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Стаття надійшла до редакції
25.01.2023

UDC 615.015:616.62-008.22-085.254.1 https://doi.org/10.26641/2307-0404.2023.2.283152

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N-ARYLSULFONYL-2-AROYLAMINO-1,4-QUINONE IMINES AND THEIR HYDROGENATED ANALOGUES: PREDICTION OF TOXICITY AND PROSPECTS FOR USE AS DIURETICS

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Цитування: Медичні перспективи. 2023. Т. 28, № 2. С. 20-28
Cited: Medicni perspektivi. 2023;28(2):20-28

Key words: *N-arylsulfonyl-2-aroylamino-1,4-quinone imines, prediction of toxicitiy, influence on excretory function of kidneys, free-radical scavenging, antibacterial activity*
Ключові слова: *N-арилсульфоніл-2-ароїламіно-1,4-хініміни, прогноз токсичності, вплив на видільну функцію нирок, поглинання вільних радикалів, антибактеріальна активність*

Abstract. *N*-arylsulfonyl-2-aroylamino-1,4-quinone imines and their hydrogenated analogues: prediction of toxicity and prospects for use as diuretics. Sokolova K.V., Podpletnia O.A., Konovalova S.O., Avdeenko A.P., Komarovska-Porokhnyavets O.Z., Lubenets V.I., Kovalenko S.I. *Continuing our research on compounds that affect urination, we have become interested in N-arylsulfonyl-2-aroylamino-1,4-quinone imines, which combine a quinone matrix with tolylsulfonamide and benzamide fragments with versatile biological activity in their structure, which has a promising value in preventing development of pathological processes in kidneys. Therefore, the search for low-toxic compounds with polyvector activity as a promising approach to the design of drug-like molecules has become an urgent aspect in this regard. The aim of this work was to investigate N-arylsulfonyl-2-aroylamino-1,4-quinone imines and their hydrogenated analogues as promising diuretic agents with antiradical and antibacterial activity using in silico, in vitro and in vivo methodologies. The virtual laboratory of the ProTox-II site is used to predict the toxicity of molecules. The study of compounds affecting the excretory function of the rat kidneys was carried out on 120 white Wistar rats according to the method of E.B. Berkhin under conditions of water stress and spontaneous urination. The interaction of the synthesised compounds with 2,2-diphenyl-1-picrylhydrazyl (DPPH) was used to study their antiradical activity in vitro. The antibacterial activity of the compounds was studied on test cultures of the bacteria Escherichia coli, Staphylococcus aureus, Mycobacterium luteum and the fungi Candida tenuis, Aspergillus niger by the method of serial dilutions in a liquid nutrient medium. Based on the results of the calculation, it was predicted that N-arylsulfonyl-2-aroylamino-1,4-quinone imines (2) and their hydrogenated analogues (3) have hepato-(immuno-, cyto-) toxicity, carcinogenicity (mutagenicity) similar to natural quinones and diuretics (toxicity class IV). This class of compounds has been shown to have both stimulatory and inhibitory effects on diuresis under conditions of water stress and spontaneous urination. At the same time, N-(5-methyl-6-oxo-3-(tosylimino)cyclohexa-1,4-dien-1-yl)benzamide (2.3) was revealed to increase daily diuresis by 67.1% compared with the control, exceeding the effect of «Furosemide» (22.2%). It was found that quinone imines (2.1-2.5) inhibited the formation of the DPPH radical by 25.99-40.09%, while their hydrogenated analogues (3.1 and 3.2) – by 61.56% and 68.28%, respectively, and are more effective acceptors of radicals. The microbiological screening revealed a number of promising compounds that inhibited the growth of S. aureus (compound 2.5, MIC 62.5 μg/ml, MBC 125.0 μg/ml), M. luteum (3.1 and 3.2, MIC 31.2 μg/ml, MBC 62.5 μg/ml) and A. niger (2.1, 2.4 and 3.2, MIC 31.2 μg/ml, MPC 62.5 μg/ml). According to the results of biological studies, among N-arylsulfonyl-2-aroylamino-1,4-quinone imines and their hydrogenated analogues, compound 2.3 has been identified, which competes with «Furosemide» in potency and has high antibacterial activity against S. aureus. Other compounds show moderate antiradical activity, high antibacterial activity against M. luteum (2.1, 3.1) and antifungal activity against A. niger (2.1, 2.4, 3.2). The obtained results support the further research for diuretics with polyvector activity within this class of compounds.*

