UDC 615.254.1:615.015:547.567:616.61-008.6-092.9 https://doi.org/10.26641/2307-0404.2024.2.307457

K.V. Sokolova [1 *],
O.A. Podpletnya [1],
S.O. Konovalova [2],
A.P. Avdeenko [2],
S.I. Kovalenko [3]

INFLUENCE OF SUBSTITUTED QUINONES ON THE EXCRETORY FUNCTION OF THE RAT KIDNEY AND EVALUATION OF THE PROSPECTS OF THEIR USE AS POTENTIAL DIURETICS

Dnipro State Medical University [1]
Volodymyra Vernadskoho str., 9, Dnipro, 49044, Ukraine
Donbas State Engineering Academy [2]
Akademichna str., 72, Kramatorsk, 84313, Ukraine
Oles Honchar Dnipro National University [3]
Nauky ave, 72, Dnipro, 49045, Ukraine
Дніпровський державний медичний університет [1]
вул. Володимира Вернадського, 9, Дніпро, 49044, Україна
Донбаська державна машинобудівна академія [2]
вул. Академічна, 72, Краматорськ, 84313, Донецька область
Дніпровський національний університет імені Олеся Гончара [3]
пр. Науки, 72, Дніпро, 49045, Україна
[*]*e-mail: cat@dmu.edu.ua*

Цитування: Медичні перспективи. 2024. Т. 29, № 2. С. 4-10
Cited: Medicni perspektivi. 2024;29(2):4-10

Key words: *substituted quinones, diuretic activity, diuretic index, urinary electrolyte excretion*
Ключові слова: *заміщені хінони, діуретична активність, діуретичний індекс, екскреція електролітів із сечею*

Abstract. Influence of substituted quinones on the excretory function of the rat kidney and evaluation of the prospects of their use as potential diuretics. Sokolova K.V., Podpletnya O.A., Konovalova S.O., Avdeenko A.P., Kovalenko S.I. *Diuretics are widely used to treat pathologies of various genesis. However, the development of side effects during their long-term use remains a problem of traditional treatment regimens. The search for diuretics that would be aimed at inhibiting a key target molecule that is involved in the regulation of salt or water balance in the kidney, and certainly have a low level of toxicity and side effects, is an urgent task for researchers. Our preliminary screening of substituted quinones using in silico and in vitro methodology identified a number of effective compounds that outperform or compete with diuretics. The compounds are not "classic" carbonic anhydrase II inhibitors, but the pronounced diuretic effect of a number of compounds requires additional explanation. Therefore, the aim of the work was to study the effect of substituted quinones on the excretory function of rat kidneys to assess the prospects of their further structural modification and use as potential diuretics. Considering the experimental data, it should be noted that compounds AVD-6, AVD-7, AVD-8 and AVD-9 have pronounced diuretic activity. Thus, according to indicators of excretory indices of electrolytes, it is possible to note the predominant influence of compounds AVD-6, AVD-7, AVD-8 and AVD-9 on excretion of sodium, potassium and chlorine from the body. Compounds AVD-6, AVD-7, AVD-8 and AVD-9, in contrast to Hydrochlorothiazide, which blocks carbonic anhydrase in the proximal part of the convoluted tubules and accelerates the excretion of potassium with from the urine, have a much lower excretory index as for these ions. Thus, our conducted research made it possible to identify a new, little-known class of hybrid molecular structures, namely (N'-(4-[(aroyloxy)imino]cyclohexa-2,5-dien-1-ylidene) aroylhydrazides (AVD-6, AVD-7, AVD-8 and AVD-9), which, in addition to affecting the excretory function of the kidneys, have significant diuretic activity and are potential diuretics.*

