




Electrochemical Determination of Antioxidant Activity of New 4-Thiosubstituted Quinoline Derivatives with Potential Radioprotecting Properties

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Abstract: The 4-thioquinolinic derivatives with potential antioxidant activity have been investigated. Their research antioxidant activity on two models has shown that they are effective traps of such free radicals as hydroxyl-ions and superoxide-anions, which confirms the compatibility of these derivatives for radioprotector activity investigation.

Keywords: quinoline-4-thiol; virtual screening; antioxidant activity; radioprotectors.

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1. Introduction

Nowadays, ionizing radiation may be considered one of the main dangerous factors. One of the cases of the post-irradiation death of the animals is the damage of the DNA molecules. Most to the DNA modification processes (60-80%) is caused by reacting oxygen species (ROS) generated during the water radiolysis. The ROS also leads to dangerous metabolic processes like free radical lipid peroxidation and oxidative protein modification [1-4]. So, the radioprotective action may be realized by means of high anti-radical activity with certain ROS [5]. It is possible to reproduce the processes occurring during the water radiolysis by electrochemical methods like impulse voltammetry.

The search for new effective and less-toxic bioactive molecules includes the research of natural and synthetic compounds, among which the quinolinic derivatives take important part as synthons and biologically active compounds with a different mechanism of action [6-12]. The most prominent quinoline derivatives in the aspect of radioprotection are 4-thiol substituted quinolines, which are effective radical traps [13].

The investigation of radioprotection activity requires much data, animal material, and time. So, in order to enhance the efficiency of these experiments, it's necessary to use theoretical PASS-screening for anti-radical, antioxidant, and membrane-protecting activities and also to realize some *in vitro* experiments of antioxidant and anti-radical activities. These

experiments include the adrenaline oxidation inhibition evaluation and impulse voltammetry. The use of an impulse voltammeter lets us clarify the mechanism of antioxidant action of the investigated compounds and test them simultaneously in order to compare their activities within a short period of time.

The goal of this work is the selection of potent antioxidants, and radioprotectors among the novel 4-thiol substituted quinolines by means of virtual screening and *in vitro* investigation of anti-radical and antioxidant activity of these compounds as radioprotectors.

2. Materials and Methods

Synthesis and physicochemical properties of the compounds (1a-x, 2a-x, 3a-f) have been described by us in the works [14, 15].

The individualities of the synthesized compounds were controlled by thin-layer chromatography. The composition of these compounds was verified by NMR spectrum.

The chromatographic investigation was realized on Sorbfil plates (obtained from «Sorbpolimer», Ukraine, UV-254) in different solvent systems. The chromatograms were manifested by using UV irradiation.

The antioxidant and radioprotective activity was conducted online by the use of the PASS (Prediction of Activity Spectra for Substances) program. The activity prediction was characterized by activity (Pa) and inactivity (Pi) probability calculations, being made by analysis of the formula of the compound and was based on the analysis of the formula of this compound and analysis of the "structure-activity" correspondence database [16].

In order to conduct the antioxidant activity (AA) investigation, using *in vitro* techniques, it is possible to use the method of adrenalin oxidation inhibition, based on the ROS inhibitions by the tested compounds. A non-enzyme reaction of adrenaline oxidation to adrenochrome is realized in alkaline media in the presence of the oxygen anion-radical O_2^- . In the biological system, this process is conducted by superoxide-dismutase, but *in vitro*, the ROS are generated in a different manner, and this reaction may be used in order to evaluate the AA of the biologically active compounds [17].

During the adrenaline-inhibition test, to a spectrophotometer (ray length 10 mm) cuvette 2 ml of 0,05 M sodium carbonate buffer (pH 10,2) with the addition $3 \cdot 10^{-4}$ M of Na_2EDTA was added. 0,1 ml of the solvent for the test compound was added to the reference solution. Yet to the analytical probe, the solution of the investigated compound has been added in the volume of 0,1 ml in the final concentration of 125 mM (25 mM). The reaction was launched by an introduction of 0,4 ml 0,01 M adrenaline hydrochloride into the system. It was realized by the temperature of 35-36 °C for 3 minutes. AA of the compounds was detected spectrophotometrically by the inhibition degree of adrenaline autooxidation into adrenochrome, which is colored. The wavelength used was equal to 484 nm, and the inhibition degree was calculated in percents as:

$$AA = (D_x - D_0) D_x * 100 (\%)$$

in which D_x – is the optic density, representing non-inhibited adrenaline autooxidation; D_0 – is the optic density, representing the autooxidation of adrenaline in the presence of the investigated substances. The reference compound was cysteamine.

