*Chem. Chem. Technol., 2023,*
*Vol. 17, No. 4, pp. 774–785*

**Chemistry**

# DESIGN, SYNTHESIS AND BIOLOGICAL ACTIVITY OF THE 4-THIOQUINOLINE DERIVATIVES

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https://doi.org/10.23939/chcht17.04.774

**Abstract.** One of the promising areas in the creation of bioregulators is the modeling of compounds that combine several pharmacophores. The design of new highly efficient and low-toxic cytoprotectors is largely based on the derivatives of nitrogen-containing heterocycles, and quinoline plays a significant role among these compounds.

The researchers evaluated the toxicity of the tested compounds *in silico*, *in vitro*, and *in vivo*, which allowed determining several factors that affect the level of toxic action of 4-thioquinoline derivatives and the direction of non-toxic substances in this sequence.

The studied 4-thioquinolines showed a moderate antiradical action in the experiment, inferior to the reference antioxidant Acetylcysteine. The most active compounds are 7-chloro-4-thioquinoline derivatives with propanoic acid residues in the 4th position. 2-(7-chloroquinolin-4-ylthio)propanoic acid and sodium salt of 2-amino-3-((7-chloroquinolin-4-yl)thio)propanoic acid showed the most promising results and their antioxidant action was higher than Tiotriazolin (the comparator) by 27 % and 41 %, respectively.

The studied compounds showed a protective effect under $H_2O_2$-induced oxidative stress against male sperm according to the main indicators of sperm fertility. It was found that the compounds with residues of succinic acid, cysteamine, or cysteine in the molecule structure are not inferior to reference drugs. On average, 2-((7-chloroquinolin-4-yl)thio)succinic acid and 2-((quinolin-4-yl)thio)ethanamine dihydrochloride exceeded the comparison drug Acetylcysteine and were on a par with the effect of Ascorbic acid.

**Keywords:** 4-thioquinolines, PASS-prognosis, toxicity, antioxidant activity, sperm cells protection.

## 1. Introduction

Sex hormone deficiency leads to various age-related diseases, among which metabolic syndrome is currently the undisputed leader.[1,2] It often leads to type 2 diabetes and androgen deficiency in men and results in a significantly increased risk of oxidative stress in sperm. The reason for the development of oxidative stress is the abnormal accumulation of molecules that contain oxygen in a non-reduced form (reactive oxygen species) – reactive oxygen species (ROS). Sperm oxidative stress is a condition in which ROS have a toxic effect due to the increased formation or as a result of disruptions of the antioxidant protection. Meanwhile, oxidative stress, along with high temperatures and radiation, is one of the leading factors that impair the fertile properties of ejaculate. Thus, oxidative stress can be considered as one of the causes of infertility.[3,4]

Despite the proven role of oxidative stress in the pathogenesis of male infertility, there is still insufficient evidence of the benefits of using laboratory tests to confirm the pathogenetic role of ROS in the pathology of fertility in men. Spermoplasm in fertile men has more complete activity than spermoplasm in infertile men. However, abnormal ROS levels detected in semen in infertile men are likely to be the result of increased ROS production.[5]

The design of new highly effective and low-toxic cytoprotectors with selective mechanisms of antioxidant activity is largely conducted with natural and artificial compounds based on derivatives of nitrogen-containing heterocycles, and quinoline (Q) plays a significant role among them.[6,7] Various quinoline derivatives are used as

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synthons in organic synthesis and molecular design, as well as known effective biologically active compounds. The heterocyclic quinoline system has highly reactive positions 2 and 4 (**Fig. 1**), which allows to modify the molecule and obtain new effective bioregulators.[7,8,9] Quinoline-based drugs have an exceptional place in the modern arsenal of antibacterial chemotherapeutic drugs. Derivatives of this azaheterocycle also have antitumor, analgesic, antipyretic, and neurotropic effects, are effective immunomodulators, and the like. In addition, quinoline derivatives are known as pesticides, veterinary drugs, dyes, analytical reagents, etc.[6,10-12]

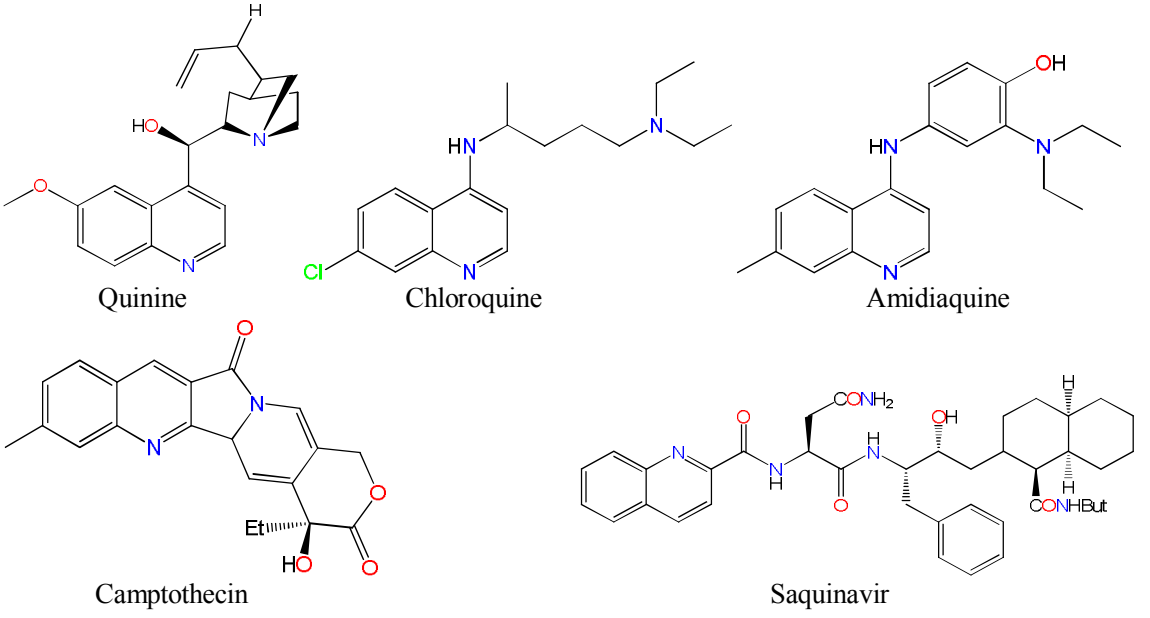
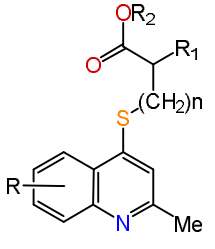



**Fig. 1.** Quinolines used in medicine

Derivatives (quinolin-4-ylthio)carboxylic acids are known as potential bioregulators. As of now, systematic studies have been conducted to purposefully search for bioactive molecules among derivatives (quinolin-4-ylthio)carboxylic acids that show antiradical, antihypoxic, cyto- and radioprotective effects.[13-15] They are effective ROS "traps", that have a positive effect on the cells metabolitotropic properties and restore their status.[9,16]

The introduction of halogens in the 6$^{th}$ position of the quinoline cycle (**Fig. 2**) led to increased lipophilicity of molecules (quinolin-4-ylthio)carboxylic acids and some increase in toxicity (acute toxicity, phytotoxicity, antibacterial action) and the emergence of new types of biological activity (analgetic, grow-regulatory, antitumor).[17,18]