Реферат. Вплив заміщених хінонів на видільну функцію нирок щурів та оцінка перспектив їх застосування як потенційних діуретичних засобів. Соколова К.В., Подплетня О.А., Коновалова С.О., Авдєєнко А.П., Коваленко С.І. *Діуретичні засоби широко застосовують для лікування патологій різного генезу. Однак розвиток побічних ефектів при довготривалому їх використанні залишається проблемою традиційних схем лікування. Пошук діуретиків, які б направлено інгібувати ключову молекулу-мішень, яка*

бере участь у регуляції сольового або водного балансу в нирках, і, безперечно, має низький рівень токсичності та побічних ефектів, є актуальною задачею для дослідників. Проведений нами попередній скринінг серед заміщених хінонів з використанням in silico та in vitro методології дозволив ідентифікувати ряд ефективних сполук, які перевищують або конкурують з сечогінними засобами. Сполуки не є «класичними» інгібіторами карбоангідрази II, але виражений сечогінний ефект ряду сполук потребує додаткового пояснення. Тому метою роботи стало вивчення впливу заміщених хінонів на видільну функцію нирок щурів для оцінки перспектив їх подальшої структурної модифікації та застосування як потенційних діуретичних засобів. Ураховуючи дані експерименту, необхідно відмітити, що сполуки AVD-6, AVD-7, AVD-8 та AVD-9 мають виражену діуретичну активність. Так, за показниками екскреторних індексів електролітів можна відмітити переважний вплив сполук AVD-6, AVD-7, AVD-8 та AVD-9 на виділення натрію, калію та хлору з організму. Сполуки AVD-6, AVD-7, AVD-8 та AVD-9, на відміну від гідрохлортіазиду, який блокує карбоангідразу у проксимальному відділі звитих канальців та прискорює виведення із сечею іонів калію, мають значно нижчий екскреторний індекс щодо цих іонів. Отже, проведені нами дослідження дозволили виділити новий маловідомий клас гібридних молекулярних структур, а саме (N'-(4-[(aroyloxy)imino]cyclohexa-2,5-dien-1-ylidene) aroylhydrazides (AVD-6, AVD-7, AVD-8 та AVD-9), які, окрім впливу на екскреторну фунцію нирок, мають значну діуретичну активність та є потенційними діуретиками.

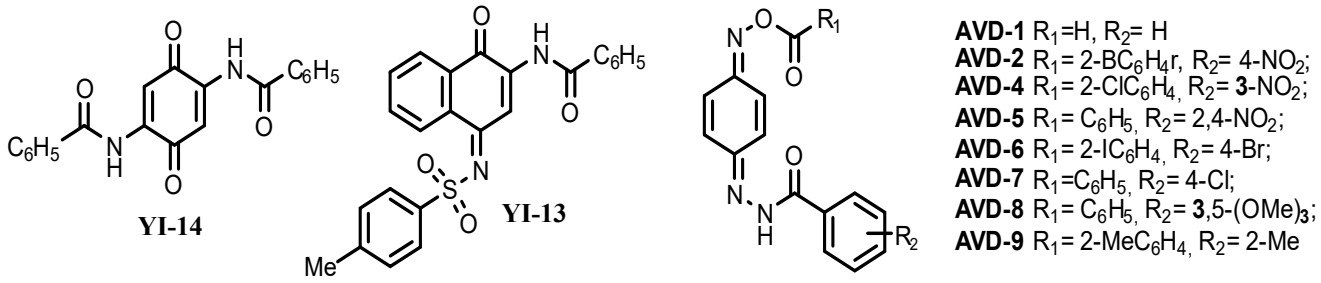
Diuretics are a vast group of drugs with a versatile mechanism of action, which are widely used in medical practice for the treatment of pathologies of various genesis. The main indications for the use of diuretics, taking into account the nature and mechanisms of their effect on nephrons, are heart, kidney and liver failure, which are accompanied by edema, arterial hypertension, diabetes insipidus of the nephrogenic type (for thiazide diuretics), etc. [1, 2, 3, 4]. Today, the possibilities of genetics and molecular physiology have fundamentally changed our understanding of the molecular mechanisms of the interaction of salts and water in the renal tubules due to the discovery of new ion transport proteins or their regulators (ROMK inhibitors, WNK-SPAK inhibitors, pendrin inhibitors, urea transporters inhibitors (UTA/B), SGLT2 inhibitors, etc.) [5, 6, 7, 8]. Despite the discovery of new targets, active target-oriented search, understanding of the mechanisms of action, unfortunately, the "ideal" diuretic agent has not been found, and the existing ones are characterized by significant side effects. Thus, the use of traditional regimens of treatment with this group of drugs is associated with a significant number of side effects [9], for example, loop and thiazide diuretics disrupt electrolyte (causing hypokalemia, hyperuricemia, hyponatremia) and acid-base balance, cause metabolic disturbances and hypovolemia. In patients with chronic kidney disease and an increasingly lower glomerular filtration rate, the effectiveness of the drugs may decrease, requiring an increase in the dose or the use of alternative drugs. To overcome diuretic resistance, combinations of drugs that act in different segments of the nephron and increase diuretic efficiency are used. Thus, electrolyte imbalance, resistance to diuretics and other problems of clinical application require further search for those that would targetly inhibit molecules involved in the mechanisms of uropoiesis in the kidneys, with low toxicity and the absence of pronounced side effects.

