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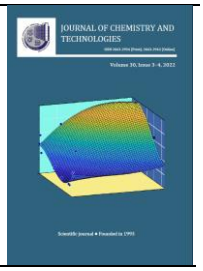

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INFLUENCE OF 3-((6-R-QUINOLIN-4- YL)THIO)PROPANOIC ACID DERIVATIVES ON RHIZOGENESIS OF PINK ROSE CLONES (ROSA DAMASCENA MILL.)

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Abstract

Today, in microclonal propagation of plants, there is a demand for effective and low-toxic rhizogenesis stimulators of plant explants. The use of such compounds significantly increases the efficiency of microclonal reproduction. The modern direction in the design of effective non-toxic substances is molecular modeling based on known natural and synthetic compounds. An important place as synthons for development is occupied by nitrogen-containing heterocycles, in particular quinoline. Results and discussion. Among the derivatives of 3-((6-R-quinolin-4-yl)thio) propanoic acid, the most toxic compounds were those that did not have alkoxy substituents in the 6th position of the quinoline cycle and no methyl radical in the 2nd position. Sodium salts are more toxic than the corresponding acids. This is due to the increase in water solubility of ionized compounds. Derivatives of 3-((6-R-quinolin-4-yl)thio)propanoic acid (sodium salt of 3-((quinolin-4-yl)thio)propanoic acid (QPA-5) showed the greatest toxic effect on the model of the study of progressive sperm motility) and 3-((quinolin-4-yl)thio)propanoic acid (QPA-1), which would reduce this indicator by 25–30 % compared to intact. The toxicity assessment of the investigated compounds made it possible to determine a number of factors and factors of the structure of molecules, which affected the level of toxic action of 3-((6-R-quinolin-4-yl)thio) propanoic acid derivatives and directions for creating non-toxic growth stimulants in this series of 4-thioderivatives of quinoline. Conclusions. The investigated compounds showed a high stimulating effect on rhizogenesis in vitro in explants of pink rose (*Rosa damascena Mill.*) variety Lada. The selection of leader compounds for further testing of potential stimulators of rhizogenesis for microclonal propagation of ornamental plants was carried out. The obtained results are of high practical importance for obtaining and further introduction of new effective, low-toxic, less expensive substances for plant reproduction, in the conditions of microclonal production.

Keywords: derivatives of quinoline and propanoic acid; stimulators of rhizogenesis; bioavailability factors; lipophilicity; toxicity, progressive mobility.

ВПЛИВ ПОХІДНИХ 3-((6-R-ХІНОЛІН-4-ІЛ)ТІО)ПРОПАНОВОЇ КИСЛОТИ НА РИЗОГЕНЕЗ КЛОНІВ ТРОЯНДИ РОЖЕВОЇ (ROSA DAMASCENA MILL.)

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Сучасним напрямком у конструюванні ефективних нетоксичних речовин є молекулярне моделювання на основі відомих природних та синтетичних сполук. Важливе місце як синтони для розробки займають азотовмісні гетероцикли, зокрема хінолін. Серед похідних 3-((6-R-хінолін-4-іл)тіо) пропанової кислоти найбільш токсичними є сполуки, які не мають в 6-му положенні хінолінового циклу алкоксизамісників та у 2-му положенні – метильного радикалу. Найбільшу токсичну дію на моделі дослідження прогресивної рухливісті сперматозоїдів показали похідні 3-((6-R-хіналін-4-іл)тіо)пропіонової кислоти (натрієва сіль 3-((хіналін-4-іл)тіо) пропіонова кислота (QPA-5) та 3-((хіналін-4-іл)тіо) пропіонова кислота (QPA-1), які знижуть цей показник на 25–30 % порівняно з інтактом. Проведена оцінка токсичності досліджуваних сполук, визначений ряд чинників та факторів будови молекул, які впливають на рівень токсичної дії похідних 3-((хіналін-4-іл)тіо) пропіонової кислоти і напрямки створення нетоксичних ростстимуляторів у цьому ряду. Досліджені сполуки виявили високу стимулюючу дію щодо різогенезу в умовах *in vitro* у експлантатів троянди рожевої (*Rosa damascena Mill.*) сорту Лада. Проведено відбір сполук-лідерів для подальшого тестування потенційних стимуляторів різогенезу для мікроклонального розмноження декоративних рослин.