The impulse voltammetry lets generate the hydroxyl radicals and other ROS in water solutions on electrodes by the electrochemical way. The electrogenerated ROS may be a model

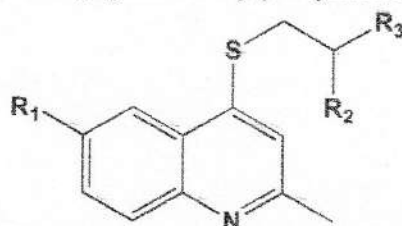
of elementary redox stages in biological systems. The investigation of the interaction of the investigated compounds with the ROS includes the obtaining and analysis of the special differential voltammogram of molecular oxygen reduction in special impulse mode on cathode-anode. These voltammograms let reveal the reduction peak of the oxygen, hydrogen peroxide, and hydroxyl radicals. Also, it is possible to obtain on the platinum cathode the peaks of the reduction of the bivalent iron [18].

The electrochemical investigations were conducted by the universal polarography PU-1 (USSR) in the mode of differential impulse voltammetry in three-electrode circuit Me/Pt/Ag, AgCl. The potential of the copper and platinum work electrode was given using the Ag|AgCl reference electrode. The auxiliary electrode was a platinum spiral (potential scan rate of 105 mV/s). The solutions of the compounds in 0,1 M NaCl were prepared before the proper experiments. The background electrolyte was obtained by the use of double-crystallized NaCl in bidistilled water. The iron ion concentration was 2,4 mM. The oxygen concentration was correspondent to the equilibrium of oxygen concentration in the conditions of normal pressures and the temperature 20 °C. The conclusions about the antioxidant activities were made by the morphological changes of voltammograms [19].

3. Results and Discussion

Cysteine is a natural amino acid, which takes part in different enzyme processes, containing the mercapto group.

Table 1. The obtained S-(2-methylquinolin-4-yl)-l-cysteines and analogous substances.



No	R ₁	R ₂	R ₃	No	R ₁	R ₂	R ₃
1a	H	NH ₂	COOH	2d	F	H	COOH
1b	OCH ₃	NH ₂	COOH	2e	Cl	H	COOH
1c	OC ₂ H ₅	NH ₂	COOH	2f	Br	H	COOH
1d	F	NH ₂	COOH	2g	H	H	COOH, HCl
1e	Cl	NH ₂	COOH	2h	OCH ₃	H	COOH, HCl
1f	Br	NH ₂	COOH	2i	OC ₂ H ₅	H	COOH, HCl
1g	H	NH ₂	COOH, 2HCl	2j	F	H	COOH, HCl
1h	OCH ₃	NH ₂	COOH, 2HCl	2k	Cl	H	COOH, HCl
1i	OC ₂ H ₅	NH ₂	COOH, 2HCl	2l	Br	H	COOH, HCl
1j	F	NH ₂	COOH, 2HCl	2m	H	H	COONa
1k	Cl	NH ₂	COOH, 2HCl	2n	OCH ₃	H	COONa
1l	Br	NH ₂	COOH, 2HCl	2o	OC ₂ H ₅	H	COONa
1m	H	NH ₂	COONa	2p	F	H	COONa
1n	OCH ₃	NH ₂	COONa	2q	Cl	H	COONa
1o	OC ₂ H ₅	NH ₂	COONa	2r	Br	H	COONa
1p	F	NH ₂	COONa	2s	H	H	COOCH ₃
1q	Cl	NH ₂	COONa	2t	OCH ₃	H	COOCH ₃
1r	Br	NH ₂	COONa	2u	OC ₂ H ₅	H	COOCH ₃
1s	H	NH ₂	COOCH ₃ , 2HCl	2v	F	H	COOCH ₃
1t	OCH ₃	NH ₂	COOCH ₃ , 2HCl	2w	OC ₂ H ₅	H	COOCH ₃ , HCl
1u	OC ₂ H ₅	NH ₂	COOCH ₃ , 2HCl	2x	Cl	H	COOCH ₃ , HCl
1v	F	NH ₂	COOCH ₃ , 2HCl	3a	H	NH ₂	H, 2HCl
1w	Cl	NH ₂	COOCH ₃ , 2HCl	3b	OCH ₃	NH ₂	H, 2HCl
1x	Br	NH ₂	COOCH ₃ , 2HCl	3c	OC ₂ H ₅	NH ₂	H, 2HCl
2a	H	H	COOH	3d	F	NH ₂	H, 2HCl
2b	OCH ₃	H	COOH	3e	Cl	NH ₂	H, 2HCl
2c	OC ₂ H ₅	H	COOH	3f	Br	NH ₂	H, 2HCl