*R = H, 6-F, Cl, Br; 6-$OCH_3$, $OC_2H_5$; 8-$OCH_3$, 5,8-$(OCH_3)_2$; $R_1$ = H, OH, $NH_2$; $R_2$ = H, $OCH_3$; n=0.1*

**Fig. 2.** (2-methylquinolin-4-ylthio)carboxylic acids derivatives

The researchers obtained the results of antimicrobial action of (quinolin-4-ylthio)carboxylic acid derivatives against resistant forms of *E. coli*. The tested compounds are active against these bacteria and inhibit its DNA gyrase B (GyrB) by forming various bonds with amino acid residues and magnesium ion in the active site of the enzyme. Substances with a methyl radical in the 2nd position of the quinoline cycle and a propanoic acid residue in the 4$^{th}$ position have the greatest effect.[19]

Modern methods for the selection of promising biologically active compounds include *in silico*, *in vitro*, and *in vivo* methods. To establish the feasibility of the synthesis, researchers employ virtual screening (*in silico* research) of new chemical structures and their combinations on the basis of a number of software developments. QSAR analysis, PASS, GUSAR (Germany), TEST (USA), AdmetSAR (PRC) methods allow the creation of reliable "structure - action", "structure - toxicity" models and predict the probable biological action of compounds.[13,20,24,25]

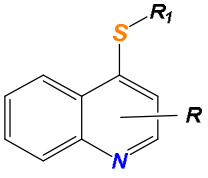
The combination of a heterocycle (Q, 7-chloroQ, 2-methylQ) and a mercaptoalkyl carboxylic acid residue or other thiols with potentially high reducing, antiradical, and antioxidant properties[7,14] in one molecule is of particular interest both in terms of chemical transformations and

potential bioregulators. To date, such compounds remain poorly understood and are a prospect for the development of new bioregulators. In view of the above, the preparation of (quinolin-4-yl)thio)carboxylic acid derivatives and their analogues, the study of chemical transformations and biological properties of these compounds determine the relevance of the study. The aim of this research is to select potential antioxidants and cytoprotectors among 4-thioquinoline derivatives by virtual screening, to study their toxicity and promising types of biological action.

## 2. Materials and Methods

### 2.1. Study Design

A combinatorial library based on 4-thioquinoline derivatives created (**Fig. 3**).




*R = H, 2-$CH_3$,*
*7-Cl $R_1$ = $CH_2COOH(Na)$,*
*$CH(CH_3)COOH(Na)$,*
*$CH_2CH_2COOH(Na)$,*
*$CH(COOH(Na))CH_2COOH(Na)$,*
*$CH_2CH_2NH_2$,*
*$CH_2CH(NH_2)COOH(Na)$*

**Fig. 3.** General structure of 4-thioquinoline derivatives

The prediction of biological activity was performed online using PASS (Prediction of Activity Spectra for Substances) software. The prognosis of probable activity was qualified by indicators of the probability of activity manifestation (Pa) and its absence (Pi). The prognosis was based on the structural formula of the chemical compound and was based on the analysis of the knowledge base, which includes data on the "structure - activity" relationship.[20]

### 2.2. Materials

The 4-chloroquinolines (**1**) ("UkrOrgSynthesis", Ukraine) were used as starting materials, as well as reagents and solvents ("UkrOrgSynthesis", Ukraine) for the synthesis of 4-thioquinolines.

### 2.3. Synthesis

The general reaction scheme for the synthesis of selected 4-thioquinolines (**2-5**) is shown by **Scheme 1.**

#### 2.3.1. General

The reactions and the purity of the synthesized compounds were controlled by the TLC on Macherey-Nagel plates (Germany). Mixtures of chloroform-methanol (1:1) and acetate-water (1:1) were used as an eluent. Manifestations of chromatograms were performed using UV rays.

The $^1$H NMR spectra were recorded on the "Bruker AC-300" (300 MHz) device in DMSO-$_{d6}$ and $D_2O$. Chemical shifts are expressed in parts per million (ppm) relative to tetramethylsilane (TMS). The coupling constants (J) are reported in Hertz (Hz).

LC-MS spectra were recorded on a high-performance liquid chromatography module of the HPLC system for Agilent 1260 Infinity and a proton-ionization diode-matrix probe.

All compounds were synthesized according to the well-known method[7] with the corresponding physico-chemical and spectral data, which correspond to the literature. The compounds were prepared according to a previously described methods.[7,15,19,21-23]

#### 2.3.2. ((Quinolin-4-yl)thio)carboxylic acids (2a,b,g-I, 4b) and its salts (3a,d, 5a,b).

Compounds were synthesized according to the previously described method.[19,21]

#### 2.3.3. ((7-Chloroquinolin-4-yl)thio)carboxylic acids (2d,e,4d) and its salts (3c).

Compounds were synthesized according to the previously described method.[15]

#### 2.3.4. 2-((Quinolin-4-yl)thio)succinic acid (2c,f,j-l) ) and its salts (3b,e).

Compounds were synthesized according to the previously described method.[21,22]

#### 2.3.5. 2-((Quinolin-4-yl)thio)ethanamine dihydrochloride (4a,c).

Compounds were synthesized according to the previously described method.[23]

### 2.4. Toxicity Tests

Toxicity studies of 4-thioquinoline derivatives were performed virtually and experimentally. Software solutions were used to build "structure – toxicity" models and predict $LD_{50}$ using GUSAR (Germany), TEST (USA) models.[24,25] Experimental studies were performed on white outbred mice of both sexes weighing 18-24 g, the mice were supplied by the nursery of the Institute of Pharmacology and Toxicology of the Academy of Medical Sciences of Ukraine (Kyiv). Animals were kept on a standard vivarium diet.[26,27] Substances were administered once intraperitoneally (i/p) in the form of a thin aqueous suspension in saline (Tween 80 stabilizer) or as a solution

(for water-soluble substances) with a volume not exceeding 1 mL. The four groups of animals were studied, each consisted of 2 animals. The researchers observed the behaviour of animals for 2 days, the condition of their skin and mucous membranes, nervous excitability, the number of living and dead animals were well examined.

The average lethal doses ($LD_{50}$) were determined by the V. Prozorovsky's method.[27] All studies met the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (http://www.arsal.ro/wp-content/uploads/2017/02/ETS-123-1.pdf).

## 2.5. Study of Antiradical Activity

Studying the effect of quinoline derivatives on the rate of adrenaline autooxidation (Epinephrine) based on ROS inhibition, was used for screening studies of antiradical activity. This method of evaluating antioxidant action under initial conditions was performed by evaluating the effect of synthesized substances on the inhibition of ROS in the autooxidation of adrenaline to adrenochrome in an alkaline environment, which leads to the formation of ROS. The more efficient the "trap" was, the less auto-oxidation of adrenaline was observed and the less amount of oxidation product – adrenochrome – was formed.[16,28]

The reaction was started by adding 0.4 mL of 0.01 M adrenalin hydrochloric acid to the system. The reaction was performed at a temperature of 36 $^0$C and exposure time of 3 minutes. The antioxidant action of the test compounds was determined spectrophotometrically by the degree of inhibition of adrenalin autooxidation in the colored product (adrenochrome) at a wavelength of 484 nm and expressed in percentage by the formula.[16,28]

Sulfur-containing reference drugs – antioxidants (Acetylcysteine, Thiotriazoline)[5,16] were used as comparison drugs. (**Fig. 5**). The study was performed using a concentration of test compounds of 25 µm.