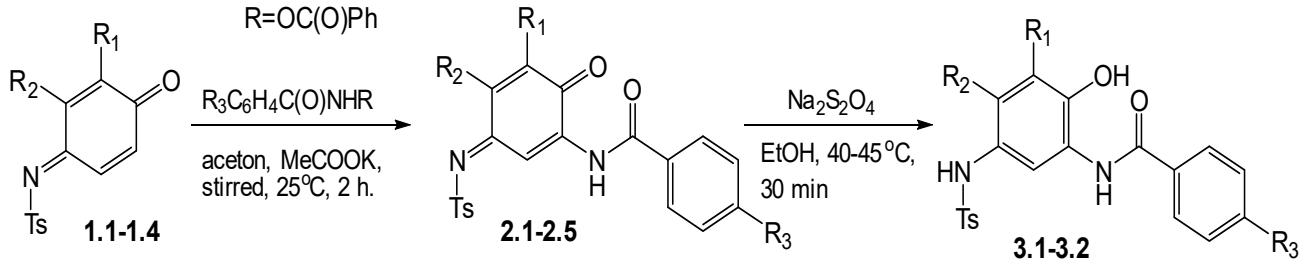
Реферат. *N*-арилсульфоніл-2-ароїламіно-1,4-хініноміни та їх гідровані аналоги: прогноз токсичності та перспективи використання як сечогінних засобів. Соколова К.В., Подплетня О.А., Коновалова С.О., Авдєєнко А.П., Комаровська-Порохнявець О.З., Лубенець В.І., Коваленко С.І. *Продовжуючи дослідження з пошуку сполук, що впливають на сечовиділення, ми зацікавились N-арилсульфоніл-2-ароїламіно-1,4-хініномінами, що поєднують у своїй структурі хінонову матрицю з толілсуфоніламідними та бензамідними фрагментами з різносторонньою біологічною активністю, що має перспективне значення в попередженні розвитку патологічних процесів у нирках. Тому актуальним аспектом цього напрямку став пошук малотоксичних сполук з полівекторною дією як багатообіцяючий підхід до дизайну лікоподібних молекул. Метою цієї роботи стало дослідження N-арилсульфоніл-2-ароїламіно-1,4-хініномінів та їх гідрованих аналогів як перспективних сечогінних агентів з антирадикальною та антибактеріальною дією з використанням методологій in silico, in vitro та in vivo. Віртуальна лабораторія сайту ProTox-II використана для прогнозування токсичності молекул. Дослідження сполук, що впливали на видільну функцію нирок щурів, проводили на 120 білих щурах лінії «Wistar» за методикою Е.Б. Берхіна в умовах водного навантаження та спонтанного сечовиділення. Дослідження антирадикальної активності in vitro ґрунтувалося на взаємодії синтезованих сполук з 2,2-дифеніл-1-пікрилгідразилом (DPPH). Антибактеріальну активність сполук вивчали на тест-культурах бактерій Escherichia coli, Staphylococcus aureus, Mycobacterium luteum та грибів Candida tenuis, Aspergillus niger методом серійних розведень на рідкому поживному середовищі. За результатами розрахункової оцінки спрогнозовано, що N-арил–сульфоніл-2-ароїламіно-1,4-хініноміни (2) та їх гідровані аналоги (3) мають подібну гепато-(імуно-, цито-)токсичність, канцеро-(мута-) генність до природних хінонів та сечогінних засобів (IV клас токсичності). Установлено, що цей клас сполук чинить як стимулюючу, так і пригнічувальну дію на діурез в умовах водного навантаження та спонтанного сечовиділення. При цьому виявлено N-(5-methyl-6-oxo-3-(tosylimino)cyclohexa-1,4-dien-1-yl)benzamide (2.3), який підвищував добовий діурез на 67,1% порівняно з контролем, перевищуючи ефект «Фуросемід» (22,2%). Виявлено, що хініноміни (2.1-2.5) пригнічують утворення DPPH-радикалу на 25,99-40,09%, тоді як їх гідровані аналоги (3.1 та 3.2) на 61,56% та 68,28%, і є більш ефективними акцепторами радикалів. Проведений мікробіологічний скринінг виявив ряд перспективних сполук, які пригнічують ріст S. aureus (сполука 2.5, МІК 62,5 мкг/мл, МБК 125,0 мкг/мл), M. luteum (3.1 та 3.2, МІК 31,2 мкг/мл, МБК 62,5 мкг/мл) та A. niger (2.1, 2.4 та 3.2, МІК 31,2 мкг/мл, МФК 62,5 мкг/мл). За результатами біологічних досліджень серед N-арилсульфоніл-2-ароїламіно-1,4-хініномінів та їх гідрованих аналогів ідентифіковано сполуку 2.3, яка конкурує за силою дії з «Фуросемід» та має високу антибактеріальну активністю до S. aureus. Інші сполуки проявляють помірну антирадикальну активність, високу антибактеріальну активність до M. luteum (2.1, 3.1) та протигрибкову відносно A. niger (2.1, 2.4, 3.2). Отримані результати обґрунтовують подальший пошук діуретиків з полівекторною дією серед цього класу сполук.*