Ключові слова: похідні хіноліну та пропанової кислоти; хемометричні методи; стимулятори різогенезу; фактори біодоступності, ліпофільнсть; токсичність; прогресивна рухливість; мікроклональне розмноження рослин.

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Introductoin

One of the modern trends in the creation of bioregulators for clonal micropropagation of plants is the molecular design of natural and synthetic compounds that combine nitrogen-containing heterocycles and carboxylic acid residues. The quinoline heterocyclic system has highly reactive properties, which makes it possible to modify the molecule and obtain libraries of new promising biologically active compounds (Brazhko et al. 2013; Zeleke et al., 2020). A promising direction in the creation of active, low-toxic growth stimulants for microclonal propagation of plants is the combination of a heterocyclic system and propanoic acid in one molecule (Brazhko et al., 2020; Kornet, M. M. et al., 2020). The effective use of 2-(naphthalene-5-yl) acetic acid and its analogues is known (Kalinin F. L. 1984). The synthesis of hybrid molecules of quinoline heterocycle and mercaptopropanoic acid residue is promising (Brazhko et al. 2018, Kornet, M. M., 2012).

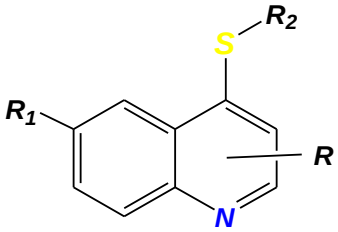
Chemometric studies of derivatives of (quinolin-4-ylthio) propanoic acid indicate the possibility of a fairly wide spectrum of biological activity of these compounds. It was established that the investigated derivs 3-((quinolin-4-yl)thio)propanoic acid promising as potential growth regulators with an antiradical and antioxidative mechanism of action. With the help of virtual screening, potential bioactive molecules based on the combination of heterocycle and succinic acid were selected.

Ethereal rose is a perennial branchy shrub of the Rosaceae family. Two types of roses are common in culture: red (French, Provencal) (Rosa gallica L.) and pink (Kazanlik, Damask) (Rosa damascena Mill.). The essential oil rose is grown to produce flowers that contain 0.14 to 0.22% essential oil. The main components of rose oil are phenylethyl alcohol (40-50%), citranellol (30-35%), geraniol (10-15%), nerol (2-3%), etc. Rose oil and its components are widely used in the manufacture of high-grade perfumery and cosmetic products, in the food, pharmaceutical and liquor industries. It is known that root formation in rose ether oil is an auxin-dependent process (Stefanov, O. V. 2001). There is a need to optimize and speed up the process of root formation and reduce the stress of regenerating plants when adapting to the conditions *in vivo*.

The purpose of this work was to study the effect of hybrid molecules 3-((quinolin-4-yl)thio)ropanoic acid on rhizogenesis *in vitro* in explants of pink rose (Rosa damascena Mill.) variety Lada and further adaptation of microplants to *in vivo* conditions. Establishing certain molecular descriptors of the structure, which reduce the toxicity of compounds of this series and increase the manifestation of the necessary biological action.

Materials and methods

Derivatives 3-((quinolin-4-yl)thio)propanoic acid were synthesized to the Department of Chemistry of the Zaporizhia National University and the Department of Horticulture of the Khortytsk National Academy (Fig. 1.).



$R = H, CH_3, R_1 = H, OCH_3, OC_2H_5,$
$R_2 = CH_2CH_2COOH$

Fig. 1. General structure of derivatives 3-((6-R-quinolin-4-yl)thio)propanoic acid

The 4-chloroquinolines (**1**) («IBS») were used as starting materials, as well as reagents and solvents («UkrOrgSynthesis», Ukraine) for the synthesis of derivatives 3-((6-R-quinolin-4-yl)thio)propanoic acid. The general reaction scheme followed for the synthesis of selected 4-thioquinolines is presented in Fig 1.

The reactions and the purity of the synthesized compounds were controlled by the TLC on Sorbton-2 plates (Russia). As an eluent, mixtures of chloroform-methanol (1:1) and acetate-water (1:1) were used. The ^1H NMR spectra were recorded on Bruker AC-300 device in DMSO 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.

Derivatives 3-((6-R-quinolin-4-yl)thio)propanoic acid were synthesized according to the well-known method ((Brazhko et al.,2013, Metelytsia, et al., 2020) with the corresponding physic-chemical and spectral data, which correspond to the literature.

