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Monka N. Ya., Stadnytska N. Ye., Buchkevych I. R., Kaplia K. O.,
Shiyan H. B., Lubenets V. I.
Lviv Polytechnic National University, Department of Technology of Biologically Active Compounds, Pharmacy and Biotechnology
vlubenets@gmail.com

IDENTIFICATION OF PROMISING OBJECTS FOR THE SYNTHESIS OF THIOSULPHONATE DERIVATIVES OF BENZOQUINONE AND HYDROQUINONE

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Benzoquinone and its reduced form hydroquinone belong to phenolic compounds and are found in living organisms in free form or in glycosides. They are active substances of some medicinal plants and have a pharmacological effect on the human body. Accordingly, their derivatives are important objects for chemical synthesis and development of new drugs. This article presents the findings of the structural design of substances with benzoquinone or hydroquinone fragment and sulfur-containing compound. By use of appropriate on-line programs a predictive screening of the biological activity and cytotoxicity of thiosulfonate derivatives of benzoquinone and hydroquinone has been conducted. It has been found that they have immense methodological potential to be synthesized by substances with a wide range of biological activities and a high value of probable activity, which substantiates the feasibility of conducting experimental studies on their biological activity, particularly anticancer.

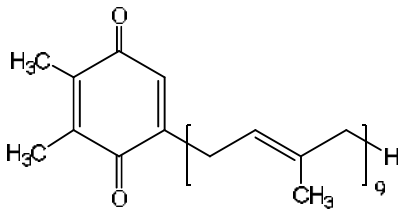
Key words: benzoquinone, hydroquinone, thiosulfonic acid esters, structural design, predictive activity, cytotoxicity.

Introduction

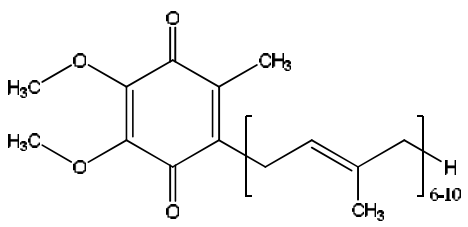
Quinones are quite common in nature and are characterized by great structural diversity. Quite often they are present in natural sources in extremely small concentrations.They are found mainly in higher plants, lichens, fungi, bacteria and some green algae. Many natural quinones have medicinal properties and are active compounds of medicinal plant raw materials. Having diverse pharmacological effects on the human body, they are used in phytopreparations and the mechanism of their action is constantly under study. All quinones are mainly divided into benzoquinones, naphthoquinones and anthraquinones.

Benzoquinones were isolated mainly from fungi and various tissues of higher plants. There are about 100 of them and almost all of them are derivatives of 1,4-benzoquinone. Benzoquinones include such biologically important molecules as plastoquinone and ubiquinone. The most common are ubiquinone-9 and ubiquinone-10 with 9 and 10 isoprene fragments.

Scheme 1

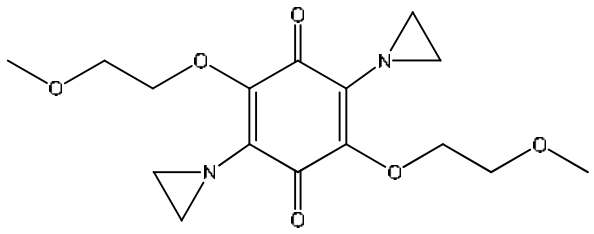


plastoquinone



ubiquinone

Benzoquinones induce a wide range of effects from vital for homeostasis to the most cytotoxic or carcinogenic. For example, ubiquinone (coenzyme Q 10), which is synthesized in the body from the precursors of phenylalanine or tyrosine, and is an electron carrier in mitochondrial respiration.



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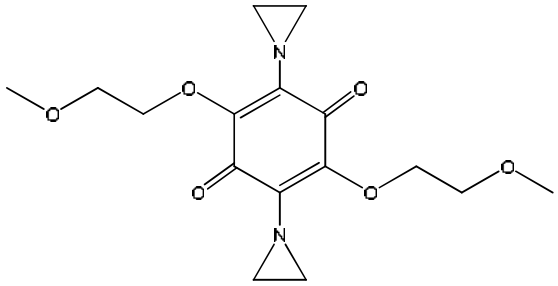
It should be noted that the results of research on1,4-benzoquinone derivatives [1] highlight the prospects of studying their properties in order to create new effective regulators of enzyme activity. Being a prooxidant, a strong antioxidant, a regulator of genetic expression and signal transduction, ubiquinone is able to affect the activity of a large number of enzymes that function in cells [1]. Influencing a large number of genes with various functions, ubiquinone acts as a promising regulator of cellular processes [2, 3]. It is common knowledge that 1,4-quinone derivatives are the basis of some coenzymes [4], drugs such as ubiquinon, ubidacarenon, neoquinone and therefore their synthesis is relevant. They also draw particular attention due to their antihypoxic and anti-ischemic properties.