Natural and synthetic quinones are an original group of organic compounds with antifungal, antibacterial, antiviral, anticancer, antioxidant, anti-inflammatory, laxative, antiallergenic and other types of activity that have found application in traditional and alternative medicine [1, 2, 3]. The main features of the chemistry of quinones, particularly their ability to participate in reversible redox reactions, electrophilic nature (Michael acceptors) and the potential affinity of binding to various groups of cell receptors, which is important in preventing key mechanisms of the development of pathological processes in the kidneys, have been and are being studied in order to find out their biological activity and influence on the level of toxicity [4, 5, 6]. These properties are used in the rational design of this class of compounds to study in more detail the mechanisms of action and the extension of biological effects such as neuro-, hepato-, nephro-, cytoprotection (toxicity) as well as carcinogenic and antitumour properties [2, 7, 8]. A less studied class of compounds are the functional derivatives of quinones – quinone oximes and quinone imines [9-16], although they are characterised by a wide spectrum of biological activity. In addition to antitumour [9, 11], trypanocidal [11], antimicrobial, larvicidal [12], herbicidal [13, 14] activity, they exhibit antidepressant [15] and diuretic [16] effects. Therefore, *N*-arylsulfonyl-2-aroylamino-1,4-quinone imines could be interesting compounds in this respect, firstly because they are characterised by the main chemical properties of quinones and their derivatives, and secondly because they combine fragments with diverse biological activities in their structure [17, 18, 19]. This suggests that the combination of a quinone matrix with tolylsulfonamide and benzamide fragments in a single molecule may be a promising approach to designing drug-like molecules with a predicted effect on the target organ.

Thus, in continuation of the search for biologically active compounds among functionalized quinones, the aim of this work is to study *N*-arylsulfonyl-2-arylamino-1,4-quinone imines and their hydrogenated analogues as promising diuretics with antiradical and antibacterial effects.

MATERIALS AND METHODS OF RESEARCH

To predict toxicity and to study biological activity, *N*-arylsulfonyl-2-arylamino-1,4-quinone imines (2) and their hydrogenated derivatives (3), whose synthesis methods are known [20, 21], were selected and are shown in Fig. 1.



1.1 R_1=R^2=H; **1.2** R_1=Me, R_2=H; **1.3** R_1=H, R_2=Me; **1.4** R_1=R_2=CH=CH-CH=CH-; **2.1** R_1=R^2=R_3 = H; **2.2**, R^1=R^2= H, R_3 = NO_2; **2.3** R_1=Me, R_2=R_3=H; **2.4** R_1=R_3=H, R_2=Me; **2.5** R_1=R_2=CH=CH-CH=CH-; **3.1** R_1=R_2=R_3 = H; **3.2** R_1=Me, R_2=R_3=H

Fig. 1. Methods of the synthesis of *N*-arylsulfonyl-2-aroylamino-1,4-quinone imines and their hydrogenated derivatives

Toxicity studies. The virtual laboratory of the ProTox-II site was used to predict the toxicity of molecules [22, 23]. It includes molecular similarity, fragment propensity, most common features and (CLUSTER cross-validation based on fragment similarity) machine learning based on a total of 33 models to predict various toxicity endpoints such as acute toxicity, hepatotoxicity, cytotoxicity, carcinogenicity, mutagenicity, immunotoxicity, adverse effects of induced limits (Tox21), ways and targets of toxicity. All methods, training set statistics and cross validation results can be found on their website. The toxicity model report illustrates the reliability of positive toxicity results compared to the average value of this class in hepatotoxicity, carcinogenicity, etc.