3-((6-R-quinolin-4-yl)thio)propanoic acid and sodium salts 3-((6-R-quinolin-4-yl)thio) propanoic acid (QPA-1-8 table 1)

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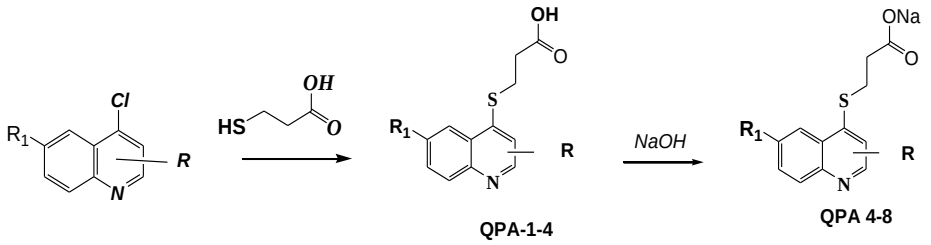
On the basis of 4-chloroquinolines (**1**) was developed synthesis methods 3-((6-R-quinolin-4-yl)thio) propanoic acid (QPA1-4, Fig 2) and it was shown to be convenient precursors for obtaining a variety of functional derivatives. Neutralization of sodium hydroxide acid synthesized corresponding to water-soluble compounds - sodium salts 3-((6-R-quinolin-4-yl)thio) propanoic acid (QPA 4-8).



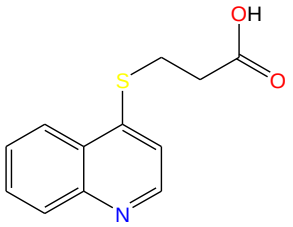
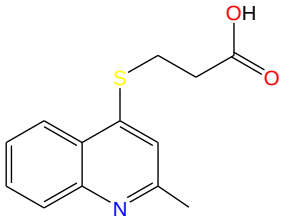
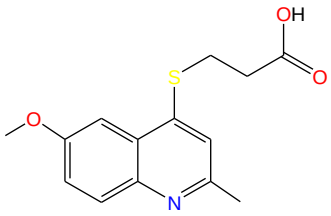
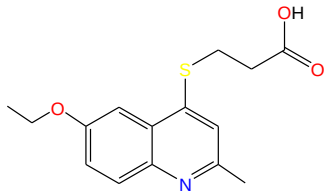
R = H; CH_3
R_1 = H, OCH_3,OC_2H_5.

Fig 2. Synthesis of *3*-((6-R-quinolin-4-yl)thio) propanoic acid of investigated derivatives

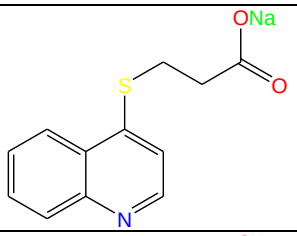
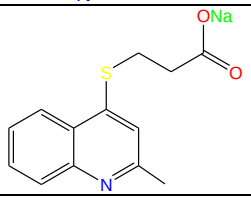
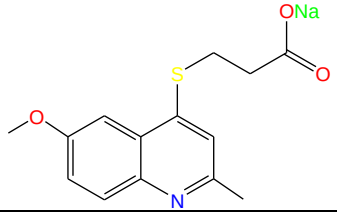
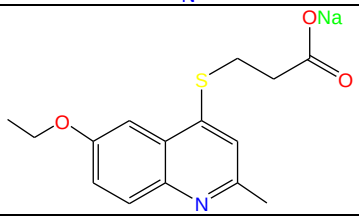
The investigated derivatives 3-((6-R-quinolin-4-yl)thio)propanoic acid are shown in Table 1. The investigated compounds are acids and their sodium salts – hybrid molecules of the quinoline heterocycle and the residue of thiocarboxylic acid (mercaptopropanoic acid). Derivatives were obtained to increase water solubility – sodium salts 3-((6-R-quinolin-4-yl)thio) propanoic acid.