Previous screening for diuretic activity among substituted quinones using *in silico* and *in vitro* methodology [10, 11] allowed identification of a number of effective compounds that exceed or compete with diuretics. Visualization of the molecular docking of the active compounds showed that they are not classical CA II inhibitors, but the pronounced diuretic effect of a number of compounds requires additional explanation. Thus, the obtained results substantiate the study of their effect on the excretory function of the kidneys of rats in comparison with reference drugs for a more detailed understanding of the mechanism of action, as well as structural modification to enhance diuretic activity.

The aim of the work is to study the effect of substituted quinones on the volume and excretion of urinary electrolytes in order to evaluate the prospects of their further structural modification for use as potential diuretics.

MATERIALS AND METHODS OF RESEARCH

To study the effect on the volume and excretion of electrolytes with urine under conditions of fluid load and spontaneous urination with a single injection, compounds (**YI-14, YI-13** та **AVD 1-9**) were selected. In this case it is 2,5-dibenzoylamino-1,4-quinone (**YI-14),** (*N*-(1-oxo-4-(tosylimino)-1,4-dihydronaphthalen-2-yl)benzamide (**YI-13**) and (*N'*-(4-[(aroyloxy)imino]cyclohexa-2,5-dien-1-ylidene)-aroylhydrazides (**AVD-1-9**), whose synthesis methods are known [20, 21] (Fig.).



Chemical structure of substituted quinones

Screening was performed on 90 white male Wistar rats weighing 100-185 g, which were kept under standard conditions in the vivarium of the Dnipro State Medical University. The research was 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 conclusion of the Biomedical Ethics Commission DSMU (protocol No. 3 dated 16.02.2022) [12]. Determination of the effect of compounds on the excretory function of the kidneys of rats was evaluated under the conditions of spontaneous daily diuresis and water load. Before the experiment, the animals were kept without food for three hours. The diuretic effect of the compounds was studied both under fluid load and without it (room temperature drinking water was administered intragastrically to the animals) at the rate of 5 ml per 100 g of animal weight. The compounds were administered to rats once intragastrically in doses of 2.6 mg/kg of body weight in the form of an aqueous suspension simultaneously with water load. Animals were placed in individual cages for urine collection for three hours and 24 hours. Additionally, the diuretic index (DI) and diuretic activity (DA) were determined according to equations 1 and 2.

$$\boldsymbol{DI}\frac{\boldsymbol{V_1}}{\boldsymbol{V_k}} \quad (1),$$

where:
V_1 – urine volume of animals that received the studied compounds;
$V_к$ – urine volume of the control group of animals

$$\boldsymbol{DA} = \frac{\boldsymbol{D}\text{I}}{\boldsymbol{D}\text{I}к} \quad (2),$$

where:
DI – diuretic index of the experimental group of animals;
$DI_к$ – diuretic index of the control group of animals (is 1.00).