Study of the influence of compounds on kidney excretory function. Screening was performed on 120 white male Wistar rats weighing 111.54±1.86 g. The animals were divided into groups, 6 in each, taking into account the homogeneity of the distribution by weight, the groups were equally divided into 2 experiments (under the conditions of fluid loading and spontaneous urination). Results are presented on the basis of 100 g rat weight. The animals were kept under standard conditions in the vivarium of the Dnipro State Medical University. Experimental

studies were conducted in accordance with the "General Ethical Principles of Animal Experiments" (Ukraine, 2001), the provisions of the "European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes" (Strasbourg, 1986) and the conclusions of the Biomedical Ethics Commission of the Dnipro State Medical University (Protocol No. 3, dated 16 February 2002) [24]. Screening of diuretic properties of newly synthesized compounds of *N*-arylsulfonyl-2-aroylamino-1,4-quinone imines and their hydrogenated analogues was carried out according to the generally accepted method of E.B. Berkhin [25, 26]. Animals were fasted for three hours prior to the start of the experiment. The experiment was carried out with fluid loading (at a rate of 5 ml per 100 g of animal weight) and spontaneous urination (free access to water). The tested compounds were administered to rats by gavage at a dose of 2.6 mg/kg bw in the form of an aqueous suspension, with and without water loading (with daily urine collection). Animals were maintained in individual cages for two and 24 hours for urine collection. "Hydrochlorothiazide" and "Furosemide" at equivalent doses for rats were selected as comparator drugs [26].

Study of the absorption activity of free radicals. The study of antiradical activity *in vitro* was based on the interaction of the synthesised compounds with 2,2-diphenyl-1-picrylhydrazyl (DPPH) [28]. DPPH is a stable free radical and its alcohol solutions are coloured intense violet (λmax=517 nm). DPPH reacts with compounds capable of scavenging free radicals to form yellow products that do not absorb light at the wavelengths above.

Research methodology. The compounds were dissolved in dimethylsulfoxide (DMSO) to obtain a 1 mM solution. 2 ml of this solution was mixed with 2 ml of a 0.1 mM solution of DPPH in methanol and incubated for 30 minutes at 25°C. The optical density (Ad) was measured [29]. Simultaneously, the optical density of 2 ml of a 0.1 mM solution of DFPH in 2 ml of methanol (ADPH) was defined. The antiradical activity (ARA) was calculated using the following formula ARA% = (ADPHH-Ad)/ADPHH × 100%. A negative value of ARA in % was estimated as 0. The weighing of reagents and synthesized compounds was carried out on an electronic balance "ANG200C" (Axis, Gdansk, Poland) and the optical density was measured using a spectrophotometer "ULAB 108UV" (Ulab, Shanghai, China).

Study of antibacterial and antifungal activity. The antibacterial and antifungal activity of the synthesized compounds was studied on test cultures of bacteria *Escherichia coli*, *Staphylococcus aureus*, *Mycobacterium luteum* and fungi *Candida tenuis*, *Aspergillus niger* by the method of serial dilutions of the substance in a liquid nutrient medium (meat-peptone broth for bacteria and unhopped beer wort 6-8^0B for fungi) in the range of 0.9-500 μg/ml using a previously prepared working solution of the substance in DMSO at a concentration of 10 000 μg/ml. Bacterial and fungal inoculum was inoculated into the nutrient medium (microbial load 10^6 CFU (colony forming units) per 1 ml). The inoculated test tubes were kept in a thermostat at the appropriate temperature (37°C for bacteria; 30°C for fungi) for 24-72 hours. The results were evaluated for the presence or absence of microbial growth by visual inspection under transmitted light, comparing the degree of microbial turbidity of the nutrient medium with the "negative control"). To determine the minimum bactericidal concentration (MBC) or minimum fungicidal concentration (MFC), 0.02 ml of medium was taken from the tubes in which the medium solutions were visually transparent and applied to sterile meat-peptone agar (MPA) (for bacteria) or wort agar (WA) (for fungi) in sterile Petri dishes incubated in a thermostat. Results were evaluated 24 hours for in test bacteria and 48-72 hours for test fungi. Based on the absence of growth of microbial colonies on the incubated Petri dishes, the MBC or MFC of the test substance was determined [30]. The experiment was reproduced three times. Nitrofural ((E)-2-[(5-nitrofuran-2-yl)methylene]hydrazine-1-carboxamide) and Ketoconazole (1-{4-(4-[(2-(1H-imidazol-1-yl)])methyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methoxy)phenyl)piperazin-1-yl]ethan-1-one) were used as control compounds with proven antibacterial/antifungal activity. In addition, generally accepted methods were used for quality control of nutrient media and solvents [30].