Table 1

Chemical structures of synthesized compounds

Compound	Chemical structure	Molecular formula, molecular mass (MW)	Chemical name
QPA-1		$C_{12}H_{11}NO_2S$ (233.05)	3-((quinolin-4-yl)thio)propanoic acid
QPA-2		$C_{13}H_{13}NO_2S$ (247.31)	3-((2-methylquinolin-4-yl)thio) propanoic acid
QPA-3		$C_{14}H_{15}NO_3S$ (277.34)	3-((6-methoxy-2-methylquinolin-4-yl)thio propanoic acid
QPA-4		$C_{15}H_{17}NO_3S$ (291.37)	3-((6-ethoxy-2-methylquinolin-4-yl)thio) propanoic acid

Continuation of table 1

QPA-5		$C_{12}H_{10}NNaO_2S$ (255.27)	Sodium 3-((quinolin-4-yl)thio) propanoic acid
QPA-6		$C_{13}H_{12}NNaO_2S$ (269.29)	Sodium 3-((2-methylquinolin-4-yl)thio) propanoic acid
QPA-7		$C_{14}H_{14}NNaO_3S$ (299.32)	Sodium 3-((6-methoxy-2-methylquinolin-4-yl)thio) propanoic acid
QPA-8		$C_{15}H_{16}NNaO_3S$ (313.35)	Sodium 3-((6-ethoxy-2-methylquinolin-4-yl)thio propanoic acid

Molecular descriptors of structure: gross formula, elemental composition, molecular weight, molecular refractive index, Log P, Log D, investigated compounds were determined using the computer software package ACD-I-Labs. LogP is the partition coefficient of the compound between n-octanol and water, and Log D is the lipophilicity of the compound depending on the pH of the medium (Brazhko O. A., et al., 2018).

A key parameter in the study of the relationship between the structure and biological activity of organic compounds is the partition coefficient in the system of n-octyl alcohol - water. Correlations between the value of P_{ow} and toxicity, penetration of artificial and natural membranes, biological activity of non-specific drugs, bioaccumulation, soil adsorption, etc. were found. However, the experimental determination of P_{ow} is very time consuming. Therefore, it is generally accepted to use calculation methods for their evaluation. Adequacy of additive methods of calculation of distribution coefficients, and completeness of a set of experimental values of P_{ow} on which this model is built.

Toxicity tests. Toxicity studies of derivatives 3-((quinolin-4-yl)thio)propanoic acid were performed virtually and experimentally. To evaluate the toxic effect of *in silico* compounds, software solutions were used to build structure-toxicity models and predict LD_{50} using models GUSAR (Germany), TEST (USA) (Martin 2016b; Brazhko O.A., et al., 2018 b).

Evaluation of the toxic effect of the studied substances on the functional state of male sperm in vitro. To conduct a study of the toxic effects of compounds using native material – ejaculate of fertile men (normozoospermia). To do this, pre-evaluate the standard spermogram according to generally accepted methods in accordance with WHO criteria (Stefanov, O. V., 2001; Tiuzikov, 2013). Measurements were performed on the sperm fertility analyzer «AFS-500-2» (NPF «Biola»). The selected ejaculate was aliquoted by 100 µl, aliquots were numbered, and the following was added:

– to the first aliquot – saline solution – 10 µL (intact);

– to the second aliquot – Acidum ascorbinicum (AA) at a concentration of 10^{-6}M – 10 µL;

– to the third aliquot – ATC at a concentration of 10^{-6}M – 10 µL;

– to the fourth aliquot – the test substance (quinoline derivative) at a concentration of 10^{-6}M – 10 µL;

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

– to the sixth – hydrogen peroxide at a concentration of 200 µM – 0.5 µL, then AA at a concentration of 10^{-6} M – 10 µL;

– to the seventh – hydrogen peroxide at a concentration of 200 μM – 0.5 μL, then ATC at a concentration of 10^{-6}M;

– to the eighth – hydrogen peroxide at a concentration of 200 μM - 0.5 μL, then the test substance at a concentration of 10^{-6} M – 10 μL;

The obtained samples were incubated at 37 °C for 2 hours. Immediately after incubation, the quality criteria of sperm were studied: concentration, movement, 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 (EO; 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 is 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.

Study of rhizogenesis. The study of rhizogenesis was performed *in vitro*, with the addition of synthesized compounds at a concentration of 1 mg / l in the nutrient medium. Murashige-Skuga nutrient medium was prepared for rhizogenesis (Murashige T., 1962), containing half the concentration of macrosalts and trace elements and 2 % sucrose. The compounds were added before sterilization of the nutrient medium. The control was nutrient media without growth regulators (MC 0). The nutrient medium was sterilized by autoclaving under a pressure of 0.11 MPa for 30 minutes. The explants were cultivated at an air temperature of 22–24 °C with a photoperiod of 16 hours, a relative humidity of 65–70 % and an illumination of 2.5 thousand lux. The results were recorded for 28 days and took into account the number, length of roots, frequency of rhizogenesis.