The previous investigations have confirmed that its modification with quinoline moiety leads to the interesting, effective bio regulating substances (Table 1) [13-15].

The PASS-prediction has shown that the mentioned compounds may be used as antioxidants as free radical traps for ROS (Fig. 2). It was interesting that the antioxidant properties were characteristic only for 6-unsubstituted quinolines (compounds 1a, 2a, 2s, 3a) and quinolines with donor substituents (1b, 2b, 2t). Nevertheless, the presence of halogen leads to the disappearance of the antioxidant properties out of the spectrum of biological activities.

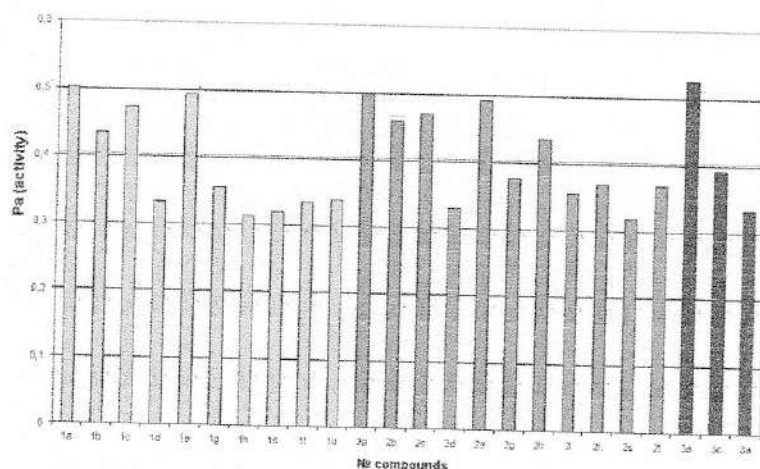


Figure 1. PASS-screening of the antioxidant properties of S-(2-methylquinolin-4-yl)-l-cysteine and its analogous compounds.

The radioprotective activity of L-cysteine derivatives was predictable (Fig. 3). L-cysteine, cysteamine, and their derivatives are known radioprotectors. The results of the screening of β -(quinolin-4-ylthio)-propionic acids (2a – x), attract attention, as they possess the probability of radioprotective effects, similar to that of the S-(quinolin-4-yl)-l-cysteines (1a – x) and of S-(quinolin-4-yl)-cysteamines (compounds 3a – f). The most prominent for radioprotection effects are the compounds with non-blocked carboxyl and without substituents in the position six, or with donor substituent in it (compounds 1a – c, 1e, 2a – c, 2e).

The results of the virtual PASS-prediction and our own investigations, described in [13-15] let us select three most effective (1i, 2i, 3c) compounds among the 54 4-thiol substituted quinolines. For them, the antioxidant and radioprotective action probability reach 47 % (Fig. 2 and 3), which makes promising the investigation of the compounds 1i, 2i, 3c. We have to pay attention that the screening includes membrane protection and the absence of negative effects – high toxicity, teratogenesis, carcinogenesis, mutagenesis, and embryotoxicity.