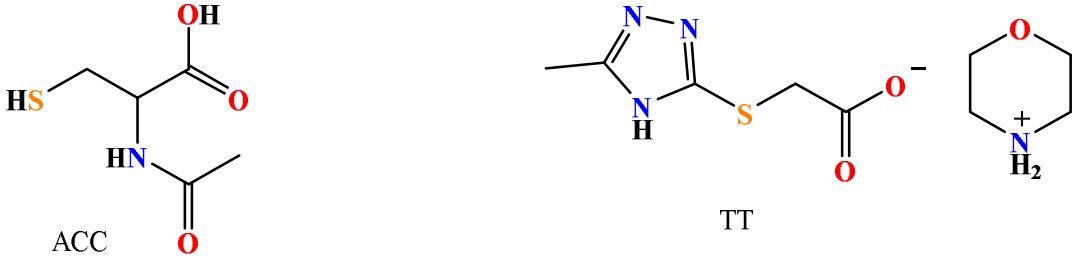



**Fig. 4.** Structures of Acetylcysteine (ACC) and Thiotriazoline (TT)

This method, endowed with high specificity and cost-effectiveness, allows to eliminate extraneous influence factors from the model system.[28]

## 2.6. Evaluation of the Effect of the Studied Substances on the Activity of Male Sperm *in Vitro*

The studies used native material – the ejaculate of fertile men (normozoospermia). To do this, researchers pre-evaluated the standard spermogram according to generally accepted methods in accordance with WHO guidelines[1,2]. Measurements were performed with the AFS-500-2 (Biola Scientific and Production Association) sperm fertility analyzer. The collected ejaculate was aliquoted to 100 µl, the aliquots were numbered, and the following substances were added:

To the first aliquot – saline solution – 10 µl (intact);

To the second aliquot – Acidum ascorbinicum with a concentration of $10^{-6}$ M – 10 µl;

To the third aliquot – ATC with a concentration of $10^{-6}$ M – 10 µl;

To the fourth aliquot – the test substance (quinoline derivative) with a concentration of $10^{-6}$ M – 10 µl;

To the fifth – saline solution – 10 µl, then hydrogen peroxide with a concentration of 200 µM – 0.5 µl (reference);

To the sixth – hydrogen peroxide with a concentration of 200 µM – 0.5 µl, then Acidum ascorbinicum with a concentration of $10^{-6}$ M – 10 µl;

To the seventh – hydrogen peroxide with a concentration of 200 µM – 0.5 µl, then ATC with a concentration of $10^{-6}$ M;

To the eighth – hydrogen peroxide with a concentration of 200 µM – 0.5 µl, then the test substance with a concentration of $10^{-6}$ M – 10 µl;

The resulted samples were incubated at 37 °C for 2 hours. Immediately after incubation, the quality criteria of sperm were studied: concentration, movement, and vital activity.

Measured indicators: total sperm concentration; total number of sperm in the ejaculate; rapid progressive motility (A); slow progressive motility (B); progressive motility (A + B); relative number of sperm with normal

morphology; concentration of functional sperm; concentration of sperm with progressive motility; concentration of immotile sperm; the total number of sperm with progressive motility; total number of functional sperm; total number of immotile and non-progressive sperm; average speed (A + B) of motile sperm; index of normal motile sperm.

Sperm vitality. To address the issues of differentiation of living and dead sperm, Bloom's supravital staining is performed. The researchers evaluated the presence or absence of cell membrane permeability for eosin dye (1% aqueous solution) according to WHO guidelines, followed by counting living and dead cells. Live sperm – not stained (transparent), dead – stained in pink. To prepare a smear, 1 drop of ejaculate and 1 drop of eosin dye are applied to a medical glass, the drops are mixed with each other with another glass just like the blood sample, and a smear is complete. After the smear was dried in air, the number of live and dead sperm was counted by microscopy under an immersion lens ($^{x}$ 100) with $^{x}$ 10 binoculars. 100 stained and unstained sperm were counted and the percentage of living and dead sperm was determined.

# 3. Results and Discussion

## 3.1. Virtual Screening

Virtual screening of 4-thioquinoline derivatives was done using the PASS software, which according to the structural formula of the compound predicts more than 1200 types of biological activity, including major and adverse pharmacological effects, action, mutagenicity, carcinogenicity, teratogenicity, and embryotoxicity.[29,30] PASS operation is based on the analysis of "structure-activity" dependences for substances from the tested sample containing more than 60,000 different biologically active substances (substances of known drugs and pharmacologically active compounds). The average accuracy of the prognosis is almost 85%, which is sufficient for the practical application of the PASS system.[31] The greater the value for a particular activity (Pa) and the smaller the value (Pi), the greater the chance to detect this activity in the experiment.[29,30] Predicting the likelihood of a substance exhibiting certain types of biological activity allows us to determine which tests are most suitable for studying the biological activity of a particular substance and which substances available to the researcher can have the desired effect.[32]