Reference drugs selected Triamterene 25 mg (dose for a rat 2.6 mg/kg), Furosemide 40 mg (4.1 mg/kg), Hydrochlorothiazide 25 mg (2.6 mg/kg), Acetazolamide 250 mg (25.8 mg/kg) [13]. Doses for animals were calculated according to generally accepted formulas [19].

Biochemical studies of blood plasma and urine were carried out using standard test kits of LLC NPV "Filisit-Diagnostika" (Ukraine). The concentration of potassium ions was determined by the reaction with tetraphenylborate in an alkaline environment [21], sodium – by the reaction with phosphonazo III [21], chlorides – by the reaction in a strongly acidic environment of rhodanide ion (released from rhodanide of mercury (II)) with iron ions (III) [20].

The urine Na^+/K^+ ratio which indicates the degree of mineralocorticoid control of electrolytes was calculated.

The obtained results were statistically processed using the Statistica 6.1 software package (StatSoft Inc., serial number AGAR909E415822FA). Arithmetic mean values and their standard errors (M±m) were calculated. The probability of intergroup differences was determined using the Student's parametric t-test and one-way analysis of variance (ANOVA). Differences were considered statistically significant for values of $p \leq 0.05$ [14, 18].

RESULTS AND DISCUSSION

The results of the effect of the studied compounds on diuresis are shown in Table 1. In the animals, in

the first hours of the experiment, against the background of water stress, moderate changes in the volume of urine under the influence of the compounds were observed in most groups. Diuretic index exceeded from 8% to 32% ($p<0.05$). Compounds YI-13, AVD-5, AVD-6, AVD-8 did not affect diuresis and had no probable changes compared to the control group. However, against the background of spontaneous urination by the 24th hour of the experiment under the influence of quinonoximes (AVD-6, AVD-7, AVD-8, AVD-9), probable changes in diuresis were observed relative to both control and comparison drugs. Diuresis exceeded control values from 51% to 93%, compound AVD-7 had the strongest effect relative to control (+93%), relative to Triamterene (+90%), relative to Furosemide (+10%), Hydrochlorothiazide (+1%) and Acetazolamide (+38%). It is important that quinonoximes AVD-6, AVD-7, AVD-8, and AVD-9 had a diuretic index (DI) of more than 1.50 units, which makes it possible to assert their high diuretic activity (Table 1). For compounds AVD-1 and AVD-2 no diuretic activity was detected. In other quinone derivatives, DI is in the range of 1.02-1.32 units, they show moderate diuretic activity. It is noteworthy that compounds AVD-8 and AVD-9 exceed the reference drugs Triamterene and Diakarb in terms of diuretic activity.

Table 1

The effect of the studied compounds and reference drugs on the volume of urine in rats under conditions of water stress and spontaneous urination in a single administration (M±m)

