SYNTHESIS AND BIOLOGICAL ACTIVITY OF DERIVATIVES (2-METHYL (PHENYL) -6-R-QUINOLIN-4-YL-SULPHANYL) CARBOXYLIC ACIDS

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Abstract. *Selection of potential bioactive molecules (2-methyl (phenyl) -6-R-quinolin-4-yl-sulfanyl) carboxylic acids and their derivatives with virtual screening (PASS-prognosis) and QSAR analysis was carried out. The most promising compounds were synthesized and their toxic effects were studied. They found themselves as little or moderately toxic biologically active substances. The conducted experiments indicate the expediency of in-depth study of derivatives (2-methyl (phenyl) -6-R-quinolin-4-yl-sulfanyl) carboxylic acids as potential bioregulators.*

Keywords*: 4-sulfanil derivative of quinoline, mercapto carboxylic acids, PASS-prognosis, QSAR-analysis, toxicity.*

Introduction. The study of the dependencies between the chemical structure of a substance and the biological action, what it shows, relies on the basic provisions of the structural theory of chemistry, which defines the physical and chemical properties of the compound as a derivative of the chemical structure. This makes it possible to study for certain chemicals certain factors (descriptors), conducting qualitative (SAR) and quantitative (QSAR) correlations between them and biological activity. Various descriptors are used for this - quantum-chemical and topological characteristics, as well as parameters related to the whole molecule [164]. Based on previously conducted studies, SAR and QSAR correlations [5, 13, 15, 38, 119, 125, 137] QuS software was developed. The use of QuS made it possible to analyze the physicochemical properties and descriptors of the molecular structure (DMS) of 4-thiohinolines [162].

The goal of this work is the selection by virtual screening and QSAR-analysis of potential bioregulators with AO mechanism of action and low toxicity among derivatives of 6-R-substituted (2-methyl (phenyl) quinolin-4-yl-sulfanyl) carboxylic acids as possible regenerators and cytoprotectors and their synthesis.

Materials and methods of research. Forecast of biological activity is carried out *online* using the PASS (Prediction of Activity Spectra for Substances) program. The forecast of probable activity was characterized by indicators of the probability of manifestation of activity (Pa) and its absence (Pi). The forecast was carried out according to the structural formula of the chemical compound and it was based on the analysis of the knowledge base, which includes the data of the connection "structure - activity" [11].

An analysis of the correlation indices of toxic effects in a series of 4-thio-derivative quinoline was conducted [10-12]. The factors of the molecular structure of the derivatives of 4-thioquinoline, which influence the size of their half-lethal dose (LD_{50}) were determined, and the corresponding QSAR model - "structure-toxicity" was constructed.

The study of acute toxicity of quinoline derivatives was determined on intact, unborn mice of both genera weighing 16-24 g. Substances were injected intraperitoneally in the form of a thin water slurry, which was stabilized by a tween 80, or in the form of a solution (water-soluble) in a volume of not more than 1 ml. The control group of animals was injected a physiological solution with the tween 80 in the same volume, as the study groups. Each group consisted of 5 animals. LD_{50} was determined by the Kerber method [13].