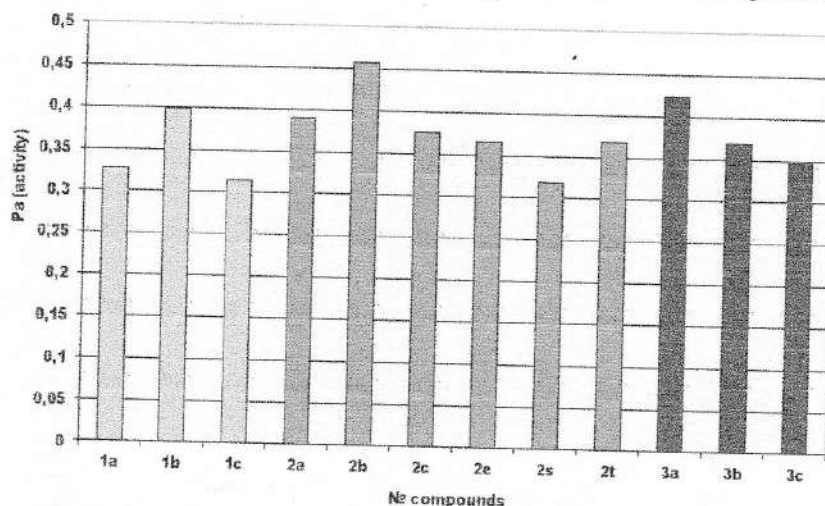


Figure 2. Computer screening of the radioprotection properties of S-(2-methylquinolin-4-yl)-l-cysteines and analogous compounds.

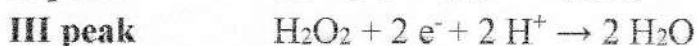
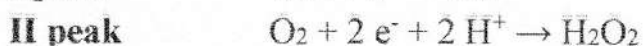
We have to admit that the structure of the 4-thioquinolines (1i, 2i, 3c) is correspondent to the Lipinski requisite, defining the bioaccessibility of each compound by simple molecular criteria (molecular weight, molar refraction, lipophilicity, the number of the hydrogen bond donors and acceptors) [20].

The selected compounds were the most active in the primary screening models (Table. 2). We have to admit that in minor concentrations (25 mM), the compounds exceed the activity of the reference compound–cysteamine.

Table 2. The results of a priori spectrophotometric screening of 4-thioquinolines antioxidant properties.

Compound number	AA*,% (125 mM)	AA,% (25 mM)
1i	29,0	21,0
2i	38,0	33,0
3c	47,0	42,0
Cysteamine (reference compound)	62,0	15,0

A more profound investigation of antioxidant activities of the compounds was made by impulse voltammetry, capable of reproducing the process of the water radiolysis. The polarization of the copper cathode in impulse mode lets us distinguish the reduction peak of oxygen (II) by $E = -0,6$ V, of hydrogen peroxide (III) by $E = -1,1$ V, and hydroxyl radicals (I) by $E = -0,2$ V, formed during the one-electron peroxide reduction:



The changes in morphology and quantitative changes in each voltammogram during the addition of the compounds in the background electrolyte let us evaluate the character, and a degree of the interaction of the compounds with oxygen and ROS formed during its reduction [16].

In the reactions of the oxygen one-electron reduction in biosystems, a transition-metal ion usually takes part. It is used as a donor of the acceptor of one electron. So, preventive antioxidant action is very important. They react with the bivalent iron ions, which cause the formation of the most aggressive ROS-hydroxyl radicals [14]. In order to detect the possibility of the use as a preventive antioxidant, the compounds were tested during the oxidation of bivalent iron on a platinum electrode (Fig. 4, 6, 8). The last process may be considered equivalent to electro-Fenton [21–28].