A group of animals (n=6)	Diuresis. ml per 100 g in 2 hours ($p<0.05$)	DI^{WL}	DA^{TWL}	DA^{FWL}	DA^{HWL}	DA^{AWL}	Diuresis. ml per 100 g in 24 hours ($p<0.05$)	DI^{SU}	DA^{TSU}	DA^{FSU}	DA^{HSU}	DA^{ASU}
K	3.39±0.30	1.00					3.23±0.28	1.00				
T	4.00±0.23*	1.18	1.00				3.28±0.17	1.02	1.00			
F	4.41±0.17*	1.30	1.10	1.00			5.61±0.38*	1.74	1.71	1.00		
H	4.74±0.38*	1.40	1.19	1.07	1.00		6.13±0.27*	1.90	1.87	1.09	1.00	
A	3.79±0.68	1.12	0.95	1.12	0.80	1.00	4.52±0.30*	1.40	1.38	0.81	0.72	1.00
YI-13	3.25±0.28	0.96	0.82	0.74	0.69	0.86	4.27±0.21*	1.32	1.30	0.76	0.70	0.94
YI-14	3.67±0.06*	1.08	0.92	0.83	0.77	1.13	3.31±0.24*	1.02	1.01	0.59	0.54	0.73
AVD-1	4.47±0.56*	1.32	1.12	1.03	0.94	1.36	2.97±0.29*	0.92	0.91	0.53	0.48	0.66
AVD-2	4.32±0.29*	1.27	1.08	0.98	0.91	1.33	3.07±0.14	0.95	0.94	0.62	0.50	0.68
AVD-4	3.88±0.23	1.15	0.97	0.88	0.82	1.19	3.91±0.45	1.21	1.03	0.70	0.64	0.87
AVD-5	3.29±0.31	0.97	0.82	0.75	0.69	1.01	4.04±0.11*	1.25	1.23	0.72	0.66	0.89
AVD-6	2.99±0.33	0.88	0.75	0.68	0.63	0.92	5.40±0.64*	1.67	1.65	0.96	0.88	1.19
AVD-7	3.45±0.38	1.02	0.86	0.78	0.73	1.06	6.22±0.72*	1.93	1.90	1.10	1.01	1.38
AVD-8	2.99±0.31	0.88	0.75	0.68	0.63	0.93	4.89±0.48*	1.51	1.49	0.87	0.80	1.08
AVD-9	3.51±0.47	1.04	0.88	0.80	0.74	1.08	5.27±0.28*	1.63	1.61	0.94	0.86	1.17

Notes: n – number of animals in the group; * – significant differences with respect to the control group (K) at $p<0.05$; DI^{WL} – diuretic index under conditions of water load; DA^{TWL} – diuretic activity under conditions of water load relative to the comparison drug Triamteren; DA^{FWL} – diuretic activity in conditions of water load relative to Furosemide; DA^{HWL} – diuretic activity in conditions of water load relative to Hydrochlorothiazide; DA^{AWL} – diuretic activity in conditions of water load relative to Acetazolamide; DI^{SU} – diuretic index in conditions of spontaneous urination; DA^{TSU} – diuretic activity in conditions of spontaneous urination relative to Triamterene; DA^{FSU} – diuretic activity in conditions of spontaneous urination relative to Furosemide; DA^{HSU} – diuretic activity in conditions of spontaneous urination relative to Hydrochlorothiazide; DA^{DSU} – diuretic activity in conditions of spontaneous urination relative to Acetazolamide; K – control; T – Triamterene; F – Furosemide; G – Hydrochlorothiazide; A – Acetazolamide.

Daily urine samples collected for 24 hours were analyzed for the content of electrolytes (Na^+, K^+ and Cl^-) (Table 2). All compounds increased sodium excretion from 2% to 339% compared to control. The analysis of excretory indices showed that compounds AVD-7, AVD-6, AVD-9, AVD-8 exerted the strongest probable influence ($p<0.05$) on sodium excretion, the changes were from +249% to +339% (AVD-7 +339%, $p<0.05$) compared to the control. A less pronounced but probable effect was observed in groups AVD-5 (+195%, $p<0.05$), AVD-4 (+131%, $p<0.05$), YI-14 (+34%, $p<0 .05$), AVD-2 (+31%, $p<0.05$). Excretion of potassium increased against the background of administration of all compounds (from 7% to 121%). Compounds AVD-7 (+121%, $p<0.05$), AVD-6 (+120%, $p<0.05$) and AVD-9 (+105%, $p<0.05$) most potently increased kaliuresis. Other quinonexime compounds moderately increased urinary potassium excretion. YI-13 and YI-14 probably increased kaliuresis by +38% and +42%, respectively. All compounds probably increased chlorine excretion from +26% to +700%. It should be noted compounds AVD-9 (+700%, $p<0.05$), AVD-6 (+617%, $p<0.05$), AVD-7 (+568%, $p<0.05$), which significantly outperformed the reference indicators and the comparison drug Furosemide. Quinonexime compounds (AVD-7, AVD-9, AVD-8, AVD-6, AVD-5, AVD-4) had a probable effect on the urine Na^+/K^+ ratio and increased it from 47% to 98%.