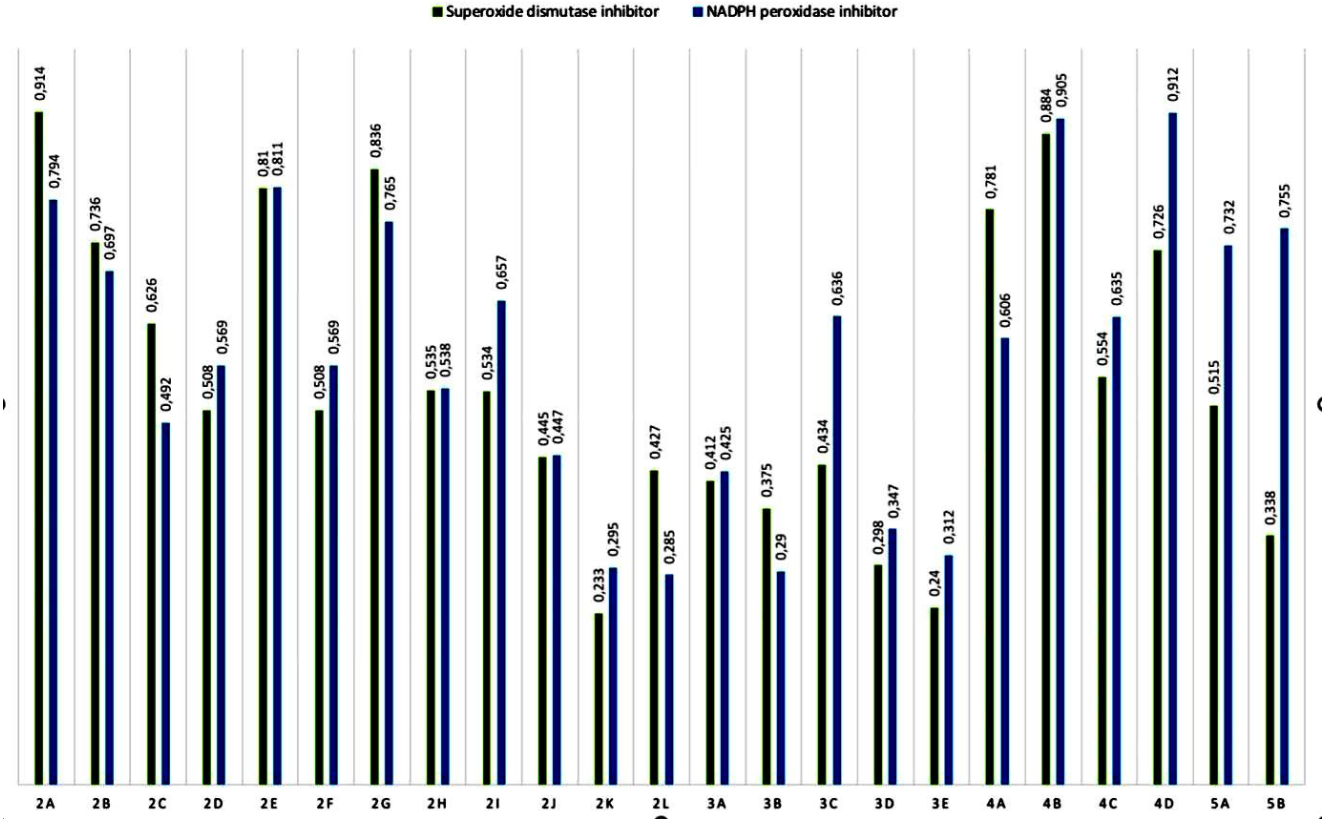



**Fig. 5.** Virtual screening of 4-thioquinolines

It should be noted that virtual screening of 4-thio derivatives of quinoline showed no high toxicity, embryotoxicity, terato- and carcinogenicity, and the prospect to find bioregulators that can affect the antioxidant defense system and show different types of activity among the above quinoline derivatives with most of the compounds.

## 3.2. Chemistry

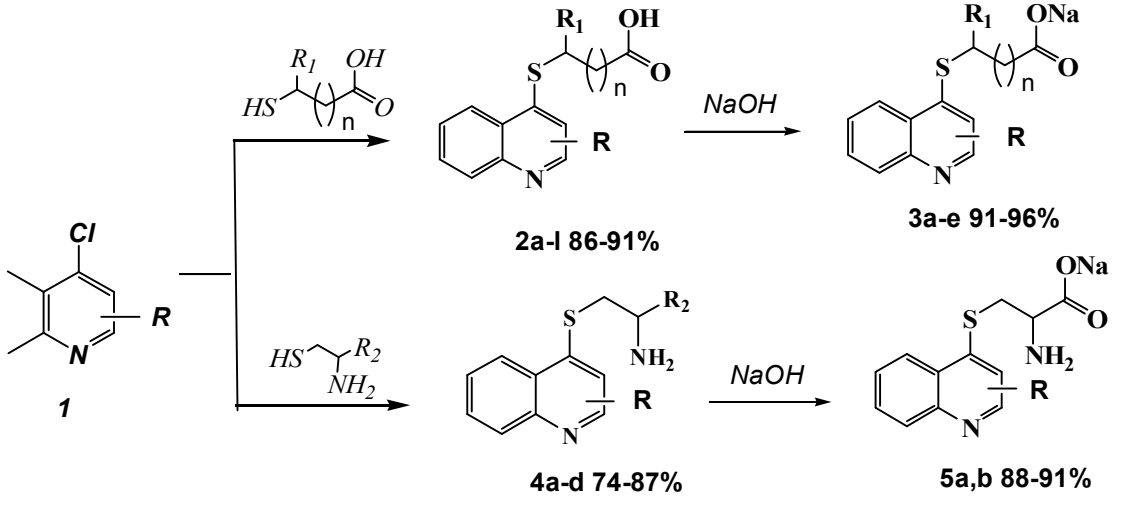
On the basis of 4-chloroquinolines (**1**), methods for the synthesis of (quinoline-4-ylthio)carboxylic acids (**2a-l, Scheme 1**) have been developed and shown to be convenient precursors for the preparation of various functional derivatives.[7] Neutralization of sodium hydroxide acid synthesized corresponding to water-soluble compounds – sodium salts (quinolin-4-ylthio)carboxylic acids (**3a-e, 5a,b**).

The investigated 4-thioderivatives of quinoline are shown in Table 1.

## 3.3. Toxicity Assessment

### 3.3.1. Virtual Assessment of Toxic Effects

A toxicity study of 4-thioquinolines using the GUSAR software (Germany) showed that they are low-toxic (**Table 2**). Their toxicity was predicted to be increased when the cysteamine residue (compounds **4a, c**) was introduced into the 4th position of the heterocycle. Unfortunately, the TEST software (USA) failed to assess the toxicity of some compounds and showed the greatest toxicity for derivatives that contain residues of thioacetic (**2a, g**) and thiolactic (**2h**) acids in the 4th position of quinoline.




***1a*** *R = H;* ***1b*** *R = 7-Cl;* ***1c*** *R = 2-CH₃*

***2a*** *R = H, R₁ = H, n = 0;* ***2b*** *R = H, R₁ = H, n = 1;* ***2c*** *R = H, R₁ = COOH, n = 1;* ***2d*** *R = 7-Cl, R₁ = H, n = 0;* ***2e*** *R = 7-Cl, R₁ = CH₃, n = 0;* ***2f*** *R = 7-Cl, R₁ = COOH, n = 1;* ***2g*** *R = 2-CH₃, R₁ = H, n = 0;* ***2h*** *R = 2-CH₃, R₁ = CH₃, n = 0;* ***2i*** *R = 2-CH₃, R₁ = H, n = 1;* ***2j*** *R = 2-CH₃, R₁ = COOH, n = 1*

***3a*** *R = H, R₁ = H, n = 1;* ***3b*** *R = H, R₁ = COONa, n = 1;* ***3c*** *R = 7-Cl, R₁ = H, n = 0;* ***3d*** *R = 7-Cl, R₁ = CH₃, n = 0;* ***3e*** *R = 7-Cl, R₁ = COONa, n = 1*

***4a**** *R = H, R₂ = H;* ***4b*** *R = H, R₂ = COOH;* ***4c**** *R = 7-Cl, R₂ = H;* ***4d*** *R = 7-Cl, R₁ = COOH;* ***5a*** *R = H,* ***5b*** *R = 7-Cl*

* – the compound is obtained in the form of dihydrochloride

**Scheme 1.** Synthesis of quinoline 4-thioderivatives

**Table 1.** The characteristics of the synthesized compounds

| Compound | Molecular formula (m. wt.) | Chemical name | Melting points, °C | $^1$H NMR (300 MHz, DMSO-*d*6 ($D_2O$)) |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |
| **2a** | $C_{11}H_9NO_2S$ (219.26) | 2-((quinolin-4-yl)thio)acetic acid | 223-5 | 8.65-7.25 (m, 6H, ArH), 3.90 (s, 2H, $SCH_2$) |
| **2b** | $C_{12}H_{11}NO_2S$ (233.29) | 3-((quinolin-4-yl)thio)propanoic acid | 216-8 | 8.90-7.70 (m, 6H, ArH), 3.50 (t, J=6.8 Hz, $SCH_2$), 2.75 (t, J=6.1 Hz, $CH_2$) |