The data obtained were statistically processed using the Statistica 6.1 software package (StatSoft Inc., serial number AGAR909E415822FA). Mean arithmetic values (M) and their errors (± m) were calculated. The probability of differences between groups was determined using Student's parametric t-test and one-way analysis of variance (ANOVA). Differences were considered statistically significant at $p<0.05$ [27].

RESULTS AND DISCUSSION

Taking into account the structural peculiarities of structures 2 and 3, particularly the presence of a sulfonamide fragment, it was decided to study the effect of the synthesised compounds on the urination process in intact rats under water stress [16, 18, 19]. Prior to biological studies, toxicity prediction was used to determine toxic doses in order to reduce the number of animals used. The results presented in

Table 1 showed that the predicted hepatotoxicity (immunotoxicity, cytoxicity) and carcinogenicity (mutagenicity) of quinone imines (2) and their hydrogenated analogues (3) are similar to natural quinones (Ubiquinone Q1, Phylloquinone) and diuretics (Hydrochlorothiazide, Furosemide). It was also predicted that the LD_{50} of compounds 2 and 3 is in the range of 877-1500 mg/kg, they are toxicity class IV and can be tested for diuretic effects at recommended doses [26].

Table 1

Prediction of the toxicity of substances

Compounds*	Oral toxicity **			Prediction: active, probability of 1				
	toxicity Index	LD_{50}, mg/kg	toxicity prediction, %	hepatotoxicity	carcinogenicity	immunotoxicity	mutagenicity	cytoto-xicity
U	5	4000	72,90	0.64	0.64	0.69	0.78	0.63
P	6	25000	100	0.89	0.69	0.53	0.78	0.77
2.1	4	1000	54,26	0.60	0.60	0.98	0.73	0.78
2.2	4	1000	23,00	0.51	0.56	0.92	0.54	0.79
2.3	4	1200	54,26	0.59	0.58	0.99	0.72	0.78
2.4	4	1000	54,26	0.59	0.58	0.99	0.72	0.78
2.5	4	1000	23,00	0.60	0.65	0.99	0.69	0.78
3.1	4	877	67,38	0.54	0.62	0.99	0.76	0.80
3.2	4	1500	54,26	0.55	0.61	0.99	0.75	0.80
H	4	1175	100	0.92	0.86	0.94	0.96	0.69
F	4	2000	100	0.51	0.62	0.99	0.89	0.59

Notes: *U - Ubiquinone Q10; P – Phylloquinone; H – Hydrochlorothiazide; F – Furosemide; ** Class I: fatal if swallowed (LD50≤5); Class II: fatal if swallowed (5<LD50≤50); Class III: Toxic if swallowed (50<LD50≤300); Class IV: harmful if swallowed (300<LD50≤2000); Class V: may be harmful if swallowed (2000<LD50≤5000); Class VI: not toxic (LD50>5000).

Compounds 2 and 3 were screened in 120 white male Wistar rats. The renal excretory function was studied in animals divided into 6 groups, the groups being divided into 2 subgroups (under conditions of water loading and spontaneous urination) according to the method of E.B. Berkhin. The studies did not show a significant diuretic effect of the *N*-arylsulfonyl-2-aroylamino-1,4-quinone imines and hydrogenated analogues (Table 2). Among the studied compounds, compound 2.5 showed the greatest activity at the second hour of the experiment, increasing diuresis by 14.7% compared to the control group. Other quinone imines (2.1-2.4), on the contrary, inhibited diuresis by 8.0-18.4% compared to the control group of animals. A similar result, in particular, inhibition of diuresis by 24.7%, was observed for *N*-(2-hydroxy-5-((4-methylphenyl)sulfonamido)phenyl)benzamide (3.1). The additional introduction of a methyl group in position 3 (compound 3.2) to structure 3.1 leads to an unreliable enhancement of the effect (2.9% compared to the control). As for the daily diuresis, the most active compound was *N*-(p-tolylsulfonyl)-2-benzoylamino-6-methyl-1,4-quinone imines (2.3), which significantly exceeded the reference drug "Furosemide" (22.2%) in terms of potency (67.1%). Other compounds (2.1, 2.2, 2.4, 2.5, 3.1, 3.2) suppressed daily diuresis by 1.9-40.7% compared to the control group of animals.