Table 2

The effect of the investigated compounds and reference drugs on the excretion of electrolytes from the urine of rats under conditions of spontaneous urination in a single administration (M±m)

A group of animals (n=6)	Excretion, μmol/ per 100 g in 24 hours			Coefficient
	Na^+ ($p<0.05$)	K^+ ($p<0.05$)	Cl^- ($p<0.05$)	Na^+ / K^+ urine ($p<0.05$)
K	2.19±0.50	16.33±2.58	0.37±0.08	0.13±0.02
T	4.01±0.67*	24.14±1.83*	1.59±0.30*	0.16±0.02
F	11.83±1.50*	40.46±2.21*	2.22±0.52*	0.29±0.02*
H	13.53±1.73*	45.86±1.38*	6.05±0.82*	0.29±0.03*
A	4.21±0.86*	28.48±1.89*	0.72±0.09*	0.15±0.02
YI-13	2.56±0.14	22.53±1.01*	0.47±0.03*	0.11±0.01
YI-14	2.94±0.41*	23.24±1.04*	0.64±0.06*	0.13±0.02
AVD-1	2.27±0.32	17.43±0.78	0.59±0.07*	0.13±0.02
AVD-2	2.88±0.31	19.78±1.16	0.68±0.05*	0.15±0.01
AVD-4	5.07±0.80*	25.74±0.55*	1.86±0.26*	0.20±0.03*
AVD-5	6.48±0.57*	29.23±1.53*	1.35±0.17*	0.22±0.01*
AVD-6	8.92±2.53*	35.95±3.23*	2.65±0.48*	0.25±0.05*
AVD-7	9.62±1.85*	36.09±2.35*	2.46±0.43*	0.27±0.03*
AVD-8	7.66±0.97*	31.07±0.77*	1.86±0.35*	0.25±0.03*
AVD-9	8.78±0.86*	34.48±1.17*	2.95±0.17*	0.26±0.03*

Notes: n – number of animals in the group; * – significant differences relative to the group of control (K) at $p<0.05$; K – Control; T – Triamterene; F – Furosemide; H – Hydrochlorothiazide; A – Acetazolamide.

Considering the experimental data, it should be noted that compounds AVD-4, AVD-5, AVD-6, AVD-7, AVD-8, AVD-9 exhibit diuretic activity. Thus, according to the indicators of excretion of electrolytes, it is possible to note the predominant effect of compounds AVD-4, AVD-5, AVD-6, AVD-7, AVD-8, AVD-9 on the release of sodium, potassium and chlorine ions from the body [15]. However, compounds AVD-4, AVD-6, AVD-7, AVD-8, AVD-9, in contrast to Hydrochlorothiazide, which blocks carbonic anhydrase in the proximal part of the convoluted tubules [21] and accelerates the excretion of potassium ions from the urine, have a much lower excretion of these ions. Certain quinonexime derivatives (AVD-4, AVD-6, AVD-7, AVD-8, AVD-9) increased the excretion of sodium and potassium and increased the Na^+/K^+ ratio of urine, which indicates a decrease in mineralocorticoid control of the distal tubules of the studied groups. In our opinion, this may be related to the peculiarity of the structure of these compounds, namely the presence of (N'-(4-[(aroyloxy)imino]cyclohexa-2,5-dien-1-ylidene)aroylhydrazides (AVD) in the molecular structure (AVD-4, AVD-5, AVD-6, AVD-7, AVD-8, AVD-9) with different chemical properties of the fragments. Thus, the aroylhydrazone fragment of the molecule, which is characterized by tautomerism, can provide the ability to inhibit carbonic anhydrase due to the formation of coordination bonds of zinc cation and amino acid residues of the active center of the enzyme [10]. While the aroyloxime fragment of the molecule, as more lipophilic, can provide interaction with epithelial sodium channels (ENaC), which are transmembrane channels and increase sodium ion absorption in exchange for ion secretion [16]. In addition, an important factor is the ability of quinone derivatives to participate in redox reactions. The biological targets of quinone derivatives depend on their reactivity, the location and speed of their formation. *In vivo,* quinones can exert a cytoprotective effect due to the induction of enzymes detoxification, anti-inflammatory activity and modification of redox status [17].