Another group of natural substances that have a pronounced therapeutic effect are sulfur-containing substances belonging to different classes. Organic sulfur-containing compounds show cardiovascular, antitumor, antiplatelet, hepatoprotective, antioxidant, anticancer, antimicrobial, antiproliferative, lipid-lowering activity [5].One of the well-studied sulfur-containing compounds is allicin, which is considered to be the main active ingredient in *Allium sativum* bulbs, as well as diallyl disulfide. Dialyldisulfide is another valuable sulfur-containing organic substance produced by garlic and extensively used to prevent several types of cancer due to its ability to significantly increase human immunity. It is common knowledge that natural polysulfonates have antimicrobial, anticancer and chemoprophylactic effects. Synthetic analogues of these substances are esters of thiosulfonic acids, which

Interestingly, there are a number of compounds among the benzoquinone derivatives that exhibit high antimicrobial activity and a wide range of biological activities. Thus, some ethyleneimino derivatives of benzoquinone (Bayer E-39, Bayer A-139) have been used as antitumor substances.



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are unfortunately unstable compounds in contrast to stable S-esters of thiosulfonic acids [25]. The latter are commonly known for a wide range of biological activities and are recommended to be used as biologically active substances with antimicrobial, antitumor, antithrombotic effects for medicine, as biocides in various sectors of the national economy, in particular for agricultural production not only as fungicides but also as plant regulators [6–21].

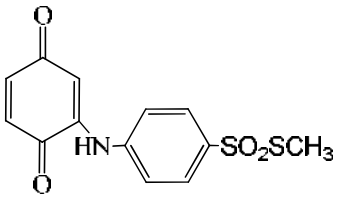
The objective of our research is to establish the predictive structure-activity relationship for thiosulfonate derivatives of benzoquinone and hydroquinone, to determine the priority areas of experimental research on the synthesis of new thiosulfonates, and to study their biological activity as well as the possibility of their practical application as promising biologically active substances.

Materials and Methods

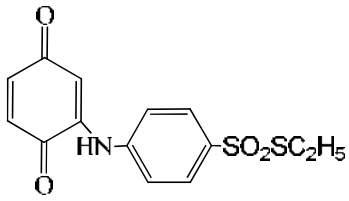
Thiosulfoester esters have been synthesized with benzo-1a-d and hydroquinone 2 a-f fragments and selected as research objects.

For the given compounds, computer prediction of biological activity was performed using the program PASS-online, which is based on the analysis of the “structure-activity” relationship [22, 23].

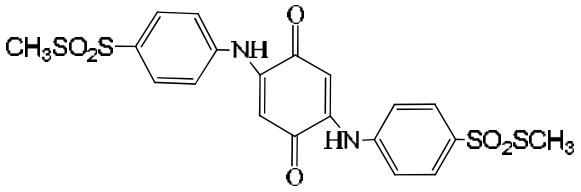
The average accuracy of the PASS program is about 85 %, which is sufficient to conclude about the biological activity of the newly synthesized substances. The predicted results inform about the available list of probable types of activity and calculated estimates of the presence (Pa) and absence (Pi) of each of the activities.



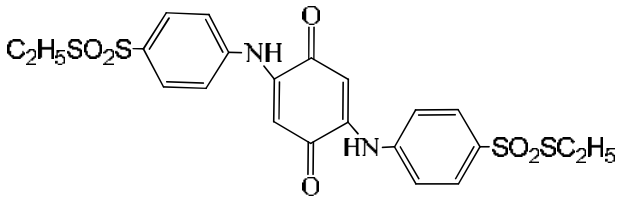
1a *S*-methyl **4**-((3,6-dioxocyclohexa-1,**4**-dien-1-yl)amino)benzenesulfonothioate



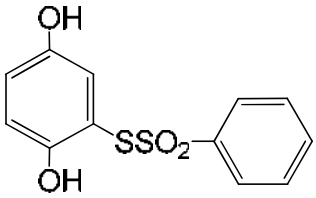
1b *S*-ethyl **4**-((3,6-dioxocyclohexa-1,**4**-dien-1-yl)amino) benzenesulfonothioate