Continuation of the **Table 1**

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| **2c** | $C_{13}H_{11}NO_4S$ (277.30) | 2-((quinolin-4-yl)thio)succinic acid | 189-1 | 8.75-7.60 (m, 6H, ArH), 4.40 (t, J =7.0 Hz, SCH), 2.75 (d, J =7.5 Hz, $CH_2$) |
| **2d** | $C_{11}H_9ClNO_2S$ (253.70) | 2-((7-chloroquinolin-4-yl)thio)acetic acid | 229-30 | 8.95-7.60 (m, 5H, ArH), 4.30 (s, 2H, $SCH_2$) |
| **2e** | $C_{12}H_{10}ClNO_2S$ (267.73) | 2-((7-chloroquinolin-4-yl)thio)propanoic acid | 212-4 | 8.70-7.65 (m, 5H, ArH), 4.65 (q, J =7.1 Hz, SCH), 1.50 (d, J =6.1 Hz, $CH_3$) |
| **2f** | $C_{13}H_{10}ClNO_4S$ (311.74) | 2-((7-chloroquinolin-4-yl)thio)succinic acid | 188-90 | 8.90-7.60 (m, 5H, ArH), 4.95 (t, J =7.0 Hz, SCH), 3.05 (d, J =7.5 Hz, $CH_2$) |
| **2g** | $C_{12}H_{11}NO_2S$ (233.29) | 2-((2-methylquinolin-4-yl)thio)acetic acid | 191-3 | 8.05-7.25 (m, 5H, ArH), 3.90 (s, 2H, $SCH_2$), 2.65 (s, 3H, $CH_3$) |
| **2h** | $C_{13}H_{13}NO_2S$ (247.31) | 2-((2-methylquinolin-4-yl)thio)propanoic acid | 186-8 | 8.15-7.35 (m, 5H, ArH), 4.60 (q, J =7.1 Hz, SCH), 2.60 (s, 3H, $CH_3$), 1.55 (d, J=6.1 Hz, $CH_3$) |
| **2i** | $C_{13}H_{13}NO_2S$ (247.31) | 3-((2-methylquinolin-4-yl)thio)propanoic acid | 217-9 | 8.75-7.50 (m, 5H, ArH), 3.40 (t, J =7.2 Hz, $SCH_2$), 2.70 (s, 3H, $CH_3$), 2.60 (t, J =7.1 Hz, $CH_2$) |
| **2j** | $C_{14}H_{13}NO_4S$ (291.32) | 2-((2-methylquinolin-4-yl)thio)succinic acid | 194-6 | 8.30-7.60 (m, 5H, ArH), 4.90 (t, J =7.0 Hz, SCH), 3.05 (d, J =7.5 Hz, $CH_2$), 2.60 (s, 3H, $CH_3$) |
| **2k** | $C_{14}H_{12}FNO_4S$ (309.31) | 2-((6-fluoro-2-methylquinolin-4-yl)thio)succinic acid | 198-201 | 8.20-7.55 (m, 4H, ArH), 4.95 (t, J =7.0 Hz, SCH), 3.00 (d, J =7.5 Hz, $CH_2$), 2.70 (s, 3H, $CH_3$) |
| **2l** | $C_{16}H_{17}NO_5S$ (335.372) | 2-((6-ethoxy-2-methylquinolin-4-yl)thio)succinic acid | 197-9 | 8.15-7.24 (m, 4H, ArH), 4.70 (k, J =7.0 Hz, SCH), 2.90 (t, J =7.5 Hz, $CH_2$), 2.55 (s, 3H, $CH_3$) |
| **3a** | $C_{12}H_{10}NNaO_2S$ (255.27) | sodium 3-((quinolin-4-yl)thio)propanoate | >250 | 8.75-7.40 (m, 6H, ArH), 3.40 (t, J=6.8 Hz, $SCH_2$), 2.55 (t, J=6.1 Hz, $CH_2$) |
| **3b** | $C_{13}H_9NNa_2O_4S$ (321.26) | disodium 2-((quinolin-4-yl)thio)succinate | >250 | ($D_2O$) 8.80-7.60 (m, 6H, ArH), 4.40 (t, J =7.0 Hz, SCH), 2.75 (d, J =7.5 Hz, $CH_2$) |
| **3c** | $C_{11}H_7ClNNaO_2S$ (275.69) | sodium 2-((7-chloroquinolin-4-yl)thio)acetate | >250 | 8.65-7.30 (m, 5H, ArH), 3.70 (s, 2H, $SCH_2$) |
| **3d** | $C_{12}H_9ClNNaO_2S$ (289.71) | sodium 2-((7-chloroquinolin-4-yl)thio)propanoate | >250 | 8.60-7.35 (m, 5H, ArH), 4.30 (q, J =7.1 Hz, SCH), 1.45 (d, J =6.1 Hz, 3H, $CH_3$)) |
| **3e** | $C_{13}H_8ClNNa_2O_4S$ (355.70) | disodium 2-((7-chloroquinolin-4-yl)thio)succinate | >250 | ($D_2O$) 8.70-7.45 (m, 5H, ArH), 4.55 (m, 1H, SCH), 3.00 (m, 2H, $SCH_2$) |
| **4a** | $C_{11}H_{14}Cl_2N_2S$ (277.21) | 2-((quinolin-4-yl)thio)ethanamine dihydrochloride | >250 | 8.90-7.80 (m, 6H, ArH), 8.75 (s, 3H, $NH_3^+$), 3.75 (t, J=7.2 Hz, 2H, $SCH_2$), 3.10 (m, J =7.1 Hz, 2H, $NCH_2$) |
| **4b** | $C_{12}H_{12}N_2O_2S$ (248.30) | 2-amino-3-((quinolin-4-yl)thio)propanoic acid | 197-8 | 9.25 (s, 3H, $NH_3^+$), 8.80-7.60 (m, 6H, ArH), 4.50 (m, J=7.1 Hz, 1H, NCH), 3.80 (m, J =7.2 Hz, 2H, $SCH_2$) |
| **4c** | $C_{10}H_{11}Cl_3N_2S$ (311.66) | 2-((7-chloroquinolin -4-yl)thio)ethanamine dihydrochloride | >250 | 9.00-7.90 (m, 5H, ArH), 8.80 (s, 3H, $NH_3^+$), 3.85 (t, J=7.2 Hz, 2H, $SCH_2$), 3.10 (m, J =7.1 Hz, 2H, $NCH_2$) |
| **4d** | $C_{12}H_{11}ClN_2O_2S$ (282.75) | 2-amino-((7-chloro-((quinolin-4-yl)thio)propanoic acid | 177-9 | 9.30 (s, 3H, $NH_3^+$), 9.00-7.70 (m, 5H, ArH), 4.55 (m, J=7.1 Hz, 1H, NCH), 3.90 (m, J =7.2 Hz, 2H, $SCH_2$) |
| **5a** | $C_{12}H_{11}N_2NaO_2S$ (270.28) | sodium 2-amino-3-((quinolin-4-yl)thio)propanoate | >250 | 8.75-7.60 (m, 6H, ArH), 6.50 (s, 2H, $NH_2$), 4.35 (m, J=7.1 Hz, 1H, NCH), 3.75 (m, J =7.2 Hz, 2H, $SCH_2$) |
| **5b** | $C_{12}H_{10}ClN_2NaO_2S$ (304.73) | sodium 2-amino-3-((7-chloroquinolin-4-yl)thio)propanoate | >250 | 8.80-7.70 (m, 5H, ArH), 6,60 (s, 2H, $NH_2$), 4.50 (m, J=7.1 Hz, 1H, NCH), 3.90 (m, J=7.2 Hz, 2H, $SCH_2$) |