Results

Molecular descriptors of the structure. To perform individual stages of calculation of molecular descriptors of the structure using a number of software tools, such as: framework JSDraw, OpenBabel, PaDEL-Descriptor, McQSAR, Pandoc, ACD-I-Labs. The following molecular descriptors of the structure were calculated: gross formula, elemental composition, molecular weight, molecular refractive index, Log P, Log D, ClogP (Table 2).

Table 2

Molecular descriptors of synthesized compounds

Compounds	M_r, g/mol	log P, (neutral form)	log D, (pH = 7)	ClogP	MR, cm^3/mol
QPA-1	233.05	2.12± 1.04	–1.50	2.28	60.55
QPA-2	247.31	2.82± 1.01	–1.12	2.78	70.15
QPA-3	277.34	2.69± 1.02	–1.02	3.08	74.91
QPA-4	291.37	3.03± 1.02	–0.38	3.61	79.72
QPA-5	255.27	–	–	2.03	–
QPA-6	269.29	–	–	2.53	–
QPA-7	285.29	–	–	2.50	–
QPA-8	313.35	–	–	3.36	–
NAA	186.21	2.53± 1.01	0.068	2.51	54.03

Based on this, we can say that the introduction in the 6th position of the methoxy group and stoxy group in the structure of 3-((quinolin-4-yl)thio)propanoic acid and its structural analogues leads to increased molar refraction. This trend is easily explained by the fact that such a change in the structure of the molecule increases the effective radii of the molecules, the molar mass, and thus increases the molar refraction. A particularly important characteristic of any biologically active substance is lipophilicity (hydrophobicity) – a model of the distribution of the substance studied between two phases that do not mix (most often used octanol: water). This characteristic is easily modulated by the use of an appropriate descriptor and is most often used to assess the ability of a substance to overcome the biological membranes of cells.

When the test substance is in the aqueous phase in the form of molecules (uncharged particles) to characterize lipophilicity use the indicator log P (P – partition coefficient at the boundary of octane – water).

If the test substance in the aqueous solution is partially dissociated in the form of charged particles (ions), there will be a certain dynamic equilibrium between the different forms of the compound, which will vary depending on the pH of the medium. The lipophilicity of such a system will be determined by the partition coefficient log D – the ratio of the sums of activities of all components of the organic and aqueous phases. For comparison, we obtained quantum-chemical values of lipophilicity log P for neutral forms 3-((quinolin-4-yl)thio)propanoic acid (compounds **1–4**) and the value of the partition coefficient log D at pH = 7. This characteristic is most often used to assess the ability of the substance to overcome biological membranes of cells of the root system depending on the pH of the medium. The pH of most plant cloning media is maintained in the range of 6.5 to 7.5.

It was found that the values of log D for the tested compounds are much smaller than the values of log P, this is due to the consideration in the second case of acid-base equilibrium, which is in solution of the test substances. The change in lipophilicity of the substance from the ability to dissociate into ions in aqueous solution is explained as follows. Since water is a polar solvent (μ = 1.86 D) and the dipole moment of octanol is much smaller (it can be taken as a non-polar solvent), the ions that will be formed in the aqueous medium will hardly diffuse into the organic layer and the concentration of ions in it will be caused mainly by the transition of uncharged molecules of matter, resulting in a significant reduction in the concentration of matter in the organic phase.

At introduction in 6 positions of a quinoline cycle of methoxy group insignificant increase in lipophilicity of a molecule is observed (Δ log D = 0.07–0.08). Thus, lipophilicity (log D) is an important characteristic for assessing the ability to penetrate cell biological membranes and stimulate rooting derivatives 3-((quinolin-4-yl)thio)propanoic acid and sodium salts 3-((6-R-quinolin-4-yl)thio) propanoic acid, which may exist as ions in aqueous solution.

All of the compounds tested (compounds **1–8**) according to Lipinski's «rule five» can show high biological activity.

Toxicity assessment. Toxicity study of 4-thioquinolines using the GUSAR program (Germany) and TEST (USA) showed that they are low-toxic (Table 3).

Among the derivatives of 2-((6-R-quinolin-4-yl)thio) acetic acid the most toxic compounds that did not have in the 6-th position of the quinoline cycle alkoxy substituents (QAC-1 and QAC-5). Sodium salts are more toxic than the corresponding acids. This is due to the increased bioavailability of ionized compounds.