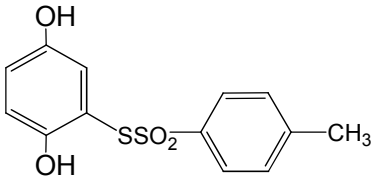
1c *S,S*'-dimethyl **4,4'**-((3,6-dioxocyclohexa-1,4-diene-1,4-diyl)bis(azanediyl))dibenzenesulfonothioate



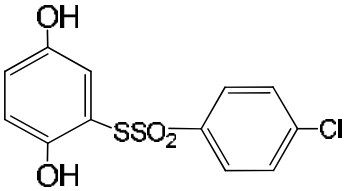
1d *S,S*'-ethyl **4,4'**-((3,6-dioxocyclohexa-1,**4**-diene-1,**4**-diyl)bis(azanediyl))dibenzenesulfonothioate



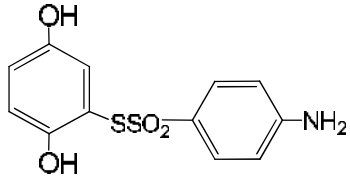
2a *S*-(2,5-dihydroxyphenyl) benzenesulfonothioate



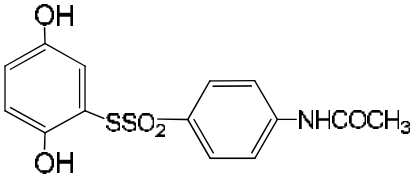
2b *S*-(2,5-dihydroxyphenyl) 4-methylbenzenesulfonothioate



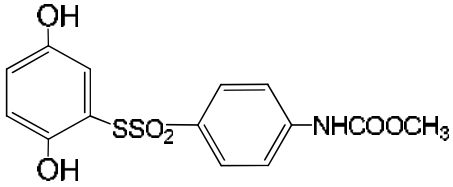
2c *S*-(2,5-dihydroxyphenyl) **4**-chlorobenzenesulfonothioate



2 d *S*-(2,5-dihydroxyphenyl) **4**-aminobenzenesulfonothioate



2e *S*-(2,5-dihydroxyphenyl) 4-acetamidobenzenesulfonothioate



2 f *S*-(2,5-dihydroxyphenyl) **4**-((methoxycarbonyl)amino)-benzenesulfonothioate

Advanced screening of biological activity can identify areas for further experimental biological studies of synthetic compounds which will be time and cost effective.

The CLC-Pred method [24] based on a combination of QNA descriptors was used for modelling of rat acute toxicity to the studied compounds.

Results and Discussion

To determine the priority areas of experimental studies of the biological activity of thiosulfoester esters with benzo-1a-d and hydroquinone 2 a-f fragments, 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 predictive biological activity according to the *PASS-online* program of thiosulfoesters with benzoquinone fragment:

S-methyl 4-((3,6-dioxocyclohexa-1,4-dien-1-yl)amino)benzenesulfonothioate 1a Aldehyde oxidase inhibitor *(Pa = 0.770);* Anaphylatoxin receptor antagonist (*Pa = 0.706);* Thioredoxin inhibitor *(Pa = 0.662)*; Para amino benzoic acid antagonist *(Pa = 0.601);* Chemopreventive; 3-Hydroxybenzoate 6-monooxygenase inhibitor *(Pa = 0.548–0.563)*.

S-ethyl 4-((3,6-dioxocyclohexa-1,4-dien-1-yl)amino) benzenesulfonothioate 1b Aldehyde oxidase inhibitor (Pa = 0.703); 3-Hydroxybenzoate 6-monooxygenase inhibitor, Para amino benzoic acid antagonist (Pa = 0.624-0,641); Chemopreventive (Pa = 0.590); Phospholipid-translocating ATPase inhibitor (Pa = 0.564).

S,S'-dimethyl 4,4'-((3,6-dioxocyclohexa-1,4-diene-1,4 diyl)bis(azanediyl))dibenzene sulfonothioate 1c Aldehyde oxidase inhibitor (Pa = = 0.738); Thioredoxin inhibitor (Pa = 0.694); Anaphylatoxin receptor antagonist (Pa = 0.670); 3-Hydroxybenzoate 6-monooxygenase inhibitor (Pa = 0.521).

S,S'-diethyl 4,4'-((3,6-dioxocyclohexa-1,4-diene-1,4-diyl)bis(azanediyl))dibenzene-sulfonothioate 1d Aldehyde oxidase inhibitor (Pa = 0.672); Thioredoxin inhibitor (Pa = 0.653); 3-Hydroxybenzoate 6-monooxygenase inhibitor (Pa = 0.612); Phospholipid-translocating ATPase inhibitor (Pa = = 0.546).

Given the obtained data, the compound leader – 1a – with the widest spectrum of action was isolated.