In our opinion, the low activity or suppression of diuresis by compounds 2 and 3 may not always be associated with the presence of nephrotoxic activity. The difference in the direction of action depends on the oxidation/reduction products of the quinones and the formation of reactive oxygen species in the kidneys. This means that reduced semiquinones are free radicals that can damage DNA. In the meantime, oxidised quinonimines are less reactive and quench reactive oxygen species. With this in mind, we investigated the antiradical activity of compounds 2 and 3 to better understand their effect on renal

excretory function. At the same time, it was found (Table 2) that quinones 2.1-2.5 were less active as radical acceptors than the comparator ascorbic acid. Indeed, they inhibited the formation of the DPPH radical by 25.99-40.09%. Then, as expected, phenols 3.1 and 3.2 showed antiradical activity at the level of 61.56% and 68.28%. However, it is not worth mentioning about the ability of compounds 2 and 3 to reduce oxidative stress by maintaining the activity of antioxidant enzymes, due to their insignificant ability to inhibit the formation of the DPPH radical.

Table 2

Effect of compounds and comparison drugs on diuresis in intact rats under conditions of water load and spontaneous urination after single administration and on antiradical activity

No.	Compounds	Diuresis, ml/100 g/2 h (M±m, n=6)*	% relative to control	Diuresis, ml/100 g/24 h (M±m, n=6)*	% relative to control	Antiradical activity (1×10^{-3} M),%
1	control	3.48±0.09	–	2.16±0.05	–	–
2	2.1	2.98±0.07	-14.4	1.94±0.29	-10.2	38.31
3	2.2	3.20±0.05	-8.0	1.73±0.07	-19.9	30.83
4	2.3	2.84±0.09	-18.4	3.61±0.30	67.1	40.09
5	2.4	2.91±0.12	-16.4	1.28±0.08*	-40.7	25.99
6	2.5	3.99±0.09	14.7	1.40±0.07*	-35.2	31.79
7	3.1	2.62±0.11	-24.7	2.12±0.10	-1.9	61.56
8	3.2	3.58±0.13	2.9	1.83±0.13	-15.3	68.28
9	Hydrochlorothiazide	5.39±0.07*	54.9	5.85±0.21*	170.8	–
10	Furosemide	4.09±0.11	17.5	2.64±0.10	22.2	–
11	Ascorbic acid	–	–	–	–	92.08

Note. * – significantly ($p<0.05$) to the control group of animals.

Given the high chemotherapeutic potential of quinones and their derivatives, it was interesting to investigate their antibacterial activity. In addition, urinary tract infections are considered one of the most common reasons for seeking medical care, and the majority of clinical cases are associated with *S. saprophyticus* and *P. mirabilis* [31, 32]. The microbiological screening carried out showed (Table 3) that compounds 2 and 3 did not inhibit the growth of *E. coli* and were ineffective against *S. aureus*. It was expected that only compound 2.5, particularly *N*-(1-oxo-4-(tosylimino)-1,4-dihydronaphthalen-2-yl)benzamide, inhibited growth and shown bactericidal activity against *S. aureus* at a concentration of 62.5 μg/ml and 125.0 μg/ml respectively. A higher antibacterial activity of compounds 2 and 3 is observed against *M. luteum*. It was found that compounds 2.1-2.4 and 3.2 inhibit growth at a concentration of 62.5-125.0 μg/ml and exhibit bactericidal activity at a concentration of 250.0-500.0 μg/ml. Whereas, *N*-(2-hydroxy-5-((4-methylphenyl)sulfonamido)phenyl)benzamide (3.1), in this case, is more effective against *M. luteum* with MIC 31.2 μg/ml and MBC 62.5 μg/ml. It should be noted that the antimicrobial activity of compounds 2 and 3 was significantly lower than that of the reference drug "Nitrofuralum".