**Table 2.** Toxicity of quinoline derivatives *in silico*

| № | TEST | | GUSAR | | | |
|---|---|---|---|---|---|---|
| | Oral rat $LD_{50}$ - Log10 (mol/kg) | Oral rat $LD_{50}$ mg/kg | mg/kg | Intravenous injection mg/kg | Orally mg/kg | Subcutaneous injection mg/kg |
| 2a | 2.41 | 852.90 | 476.5 | 259.0 | 976.4 | 1045.0 |
| 2b | 2.39 | 952.69 | 339.1 | 364.4 | 715.0 | 590.0 |
| 2c | 2.40 | 1110.12 | 329.9 | 415.9 | 866.0 | 394.2 |
| 2d | 2.46 | 879.47 | 292.3 | 355.4 | 758.5 | 1079.0 |
| 2e | 2.53 | 786.76 | 312.8 | 271.1 | 308.4 | 1346.0 |
| 2f | 2.59 | 802.42 | 175.3 | 443.2 | 901.3 | 1125.0 |
| 2g | 2.62 | 558.02 | 633.3 | 377.1 | 935.8 | 699.0 |
| 2h | 2.66 | 545.01 | 489.5 | 246.9 | 608.2 | 638.8 |
| 2i | 2.19 | 1598.49 | 494.8 | 500.4 | 560.8 | 687.5 |
| 2j | - | - | 282.0 | 266.6 | 613.4 | 515.8 |
| 2k | 2.20 | 1938.28 | 245.8 | 544.1 | 946.3 | 603.8 |
| 2l | 2.09 | 2707.40 | 377.2 | 241.7 | 692.6 | 1342.0 |
| 3a | - | - | 253.9 | 171.1 | 410.9 | 262.7 |
| 3b | - | - | 645.4 | 60.85 | 228.2 | 242.6 |
| 3c | - | - | 385.4 | 217.3 | 589.0 | 742.4 |
| 3d | - | - | 542.6 | 118.5 | 235.1 | 1222.0 |
| 3e | - | - | 331.7 | 73.98 | 498.0 | 454.5 |
| 4a | - | - | 240.8 | 94.02 | 1490.0 | 853.6 |
| 4b | 2.34 | 1145.01 | 1271.0 | 512.1 | 2905.0 | 1027.0 |
| 4c | - | - | 309.5 | 127.1 | 750.5 | 2121.0 |
| 4d | 2.33 | 1332.03 | 610.9 | 486.5 | 929.9 | 1583.0 |
| 5a | - | - | 584.3 | 132.5 | 154.5 | 291.9 |
| 5b | - | - | 506.8 | 145.0 | 712.9 | 1245.0 |

### 3.3.2. Assessment of Toxic Effect on the Progressive Sperm Motility

The total number of sperm with progressive motility is an important indicator of the toxic effect of compounds, the value of which is directly proportional to the value of the toxic effect of the substance.[2] Native material was used for the study – the ejaculate of fertile men (normozoospermia). The greatest toxic effects in this model were shown by cysteamine derivatives (2-(quinolin-4-ylthio)ethanamine (**4a**) and 2-(7-chloroquinolin-4-ylthio)ethanamine (**4c**) dihydrochlorides), which reduce this value by 85-90 % compared to intact one (**Fig. 6**). 4-Thioquinolines, which contain an acetic acid residue (**2d, 3c**) and / or a chlorine atom in the 7th position of quinoline (**2d** and **3c, e**) show moderate toxicity, and reduce the rate of progressive motility by 12-20 %. A number of compounds, on the other hand, increase the rate of progressive motility, which means that they are non-toxic. Thus, compounds **2e** and **3b** (2-((quinolin-4-yl)thio) succinic acid and its disodium salt) increase the rate of progressive sperm motility by 25-0 % compared to intact one and compete with the reference substances Acidum ascorbinicum and ATC.

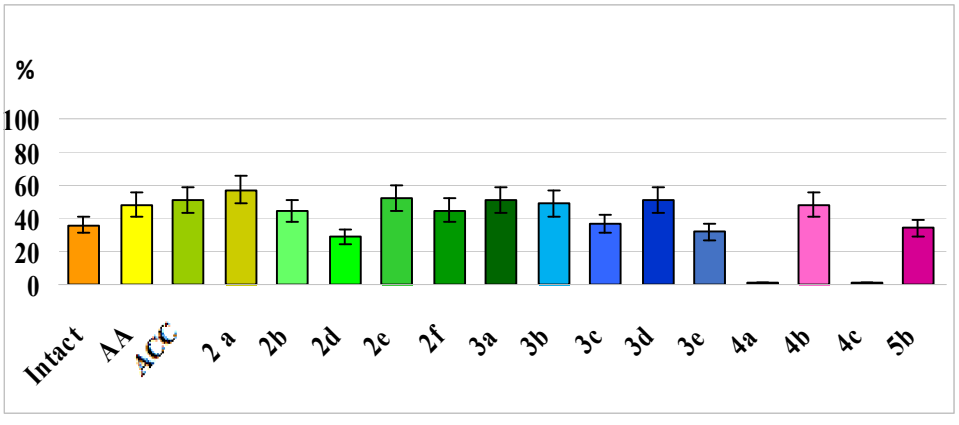



**Fig. 6.** Progressive motility of 7-*R*-4-thioquinoline derivatives *in vitro*

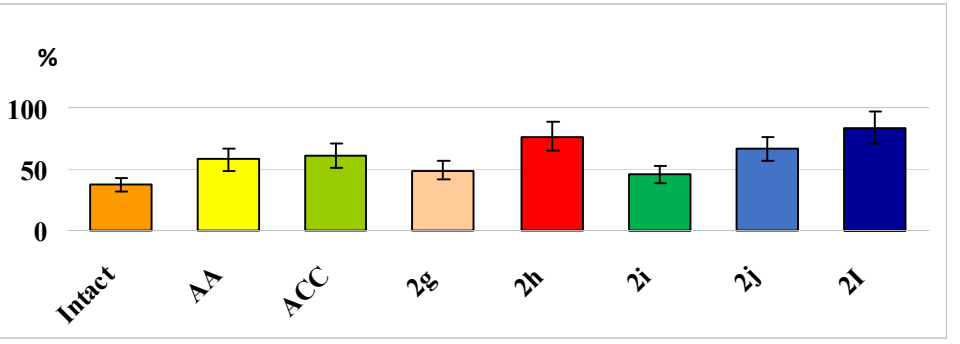



**Fig. 7.** Progressive motility of (2-methylquinolin-4-ylthio)carboxylic acids derivatives *in vitro*

Among the derivatives of (2-methylquinolin-4-ylthio)carboxylic acids, the most toxic compounds had acetic and propionic acid residues in the 4th position (**2g** and **2i**, **Fig. 7**). They showed moderate toxicity, inhibiting progressive motility by 19 and 24 %, respectively.