Table 3

Toxicity indicators of the studied compounds

Compounds	TEST computer program (USA)	GUSAR computer program (Germany)			Progressive sperm motility, %
	Oral rat LD_{50}, mg/kg	Intravenous administration, mg/kg	Oral administration, mg/kg	Subcutaneous injection, mg/kg	
QPA-1	252.90	219.01	415.00	394.20	23.2
QPA-2	312.69	345.42	676.41	490.00	26.5
QPA-3	410.12	344.41	658.55	845.01	31.4
QPA-4	579.47	415.92	766.04	979.01	36.0
QPA-5	186.76	171.10	308.41	238.81	19.1
QPA-6	302.42	246.90	508.21	425.03	28.4
QPA-7	418.02	367.11	701.33	499.00	39.3
QPA-8	545.01	413.22	836.82	713.01	41.1
Intact	–	–	–	–	37.0

According to chemometric calculations, the greatest toxic effects on these calculation models showed derivatives 3-((6-R-quinolin-4-yl)thio) propanoic acid (sodium salt 3-((quinolin-4-yl)thio)propanoic acid (QPA-5) and 3-((quinolin-4-yl)thio)propanoic acid (QPA-1)). Derivatives 3-((quinolin-4-yl)thio) propanoic acid, which contain in the 2nd position a metal radical (QPA-2, QPA-6) will have moderate toxicity. Number (QPA-3, QPA-4, QPA-7, QPA-8) compounds containing in the 6th position alkoxy substituents ($-OCH_3$, $-OC_2H_5$) on the contrary will be low-toxic.

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. The study uses native material - ejaculate of fertile men (normozoospermia). Derivatives showed the greatest toxic effects in this model 3-((quinolin-4-yl)thio)propanoic acid (sodium salt 3-((quinolin-4-yl)thio)propanoic acid (QPA-5) та 3-((quinolin-4-yl)thio)propanoic acid (QPA-1)), which will reduce this figure by 25-30% compared to intact (Table 3). Derivatives 3-((quinolin-4-yl)thio)propanoic acid, which contain in the 2nd position a metal radical (QPA-2, QPA-6) show moderate toxicity, and reduce the rate of progressive mobility by 18–26 %. Number (QPA-3, QPA-4, QPA-7, QPA-8) compounds containing in the 6th position alkoxy substituents ($-OCH_3$, $-OC_2H_5$) on the contrary, it increases the rate of progressive mobility, which means that they are non-toxic.

Assessment of rhizogenesis. Study of rhizogenesis. The study of rhizogenesis was performed in vitro, with the addition of synthesized compounds QPA-1, QPA-2, QPA-3, QPA-4, QPA-5, QPA-6, QPA-7, QPA-8, NAA at a concentration of 1 mg / l in the nutrient medium. For rhizogenesis prepared nutrient medium Murashige-Skuga, which contained half the concentration of macrosalts and trace elements and 2 % sucrose. The compounds were added before sterilization of the nutrient medium. The control was nutrient media without growth regulators (MS 0). The nutrient medium was sterilized by autoclaving under a pressure of 0.11 MPa for 30 minutes. The explants were cultivated at an air temperature of 22–24 °C with a photoperiod of 16 hours, a relative humidity of 65–70 % and an illumination of 2,5 thousand lux. The results were recorded for 28 days and took into account the number, length of roots, frequency of rhizogenesis.

Evaluation of the impact on rhizogenesis in vitro In vitro rhizogenesis was studied with the obtained compounds, with the addition of synthesized compounds QPA-1, QPA-2, QPA-3, QPA-4, QPA-5, QPA-6, QPA-7, QPA-8, NAA at a concentration of 1 mg/l in the nutrient medium. Murashige T. Scoog medium was prepared for rhizogenesis, which contained half the concentration of macrosalts and trace elements and 2 % sucrose. The compounds were added before sterilization of the nutrient medium. The control was nutrient media without growth regulators (MS 0). Comparison drug - 2 - (naphthalene-5-yl) acetic acid (NAA). The nutrient medium was sterilized by autoclaving under a pressure of 0.11 MPa for 30 minutes The explants were cultivated at an air temperature of 22–24 °C with a photoperiod of 16 hours, a relative humidity of 65–70 % and an illumination of 2.5 thousand lux. The results were recorded for 28 days and took into account the number, length of roots, frequency of rhizogenesis.