For the synthesized thiosulfoester esters with the benzoquinone moiety, general inhibitory activity was observed against Aldehyde oxidase Thioredoxin, 3-Hydroxybenzoate 6-monooxygenase Chemopreventive activity is also predicted for compounds 1a and 1b.

Results of computer screening of predicted biological activity according to the PASS-online program of thiosulfoesters with hydroquinone fragment:

S-(2,5-dihydroxyphenyl) benzenesulfonothioate 2a Aspulvinone dimethylallyltransferase inhibitor; Arylacetonitrilase inhibitor; Thioredoxin inhibitor (Pa = 0.802–0.895); Arylsulfate sulfotransferase inhibitor; Feruloyl esterase inhibitor; Antiseborrheic; NADPH peroxidase inhibitor; Glutamyl endopeptidase II inhibitor; Dehydro-L-gulonate decarboxylase inhibitor;Glucan endo-1,6-beta-glucosidase inhibitor; Glycosylphosphatidylinositol phospholipase; D inhibitor (Pa = 0.734–0.799);

S-(2,5-dihydroxyphenyl) 4-methyl-benzenesulfono-thioate 2b Aspulvinone dimethylallyltransferase inhibitor; Arylsulfate sulfotransferase inhibitor; Glutamyl endopeptidase II inhibitor; Antiseborrheic (Pa = 0.818–0.855); Arylacetonitrilase inhibitor; CYP2C12 substrate; Feruloyl esterase inhibitor; Chlordecone reductase inhibitor (Pa = 0.706–0.753).

S-(2,5-dihydroxyphenyl) 4-chlorobenzenesulfono-thioate 2c Antiseborrheic; Chlordecone reductase inhibitor; Arylsulfate sulfotransferase inhibitor; Glycosylphosphatidylinositol phospholipase; D inhibitor; Aspulvinone dimethylallyltransferase inhibitor (Pa = 0.808–0.829); NADPH peroxidase inhibitor: 2-Hydroxyquinoline 8-monooxygenase inhibitor; Aldehyde oxidase inhibitor (Pa = 0.702–0.780).

S-(2,5-dihydroxyphenyl) 4-aminobenzenesulfono-thioate 2d Arylacetonitrilase inhibitor (Pa = 0.870); NADPH peroxidase inhibitor; Aspulvinone dimethylallyltransferase inhibitor; Linoleoyl-CoA desaturase inhibitor; Peroxidase inhibitor (Pa = 0.700–0.755); Linoleate diol synthase inhibitor; Thioredoxin inhibitor; Para amino benzoic acid antagonist; Membrane permeability inhibitor (Pa = 0.618–0.675); Antiseborrheic (Pa = 0.595).

S-(2,5-dihydroxyphenyl) 4-acetamidobenzene-sulfonothioate 2e Cl--transporting ATPase inhibitor; Aspulvinone dimethylallyltransferase inhibitor (Pa = 0.610–0.697); Thioredoxin inhibitor; N-acylmannosamine kinase inhibitor; Aminobutyraldehyde dehydrogenase inhibitor; Arylacetonitrilase inhibitor; Phospholipid-translocating ATPase inhibitor; Membrane integrity agonist (Pa = 0.525–0.588).

S-(2,5-dihydroxyphenyl) 4-((methoxycarbonyl) amino)-benzenesulfonothioate 2f/ Membrane permeability inhibitor; Antihelmintic (Nematodes) (Pa = 0.631–0.682); Aspulvinone dimethylallyl transferase inhibitor (Pa = 0.599).

All synthesized thiosulfoester esters with a hydroquinone moiety are characterized by inhibitory activity against the Aspulvinone dimethyl-allyltransferase inhibitor. Esters 2 a, b, d, e are quite likely to act as inhibitors of Arylacetonitrilase, and for compounds **2a: – d** antiseborrheic activity is predicted, and for compound **2f –** anthelmintic action.

We also predicted the probable cytotoxic effect on the corresponding to each organ-specific cancer cell lines using the web resource *Cell Line Cytotoxicity Predictor* (CLC-Pred) (таble).