### 3.3.3. Toxicity Assessment *in Vivo*

A randomized toxicity study was performed on mice. The most toxic compounds contain a residue of acetic acid or cysteamine (S-cysteamines). Interestingly, the introduction of a carboxyl group into the structure of S-cysteamine (cysteine derivatives **5a, b**) led to a significant (2.5-3 times) decrease in toxicity. 4-Thio derivatives with chlorine residue in the 7th position of the azaheterocycle are 30-50% more toxic than their analogues without a substitute.

Thus, the introduction of the quinoline cycle of methyl radical into the 2nd position or chlorine into the 7th had no significant effect on the toxicity of compounds of this series; the nature of the substituent in the 4th position of the heterocycle had more importance for the toxicity levels.

## 3.4. Study of Antioxidant Action

### 3.4.1. Study of Antioxidant Activity *in Vitro*

A purposeful search of BAS with antioxidant action involves a detailed study of the effect of experimental models of free radical oxidation. This is primarily due to the fact that free radical oxidation is a leading link in many diseases, which differ in etiopathogenetic factors, and thus in the action of the free radicals' initiation. One of the methods of studying antioxidant action, which reflects the primary mechanisms is *in vitro* testing of the studied compounds on the superoxide radical (SOR) ($O_2 + e^- \rightarrow O_2^{\bullet -}$). The structural features of the oxygen molecule (biradical nature, two unpaired electrons with parallel spins in the outer orbital), which manifest themselves in interaction with substances capable of oxidation, lead to the formation of ROS − compounds with a short lifetime. In particular, a superoxide radical (superoxide anion radical; dioxide) can be formed, which is a good reducing agent, a moderate oxidizing agent, has the properties of an intracellular messenger, and is involved in the oxidative modification of sulfur-containing and amino groups of low-molecular-weight compounds.[5,7,16] Most of the tested compounds for further experimental tests were selected based on the virtual screening.

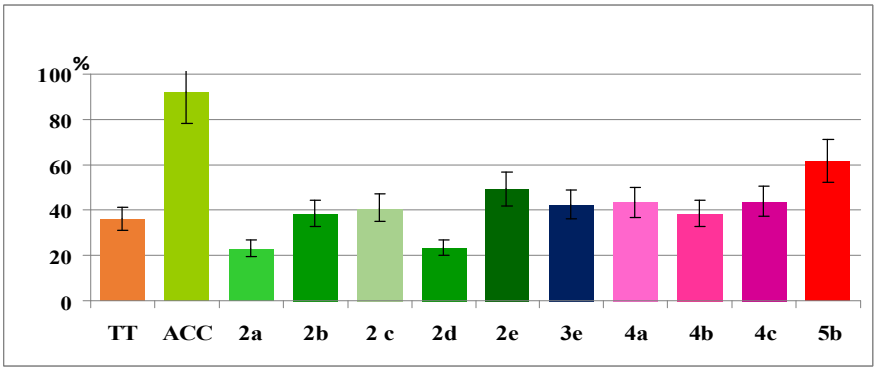



**Fig. 8.** Antioxidant action of 4-thioquinoline derivatives

The studied 4-thioquinolines in most cases showed a moderate antiradical action in an experiment inferior to the reference antioxidant ATC. The most active compounds are 7-chloro-4-thioquinoline derivatives with propanoic acid residues in the 4th position (**Fig. 8**). Thus, 2-(7-chloroquinolin-4-ylthio)propanoic acid (**2e**) and the sodium salt of 2-amino-3-((7-chloroquinolin-4-yl)thio)propanoic acid (**5a**) were the most promising; their antioxidant action was more efficient than that of the TT comparison drug by 27 % and 41 %, respectively. Other compounds that deserve attention include cysteamine derivatives (**4a, 4c**), which in the experimental conditions show a pronounced antioxidant effect that is on a par with the TT comparison drug, but their effect is inferior to the antioxidant effect of ATC.

### 3.4.1. Evaluation of Protection of Male Sperm from $H_2O_2$-Induced Oxidative Stress *in Vitro*

Oxidative stress of sperm is known as a condition in which ROS have a toxic effect due to their excess formation or as a result of disruptions in antioxidant protection. After oxidative stress is developed, ejaculate develops an imbalance between ROS and substances with antioxidant action in the cell. Excess production of ROS correlates with decreased sperm motility. Studies indicate that high levels of ROS are found in sperm samples in up to 40 % of infertile men. When it comes to repair, unfortunately, sperm are unable to repair damage caused by oxidative stress because their cytoplasm lacks antioxidant defense enzymes that should invariably lead to repair.

In order to study the effect of oxidative stress, which was created in ROS cells, including hydrogen peroxide, on the concentration, movement, viability of sperm, *in vitro* experiments were performed using 3 % hydrogen peroxide. To protect cells from oxidative stress caused by hydrogen peroxide 4-thioquinolines and reference drugs with antioxidant properties (Ascorbic acid and ATC) were used.

The study is based on the evaluation of the male sperm protection from $H_2O_2$-induced oxidative stress *in vitro* using 4-thioquinoline derivatives. There are no known studies performed or being performed on the matter.

The results presented in the tables and graphs (Figs. 9, 10) show that the studied compounds have a protective effect for male sperm. According to such spermogram parameters as progressive motility, rapid and progressive motility, concentration of functional sperm, concentration of sperm with progressive motility, total number of sperm with progressive motility of compounds **2f, 2I, 4a, 4c, 5a**, which have acid residues in the structure of the molecule cysteamine or cysteine, were on par with the comparison drugs. The average motility for 2-((7-chloroquinolin-4-yl)thio)succinic acid (**2f**) and 2-(quinolin-4-yl)thio)ethanamine dihydrochloride (**4a**) exceeded the ATC comparison drug by 8-10 % and were on par with Acidum ascorbinicum (Fig. 9). Derivatives of (2-methylquinolin-4-ylthio)carboxylic acids with the $H_2O_2$-induced oxidative stress were generally inferior to the comparison drugs Acidum ascorbinicum and ATC (Fig. 10). The data presented correlates with the results of calculated prognosis and the study of antiradical action.

These results indicate that 4-thioquinoline derivatives are promising for the protection of male sperm under conditions of oxidative stress and require further in-depth studies of the antioxidant protection mechanisms.