CONCLUSIONS

The conducted studies made it possible to identify a new, little-known class of hybrid molecular structures, namely (*N'*-(4-[(aroyloxy)imino]cyclohexa-2,5-dien-1-ylidene)aroylhydrazides (especially compounds AVD-6, AVD-7, AVD-8 and AVD-9), which have significant diuretic activity and are potential diuretics. It should be noted that these compounds have a predominant effect on the excretion of sodium, potassium and chlorine ions with the urine. The ability of these compounds to weaken the mineralocorticoid control of the distal tubules of the nephron may be one of the links in the mechanism of action of these drugs.

Recommendations. We identified a new, little-known class of hybrid molecular structures, namely (*N*'-(4-[(aroyloxy)imino]cyclohexa-2,5-dien-1-ylidene)aroylhydrazides (AVD-6, AVD-7, AVD-8 and AVD-9), which is promising from the point of view of further structural modification, experimental confirmation and use as potential diuretics. This direction requires in-depth research, which can be a continuation of our work.

Contributors:

Sokolova K.V. – visualization, writing – original draft, resources, investigation;

Podpletnya O.A. – writing – review & editing;

Konovalova S.O. – visualization, writing – original draft, resources, investigation;

Avdeenko A.P. – project administration, methodology, conceptualization, writing – review & editing;

Kovalenko S.I. – project administration, methodology, conceptualization, writing – review & editing.

Funding. The work was carried out under the budget topic of the Ministry of Education and Culture of Ukraine "Design and modification of N-substituted-1,4-quinonimines: directed synthesis, study of bioactivity by *in silico*, *in vitro*, *in vivo* methods" (No. 0122 U000969, execution period 2022-2024) and as part of the research work of the department of general and clinical pharmacy of the State Medical University "Pharmacological substantiation of the effectiveness and toxicity of medicinal substances of plant and synthetic origin" (implementation period 2022-2026).

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

Gratitude. The authors express their gratitude to all brave defenders of Ukraine.

REFERENCES

1. Akbari P, Khorasani-Zadeh A. Thiazide Diuretics. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Feb 23]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532918/

2. Roush GC, Sica DA. Diuretics for Hypertension: A Review and Update. Am J Hypertension. 2016:29(10):1130-7. doi: https://doi.org/10.1093/ajh/hpw030

3. Trujillo H, Caravaca-Fontán F, Caro J, Morales E, Praga M. The Forgotten Antiproteinuric Properties of Diuretics. Am J Nephrol. 2021;52(6):435-49. doi: https://doi.org/10.1159/000517020

4. Kehrenberg MCA, Bachmann HS. Diuretics: a contemporary pharmacological classification? Naunyn-Schmiedeberg's Arch Pharmacol. 2022;395:619-27. doi: https://doi.org/10.1007/s00210-022-02228-0

5. Livero FA, Menetrier JV, Lourenco ELB, Junior AG. Cellular and Molecular Mechanisms of Diuretic Plants: An Overview. Curr Pharm Des. 2017;23(8):1247-52. doi: https://doi.org/10.2174/1381612822666161014114437