Computer screening results predicted biological activity according to PASS-online

		1a		1b		1c		1d		2a		2b		2c		2d		2e		2f	
Affected organ	Cancer cell line name / code	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
Haemato poietic and lymphoid tissue	Adult immunoblastic lymphoma SR	0.991	0.001	0.991	0.001	0.993	0.001	0.992	0.001	0.995	0.001	0.991	0.001	0.992	0.001	0.991	0.001	0.981	0.002	0.973	0.002
Lung	Lung carcinoma A549	0.995	0.004	0.982	0.004	0.995	0.004	0.985	0.004	0.996	0.003	0.992	0.004	0.994	0.004	0.986	0.004	0.952	0.005	0.973	0.004
	Non-small cell lung carcinoma HOP-92,	0.961	0.003	0.960	0.003	0.969	0.003	0.967	0.003	0.976	0.002	0.961	0.003	0.970	0.002	0.960	0.003	0.931	0.004	0.898	0.004
	Non-small cell lung carcinoma NCI-H522	0.959	0.002	0.957	0.002	0.965	0.002	0.963	0.002	0.967	0.002	0.950	0.003	0.957	0.002	0.948	0.003	0.906	0.003	0.898	0.003
Ovarium	Ovarian adenocarcinoma /IGROV-1	0.871	0.004	0.871	0.004	0.901	0.004	0.899	0.004	0.940	0.003	0.899	0.004	0.914	0.003	0.898	0.004	0.803	0.004	0.697	0.005
Blood	Acute T-lymphoblastic leukemia MOLT-4	0.860	0.004	–	–	–	–	–	–	0.919	0.004	–	–	–	–	0.899	0.004	–	–	–	–
Skin	Melanoma/ IGROV-1	–	–	0.940	0.003	–	–	–	–	–	–	–	–	–	–	–	–	0.914	0.003	0.891	0.004
	Melanoma/ UACC-257	–	–	0.847	0.004	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Melanoma/ SK-MEL-5	–	–	–	–	0.960	0.003	0.956	0.003	0.976	0.002	0.955	0.003	0.965	0.003	0.948	0.003	–	–	–	–
Colon	Colon adenocarcinoma/HCC 2998	–	–	0.873	0.004	–	–	–	–	0.909	0.004	–	–	–	–	–	–	–	–	–	–
Breast	Breast carcinoma/ MCF7	–	–	–	–	–	–	–	–	0.947	0.004	–	–	–	–	–	–	0.806	0.010	0.796	0.011

The studied thiosulfonate esters with benzo- and hydroquinone fragments have proved able to inhibit Aldehyde oxidase Thioredoxin, 3-Hydroxybenzoate 6-monooxygenase and Aspulvinone dimethylallyltransferase inhibitor. Compounds **1a** and **1b** can be tested as substances with Chemopreventive action, and **2a-d** as substances with antiseborrheic activity and compound **2f** as substance with anthelmintic action.

Analysis of the predictive cytotoxicity results revealed that all compounds were predicted to have cytotoxic activity against various cancers of Haematopoietic and lymphoid tissue (Adult immunoblastic lymphoma SR), Lung (Lung carcinoma A549, Non-small cell lung carcinoma HOP-92, Non-small cell lung carcinoma NCI-H522), Ovarium (Ovarian adenocarcinoma / IGROV-1), as well as frequent effects on Blood, Skin, Colon, Breast.

Conclusions

The obtained results regarding the spectrum of the predictive activity testify to the expediency of developing methods for the synthesis of selected thiosulfonate derivatives of benzoquinone and hydroquinone and conducting experimental studies of their biological activity.

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Н. Я. Монька, Н. Є. Стадницька, І. Р. Бучкевич, К. О. Капля, Г. Б. Шиян, В. І. Лубенець
Національний університет "Львівська політехніка",
кафедра технології біологічно активних сполук, фармації та біотехнології
vlubenets@gmail.com

ІДЕНТИФІКАЦІЯ ОБЄКТІВ ДЛЯ СИНТЕЗУ ТІОСУЛЬФОНАТНИХ ПОХІДНИХ БЕНЗОХІНОНУ І ГІДРОХІНОНУ

Бензохінон та його відновлена форма гідрохінон належать до фенольних сполук і містяться у живих організмах у вільній формі або у глікозидах. Вони є активними речовинами деяких лікарських рослин і мають фармакологічну дію на організм людини. Відповідно, їх похідні є важливими об'єктами для хімічного синтезу та розроблення нових лікарських засобів. Наведено результати структурної конструкції речовин з фрагментом бензохінону або гідрохінону та сполукою, що містить сірку. За допомогою відповідних онлайн-програм проведено прогнозований скринінг біологічної активності та цитотоксичності похідних тіосульфонатів бензохінону та гідрохінону. Виявлено, що вони мають величезний потенціал для синтезу речовин з широким спектром біологічної активності та високим значенням ймовірної активності, що обґрунтовує можливість проведення експериментальних досліджень щодо їхньої біологічної активності, зокрема протиракових.

Ключові слова: бензохінон, гідрохінон, естери тіосульфокислот, структурна конструкція, прогнозована активність, цитотоксичність.