The data obtained show that the compounds of all tested compounds when added to the nutrient medium for rhizogenesis containing ½ MS and 1 mg/l of the compound caused the maximum increase in rhizogenesis pink rose plants (*Rosa damascena Mill*.) variety Lada.

Table 4

Indicators of root formation of pink rose plants (*Rosa damascena Mill*.) variety Lada (28 days) on nutrient medium:

Options for environments	Rosa damascena Mill		
	Number of roots, number of roots	Length of roots, mm	Frequency of rhizogenesis,%
MC 0 (control, environment without growth stimulants)	–	–	–
QPA-1	3.41 ± 0.70***	3.60 ± 1.11***	75.4
QPA-2	2.02 ± 0.51**	2.74 ± 1.41**	61.2
QPA-3	2.43 ± 0.81***	2.23 ±1.42**	65.3
QPA-4	2.92 ± 0.54**	2.73 ± 1.31**	68.1
QPA-5	4.32 ± 0,43***	4.12 ± 0,80***	79.0

Continuation of table 4

QPA-6	2.50 ± 0.82**	2.81 ± 1.23**	67.2
QPA-7	2.32 ± 0.42**	2.15 ± 0.82**	58.3
QPA-8	2.31 ± 0.41**	2.74 ± 0.71**	54.1
NAA (comparison drug – 2 - (naphthalene-5-yl) acetic acid	2.23±0.42**	2.14±1.42**	68.0

Note: This table takes into account statistically significant differences compared to controls - MS 0 medium without growth stimulants: * - P < 0.05; ** - P < 0.01; *** - P < 0.001.

The most important point in the clonal micropropagation of pink rose plants (*Rosa damascena Mill*.) of the Lada variety is obtaining an optimal root system that will provide nutrition and growth of regenerants. Damask rose does not form roots in 28 days on nutrient medium without MC 0 hormones. When planting roses without roots in the substrate, 34 % of plants took root, which makes production unprofitable. In contrast to nutrient media that contained synthesized compounds. From the change in rhizogenesis indicators, it is clear that the studied compounds exhibit auxin properties (Table 4).

On a nutrient medium with the addition of compounds QPA-1та QPA-5 cloned plants of the pink rose (Rosa damascena Mill.) variety Lada form 3.41 ± 0,70 (p<0.001) and 4.32 ± 0,43 roots (p < 0.001). Addition of the above-mentioned compounds to the medium maximally contributed to the formation of 7–8 roots and the frequency of rhizogenesis was more than 75%. Reliably the longest roots were observed on the medium also with compounds acid (sodium salt 3-((quinolin-4-yl)thio)propanoic acid (QPA-5) (p≤0,05), and 3-((quinolin-4-yl)thio)propanoic acid (QPA-1)) (p<0,001), compared to control. Indicators of rhizogenesis for compounds QPA-1та QPA-5 exceeded the comparison drug - 2 - (naphthalene-5-yl) acetic acid more than 10%. At the same time, the rooting of plants on the substrate is universal peat:sand:vermiculite in the ratio 2:1:1 and was 82%. Instead, the media containing the compounds, all investigated compounds caused a significantly greater number of roots (p < 0.001), and the media with the compounds QPA-6, QPA-7 and QPA-8 had the maximum number (p < 0.001) of roots compared to the control, as on nutrient medium without hormones (MS 0) damask rose does not form roots in 28 days. (p < 0.001) (Table 4, Fig. 3). They had a better effect compared to the corresponding acids.

Thus, the addition of ionized compounds, which are more water-soluble, to the nutrient medium for rhizogenesis of compounds contributed to a significant increase in the number and length of roots (p<0.001) with the maximum percentage of the frequency of rhizogenesis (Fig. 3).