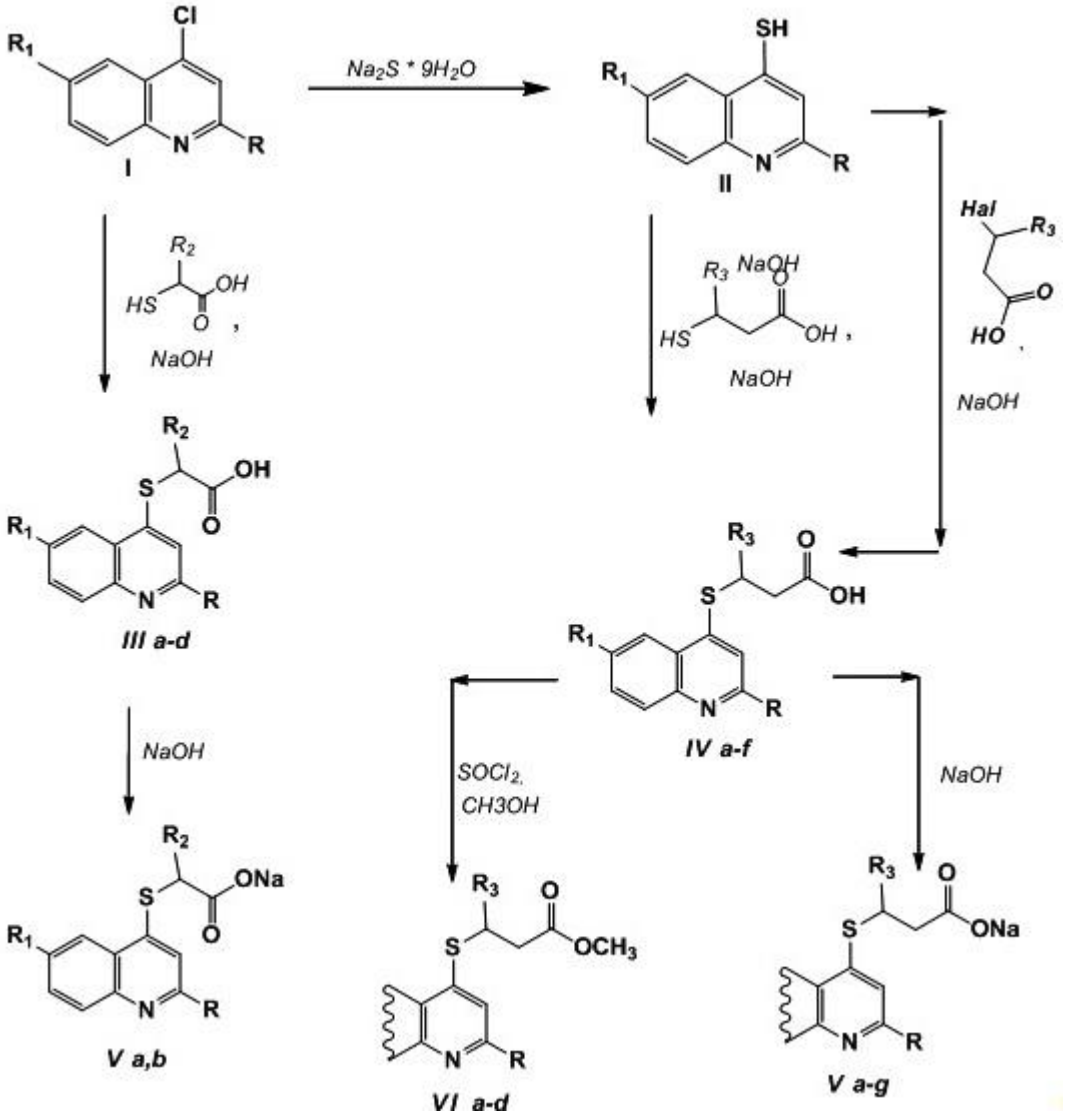
Results. New derivatives of (2-methyl (phenyl) -6-R-quinolin-4-yl-sulfanyl) carboxylic acid were tested by virtual screening (PASS-prognosis) for their potential biologically active properties. A combinatorial library was created for compounds, whose structures correspond to the "Lipinsky Rules" (the rule of "five") [17], which defines the criteria for predicting the bioavailability of any molecule. The compounds in the prognosis showed cerebroprotective and hepatoprotective, antiparasitic, antiviral, diuretic, antioxidant effects. The QSAR-analysis of 2-methyl (phenyl) quinoline-4-thiol

derivatives was performed, the factors of molecular structures of the 2-methylquinolin-4-thiol derivatives, that had an effect on their half-lethal dose were determined, corresponding QSAR-models were constructed and their predictive power was compared with already existing data "structure-toxicity". Several thousand regression equations with different statistical reliability and predictive power were constructed using QuS - own software development. Ultimately, statistically reliable QSAR-models were constructed that linked the LD_{50} values of the 2-methyl (phenyl) quinolin-4-thiol derivatives studied with their molecular structure.

A number of factors that influence the level of toxic activity in a number of derivatives (2-methyl (phenyl) -6-R-quinolin-4-yl-sulfanyl) carboxylic acids were determined and the direction of creating the most non-toxic compounds was defined.

Based on the results obtained *in silico* (virtual screening and QSAR-analysis), the directions of promising experimental biological research and the most promising low-toxic compounds with a wide spectrum of potential biological properties were worked out.

A purposeful synthesis of these compounds was carried out according to the scheme.



R=CH3, C6H5; R1=H, 6-F, 6-OCH3, 6-OC2H5; R2=H, CH3; R3=H, COOH; Alk=CH3

Fig. 1. Scheme
Synthesis of derivatives (2-methyl (phenyl) -6-R-quinolin-4-yl-sulfanyl) carboxylic acids

As a result of experimental studies, acute toxicity (2-methyl (phenyl) -6-R-quinolin-4-ylsulfanyl) carboxylic acids and their derivatives (in depending on the presence in their molecules of certain functional groups) was studied. The results of the tests indicate that the 6-substituted sulfanil derivatives are moderately or low-toxic substances [19] - their LD_{50} is within the range of 43-190 mg /

kg. Most of the new synthesized compounds are more toxic (1.5-3 times) than their analogues without a substituent [10]. This is confirmed by the fact that the input of the lipophilic substituent in the second position of the quinoline cycle leads to an increase in the toxic effect [6].

These substances have proven themselves as promising antioxidants [6], as well as bioregulators with a variety of biological effects, which will be reported in addition.

Conclusions. A virtual screening and mathematical models that link the peculiarities of the structure of the 2-methyl (phenyl) quinoline-4-thiol derivatives with their half-lethal dose and the determination of the most influential molecular structures that influence the toxicity were constructed. New low-toxic (6-R-2- (phenyl) methylquinolin-4-yl-sulfanyl) carboxylic acids and their derivatives were synthesized as potential bioregulators. Experimental studies of toxicity of compounds were carried out and it indicates that 6-substituted sulfanil derivatives are moderately or low-toxic substances [19] - their LD_{50} is within the range of 43-190 mg / kg. This is confirmed by QSAR-correlation data that the input of a lipophilic substituent in the second position of the quinoline cycle leads to an increased toxic effect.

It was found that computer prediction of biological activity and QSAR analysis is a significant argument for the relevance of the search for potential low-toxicity bioregulators among derivatives of 4-sulfanilquinolines.

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