6. Denton JS, Pao AC, Maduke M. Novel diuretic targets. AJP: Renal Physiology. 2013;305(7):F931-F942. doi: https://doi.org/10.1152/ajprenal.00230.2013

7. Titko T, Perekhoda L, Drapak I, Tsapko Y. Modern trends in diuretics development. Eur J Medicinal Chemistry. 2020;208:112855. doi: https://doi.org/10.1016/j.ejmech.2020.112855

8. Zhao Y, Cao E. Structural Pharmacology of Cation-Chloride Cotransporters. Membranes. 2022;12:1206. doi: https://doi.org/10.3390/membranes12121206

9. Dhondup T, Qian Q. Acid-Base and Electrolyte Disorders in Patients with and without Chronic Kidney Disease: An Update. Kidney Dis (Basel). 2017;3(4):136-48. doi: https://doi.org/10.1159/000479968

10. Sokolova KV, Stavytskyi VV, Konovalova SO, Podpletnya OA, Kovalenko SI, Avdeenko AP. Design and search for prospective diuretics (CA II Inhibitors) among aroylhydrazones of esters quinone oxime using in silico and in vivo methodology. Medicni perspektivi. 2022;27(4):27-37. doi: https://doi.org/10.26641/2307-0404.2022.4.271120

11. Sokolova KV, Podpletnya OA, Konovalova SO, Avdeenko AP, Komarovska-Porokhnyaves OZ, Lubenets VI, et al. N-Arylslfonyl-2-aroylamino-1,4-quinone imines and their hydrogenated analogues: toxicity prediction and prospects for use as diuretic agents. Medicni perspektivi. 2023;28(2):20-8. doi: https://doi.org/10.26641/2307-0404.2023.2.283152

12. European convention for the protection of vertebrate animal used for experimental and other scientific purposes [Internet]. Council of Europe, Strasbourg. 1986 [cited 2024 Feb 23]. 11 p. Available from: https://rm.coe.int/168007a67b

13. Stefanov OV. [Preclinical studies of medicines]. Kyiv: Avitsena; 2001. 528 p. Ukrainian.

14. Strahova OP, Androsov OI. [Statistical methods of processing the results of medical and biological research]. Lviv; 2021. 164 p. Ukrainian.

15. Sica DA, Carter B, Cushman W, Hamm L. Thiazide and loop diuretics. J Clin Hypertens (Greenwich). 2011;13(9):639-43. doi: https://doi.org/10.1111/j.1751-7176.2011.00512.x

16. Horisberger JD, Giebisch G. Potassium-sparing diuretics. Ren Physiol. 1987;10(3-4):198-220. doi: https://doi.org/10.1159/000173130

17. Bolton JL, Dunlap T. Formation and Biological Targets of Quinones: Cytotoxic versus Cytoprotective Effects. Chem Res Toxicol. 2017;30(1):13-37. doi: https://doi.org/10.1021/acs.chemrestox.6b00256

18. Antomonov MYu. [Mathematical processing and analysis of medical and biological data]. Kyiv: MYCz "Medynform"; 2018. p. 579. Ukrainian.

19. Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. J Basic Clin Pharm. 2016 Mar;7(2):27-31. doi: https://doi.org/10.4103/0976-0105.177703

20. Lunova HH, Lipkan HM, Viunytska LV, et al. [Clinical biochemistry: textbook: in 3 vol.] Lviv: PP «Mahnoliia 2006; 2023;2:372. Ukrainian.

21. Pickkers P, Garcha RS, Schachter M, Smits P, Hughes AD. Inhibition of carbonic anhydrase accounts for the direct vascular effects of hydrochlorothiazide. Hypertension. 1999 Apr;33(4):1043-8. doi: https://doi.org/10.1161/01.hyp.33.4.1043

Стаття надійшла до редакції 12.03.2024;
затверджена до публікації 03.05.2024