A. Stepanchikova, D. Filimonov, V. Poroikov (2000). PASS: prediction of activity spectra for biologically active substances. *Bioinformatics*. 16 (8), 747–748.

23. Lagunin A. A., Dubovskaja V. I., Rudik A. V., Pogodin P. V., Druzhilovskiy D. S., Gloriozova T. A., Filimonov D. A., Sastry G. N., Poroikov V. V. (**2018**). CLC-Pred: a freely available web-service for in silico prediction of human cell line cytotoxicity for drug-like compounds. *PLOS One*, 13 (1), e0191838. DOI: 10.1371/journal.pone.0191838

24. Pylypets A. Z., Iskra R. Y., Havryliak V. V., Nakonechna A. V., Novikov V. P. Lubenets, V., (2017). Effects of thiosulfonates on the lipid composition of rat tissues. *Ukr. Biochem. J.,* Vol. 89, № 6, 56–62 doi: **https://doi.org/10.15407/ubj89.06.056**

25 Oriabinska L. B., Starovoitova S. O., Vasylyuk S. V., Novikov V. P. (2017). Ethylthiosulfanilate effect on Candida tropicalis. *Ukr. Biochem. J.,* Vol. 89, № 5 70–76 doi: **https://doi.org/10.15407/ubj89.05.070**

Н. Я. Монька, Л. Р. Журахівська, М. С. Курка, Г. Б. Шиян, Ю. М. Семенчук, В. І. Лубенець
Національний університет «Львівська політехніка»,
кафедра технології біологічно активних сполук, фармації та біотехнології
vlubenets@gmail.com

СИНТЕЗ ТІОСУЛЬФОНАТНИХ ТА АМІНОКИСЛОТНИХ ПОХІДНИХ БЕНЗОХІНОНУ ТА ПРОГНОЗОВАНИЙ СКРИНІНГ ЇХ БІОЛОГІЧНОЇ АКТИВНОСТІ

Похідні хіноїдного ряду приваблюють, не лише як цікаві синтони для синтезу, а також як потенційні біологічно активні речовини, тому актуальним є модифікація сполук хінонового ряду різними фармакоформними фрагментами. Проведено структурний дизайн хлор- та броманілу дисульфуровмісними фрагментами, а саме тіосульфонатними, та хлоранілу – фрагментом 4-амінобутанової кислоти. Розроблено методики синтезу та досліджено фізико-хімічні характеристики тіосульфонатних та амінокислотних похідних: 2,5-біс(тіосульфонатних)-3,6-галоген-1,4-бензохінонів та 2,5-біс(3-карбоксипропіламіно)-3,6-дихлорбензохінону. Перспективність дизайну хлор- та броманілу тіосульфонатними фрагментами та хлоранілу фрагментом 4-амінобутанової кислоти підтверджена результатами прогнозування біологічної активності 5 a, b, 6 a, b, 7 з використанням онлайн-ресурсу PASS Online. Зокрема субстанція 5b, яку одержали, є перспективною для досліджень на Antiviral (Picornavirus). Одержані результати прогнозованого скринінгу цитотоксичності свідчать про доцільність проведення експериментальних досліджень методами in vitro на протиракові активності стосовно лінії ракових клітин гематопоїдної і лімфоїдної тканини, легень, шкіри, яєчників, крові, молочної залози, нирок, товстої кишки, головного мозку.

Ключові слова: бензохінон, хлораніл, броманіл, тіосульфонат, прогнозована активність, цитотоксичніть.