As for the antifungal activity, the studied compounds are not effective against *C. tenuis*, but have high fungicidal activity against *A. niger* (Table 3). Thus, compounds 2.1, 2.4 and 3.2 inhibited the growth of the strain at a concentration of 31.2 μg/ml and showed fungicidal effect at a concentration of 62.5 μg/ml, which exceeded that of the comparator drug "Ketoconazole".

The research we have carried out among *N*-arylsulfonyl-2-aroylamino-1,4-quinone imines and their hydrogenated analogues on some types of biological action allows us to state that this class of compounds is promising in the research for drug-like

molecules. Furthermore, the confirmation of similar studies in the available literature is extremely limited or there are isolated similar results, which are partly identical to our study [1, 3]. Therefore, the appropriate directions for further research are the structural modification of quinone imines, particularly the introduction of other arylsulfonyl and aroyl (heteroyl) amine fragments into the molecule, with the aim of creating a wider combinatorial library and studying their effect on diuresis, antimicrobial activity and toxicity. In addition, this direction is also promising for the development of urease inhibitors, among which the structures of the quinoid structure are known [33].

Table 3

Antimicrobial and antifungal activity of the studied compounds

Compounds	Bacterial cultures						Fungi cultures			
	E. coli		*St. aureus*		*M. luteum*		*C. tenuis*		*A. niger*	
	MIC, µg/ml	MBC, µg/ml	MIC, µg/ml	MBC, µg/ml	MIC, µg/ml	MBC, µg/ml	MIC, µg/ml	MFC, µg/ml	MIC, µg/ml	MFC, µg/ml
2.1	+	+	+	+	**125.0**	**500.0**	**250.0**	**500.0**	**31.2**	**62.5**
2.2	+	+	**500.0**	–	**62.5**	**250.0**	+	+	+	+
2.3	+	+	**250.0**	–	**125.0**	**250.0**	+	+	+	+
2.4	+	+	+	+	**125.0**	**500.0**	**250.0**	**500.0**	**31.2**	**62.5**
2.5	+	+	**62.5**	**125.0**	+	+	+	+	+	+
3.1	+	+	**500.0**	–	**31.2**	**62.5**	**500.0**	+	**500.0**	–
3.2	+	+	+	+	**125.0**	**250.0**	**500.0**	+	**31.2**	**62.5**
Nitrofuralum	**1.5**	–	**6.25**	–	**6.25**	–	–	–	–	–
Ketoconazole	–	–	–	–	–	–	**25**	**50**	**25**	**50**

Notes: "+" growth of the microorganism at the control level was observed at the studied concentrations; "-" compounds were not tested for this type of activity; MIC – Minimum Inhibitory Concentration; MBC – Minimum Bactericidal Concentration; MFC – Minimum Fungicidal Concentration.

CONCLUSIONS

1. The study of the effect of N-arylsulfonyl-2-aroylamino-1,4-quinone imines and their hydrogenated analogues on the excretory function of the kidneys of water-stressed rats showed that they are characterized by both stimulation and inhibition of diuresis. It was found that N-(5-methyl-6-oxo-3-(tosylimino)cyclohexa-1,4-dien-1-yl)benzamide (2.3) increased daily diuresis by 67.1% compared with the control group, at the same time exceeding the effect of the reference drug "Furosemide" (22.2%).
2. It was found that the studied compounds exhibit moderate antiradical activity, high antibacterial activity against *S. aureus* (compound 2.3), *M. luteum* (2.1, 3.1) and antifungal activity against *A. niger* (2.1, 2.4, 3.2).
3. The obtained results justify further search for diuretics with polyvector action among this class of compounds, study of their toxicological parameters and study of the mechanism of action.

Acknowledgments. The authors would like to thank the Armed Forces of Ukraine and the Territorial Defense Forces of the Armed Forces of Ukraine for preparing this article in the safe conditions of Dnipro, Ukraine.

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Financing. The work was carried out under the budget topic of the Ministry of Education and Science of Ukraine "Design and modification of *N*-substituted-1,4-quinone imines: directed synthesis, study of bioactivity by *in silico*, *in vitro*, *in vivo* methods." (No. 0122U000969, study period 2022-2024).

Conflict of interest. The authors declare no conflict of interest.

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Стаття надійшла до редакції
15.03.2023