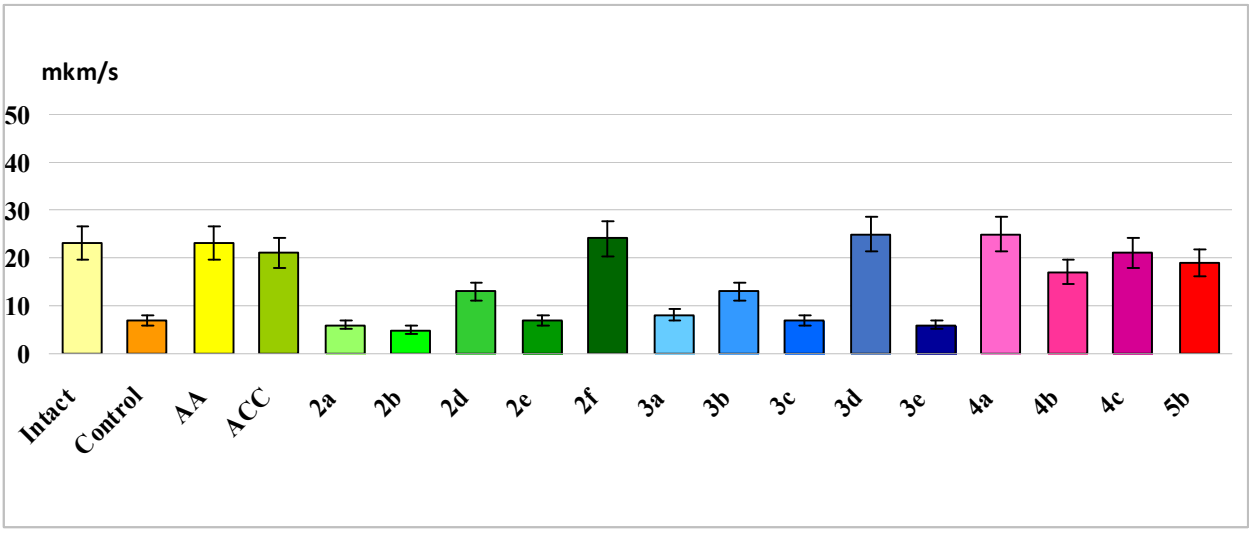



**Fig. 9.** The average sperm motility speed (A + B) with the introduction of 7-R-4-thioquinoline derivatives during $H_2O_2$-induced oxidative stress *in vitro*

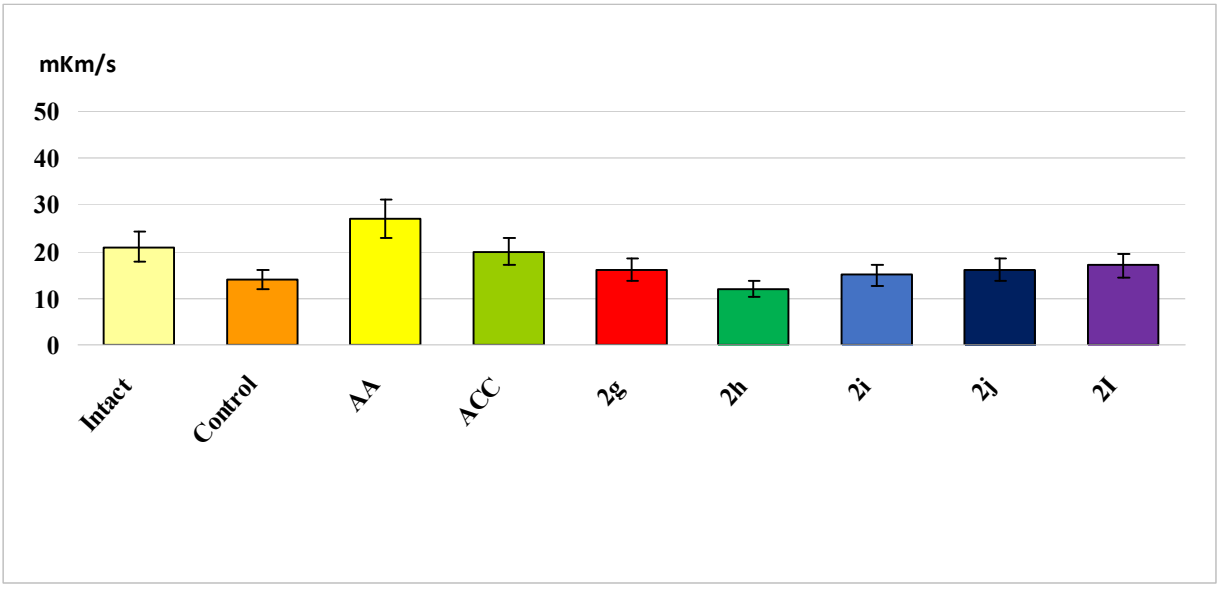



**Fig. 10.** The average sperm motility speed (A + B) with administration derivatives of (2-methylquinolin-4-ylthio)carboxylic acids during $H_2O_2$-induced oxidative stress *in vitro*

## 4. Conclusions

Virtual (PASS, GUSAR, TEST) and experimental studies *in vitro* and *in vivo* have shown their high biological potential with low toxicity. The most toxic compounds were cysteamine residue, which in the experimental conditions show a pronounced antioxidant effect, which is on par with the comparison drugs. 4-Thioquinoline derivatives had the properties to create SOR traps and showed protective activity for male sperm under conditions of oxidative stress. This number of substances is promising in terms of finding bioregulators with a protective effect in disorders of spermatogenesis.

## Conflict of Interest

The authors declared no conflict of interest.

## Supporting Information

The supporting information document contains technical description of computational procedures, additional figures and tables.

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*Received: April 02, 2023 / Revised: August 09, 2023 / Accepted: October 25, 2023*

## СТВОРЕННЯ, СИНТЕЗ І БІОЛОГІЧНА АКТИВНІСТЬ ПОХІДНИХ 4-ТІОХІНОЛІНУ

***Анотація.*** *Одним із перспективних напрямів у створенні біорегуляторів є моделювання сполук, що поєднують декілька фармакофорів. Створення нових високоефективних і малотоксичних цитопротекторів значною мірою базується на похідних азотовмісних гетероциклів, серед яких значну роль відіграє хінолін.*

*Проведені дослідження дозволили оцінити токсичність досліджуваних сполук in silico, in vitro та in vivo, що дало змогу визначити декілька факторів, які впливають на рівень токсичної дії похідних 4-тіохіноліну, і напрям пошуку нетоксичних речовин у цьому ряду сполук.*

*Досліджувані 4-тіохіноліни показали в експерименті помірну антирадикальну дію, поступаючись референтному антиоксиданту – ацетилцистеїну. Найбільш активними сполуками є похідні 7-хлор-4-тіохіноліну із залишками пропанової кислоти в 4-му положенні – 2-(7-хлорхінолін-4-ілтіо)пропанова кислота та натрієва сіль 2-аміно-3-((7-хлорхінолін-4-іл)тіо)пропанової кислоти. Антиоксидантна дія цих сполук була вищою, ніж тіотриазолін (препарат порівняння) на 27 % та 41 % відповідно.*

*Досліджувані сполуки показали високу захисну дію при $H_2O_2$-індукованому окисному стресі щодо чоловічої сперми за основними показниками фертильності сперми. Встановлено, що сполуки із залишками янтарної кислоти, цистеаміну або цистеїну в структурі молекули не поступаються препаратам порівняння. У середньому 2-((7-хлорхінолін-4-іл)тіо) бурштинова кислота та 2-((хінолін-4-іл)тіо) етанаміну дигідрохлорид перевищували препарат порівняння ацетилцистеїн і були на рівні з аскорбіновою кислотою.*

***Ключові слова:*** *4-тіохіноліни, PASS-прогноз, токсичність, антиоксидантна активність, захист сперматозоїдів.*