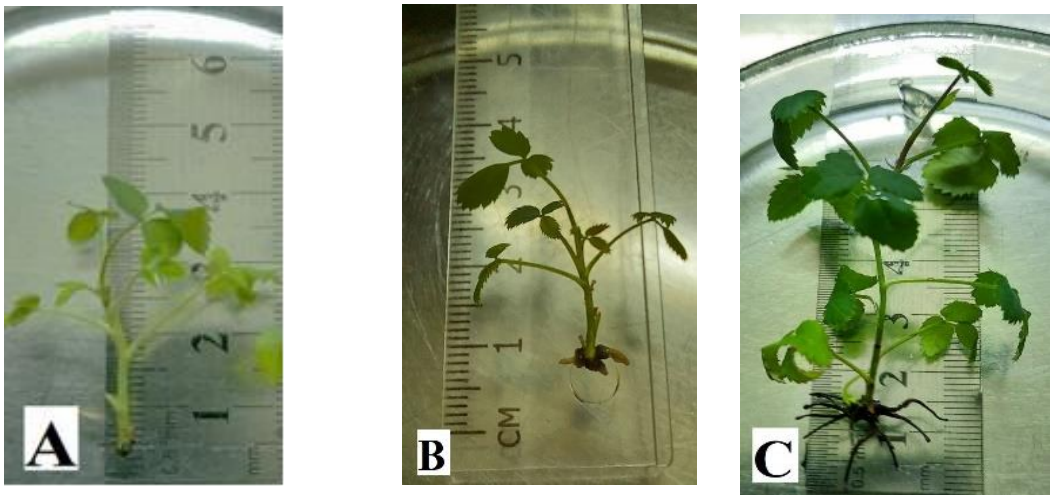


Fig. 3. Plants of Rosa damascena Mill for 28 days:
(A)- on a nutrient medium with the addition of 2-(naphthalene-5-yl)acetic acid;
(B) - with the addition of QPA-1; (C) - with the addition of QPA-5

Discussion

Various quinoline derivatives are used both as synthons in organic synthesis and molecular design, and as known effective biologically active compounds. During the synthesis of a new compound, there is a need to calculate the

molecular descriptors of the structure, physical and chemical properties, the main constants that affect the manifestation of toxic effects. Such problems are solved using modern chemometric research methods. This makes it possible to determine the molecular determinants of the structure, which reduce the toxicity of compounds and increase the necessary biological effect (Brazhko, O. A., et al. 2020., Metelytsia, L., et al. 2020.). A number of studies indicate that the introduction into the 6th position of quinoline of alkoxy radicals reduces the toxicity of the compounds (Brazhko, O. A., et al. 2013, Brazhko, O. A., et al. 2018). The selection of substances for the substrate during microclonal propagation of plants is an urgent problem. Stimulation of rhizogenesis is the most problematic task for the efficiency of plant reproduction (Derevianko, N. P, et al. 2021, Aremu, A. et al. 2015). It is known that each plant has its own individual characteristics that affect the composition of the nutrient medium for explants. The nutrient medium was sterilized by autoclaving under a pressure of 0.11 MPa. Therefore, the compounds that are added to the nutrient medium must have the necessary chemical resistance to decomposition (Awada, R., et al. 2020, Batukaev, A. A., et al. 2020, Bogdan, A. M., et al. 2019).

The most important moment in the clonal micropropagation of any culture is the planting of plants in the substrate, it is at this stage that there is a danger of the death of plants – regenerants, therefore it is important to obtain an optimal root system that will provide nutrition and growth of regenerants (Kornet, M. M. et al. 2020, Grishchenko, O. V., et al. 2020, Ivashchuk, O. A., et al. 2018). It is known that when explants of plants without roots or with poorly developed root systems were planted in the substrate, 34 % of plants took root, which makes production unprofitable. Stimulation of root formation is the result of the interaction of a substance with plant cells. It depends on the characteristics of the substance (molecular structure, physical and chemical properties), biological object and mode of action.

The studied derivatives of 3-((6-R-quinolin-4-yl)thio)propanoic acid are synthetic analogs of known growth stimulants, such as 2 – (naphthalene-5-yl)acetic acid. From the change in rhizogenesis indicators, it is clear that the studied compounds exhibit auxin properties. Therefore, the conducted research has a high practical potential for obtaining new effective, low-toxic, less expensive substances for plant propagation, in the conditions of microlonal production.

Conclusion

The effect of 3-((6-R-quinolin-4-yl)thio)ropanoic acid and its sodium salt on rhizogenesis under in vitro conditions in pink rose (*Rosa damascena Mill*.) variety Lada explants was studied and further adaptation of micro-plants in vivo. The conducted chemometric studies made it possible to identify molecular structure descriptors that reduced the toxicity of compounds and increased their permeability through the membranes of explant cells.The obtained data indicate that the study of the compound showed a high biological potential for rhizogenesis in vitro in explants of pink roses (*Rosa damascena Mill*.) variety Lada.

Research results can be implemented in the reproduction of both agricultural and ornamental plants. The most effective compounds were selected, which could be recommended as new effective competitive stimulators of rhizogenesis in microclonal propagation of plants.

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