The compound 1i, containing in its structure carboxy and amino group, influences all the oxygen reduction peaks on copper (Fig. 3). If the concentration is equal to $0,2 \cdot 10^{-3}$ mol l⁻¹, the peaks I and III reduce their intensity to $H/H_0 = 0,8$, and the peak II is slightly enhanced and shifted to more cathodic values. When the concentration is equal to $0,38 \cdot 10^{-3}$ mol l⁻¹, the peak I enhanced, the III peak remains on the same level, yet the peak II diminishes, and its shift to more positive potentials is observed. The subsequent increase of the concentration of the compound leads to the maximal reduction of the peaks I and III (H/H_0 , if $C = 0,9 \cdot 10^{-3}$ mol l⁻¹ is equal, correspondently, to 0,45 and 0,35). If the concentration is $1,07 \cdot 10^{-3}$ mol l⁻¹, the peak III doesn't exist.

The differential voltammogram of the 1i compound, measured on the platinum cathode (Fig. 4) in the presence of Fe²⁺ ($C = 2,42 \cdot 10^{-3}$ mol l⁻¹), we may see that the presence of the compounds makes the Fe²⁺ oxidation peak reduce in the concentration of $0,099 \cdot 10^{-3}$ mol l⁻¹, yet if the concentration of the compound is equal to $0,57 \cdot 10^{-3}$ mol l⁻¹ a new peak, correspondent

to the presence of Fe^{3+} , appears. So, the compound 1i may be considered a preventive antioxidant.

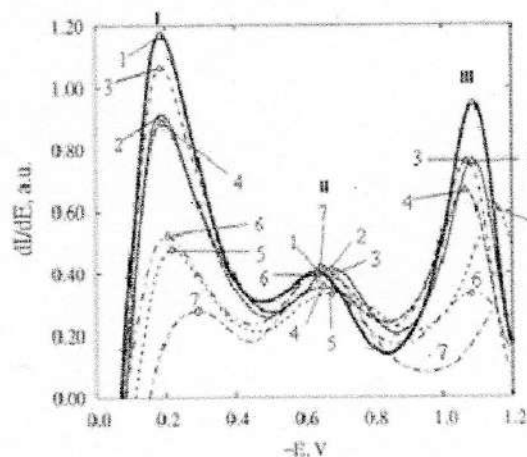


Figure 3. The differential voltammogram of the oxygen reduction on copper in the presence of different concentrations (2-6) of the compound 1i:
 1 - background 0,1 M NaCl;
 2 - 0,2; 3 - 0,38; 4 - 0,57; 5 - 0,74;
 6 - 0,90; 7 - 1,07 mM.

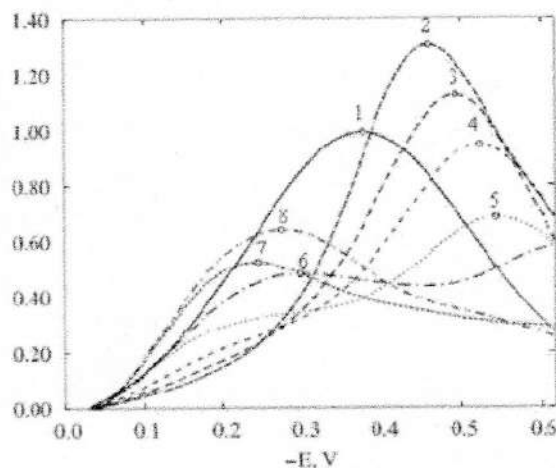


Figure 4. The differential voltammograms of the oxygen reduction on platinum in the background of 0,1 M NaCl in water (1), containing Fe^{2+} (2-2,42), in different concentrations of the compound 1i:
 3 - 0,09; 4 - 0,20; 5 - 0,38; 6 - 0,56,
 7 - 0,74; 8 - 0,9 mM.

The compound 2i, which contains only carboxy group in its structure, begins influencing the peak I beginning on the concentration of $0,60 \cdot 10^{-3} \text{ mol l}^{-1}$, yet the peak II firstly becomes more intensive if the potential is shifted to more positive values, and then it is reduced, and the value of the potential is returned to the initial value (Fig. 6). The intensity of the peak III is reduced proportionally to the compound concentration increase. Nevertheless, its maximal value for H/H_0 , which is equal to 0,45, for the peaks I and III, is achieved for higher concentrations of 2i than for 1i.

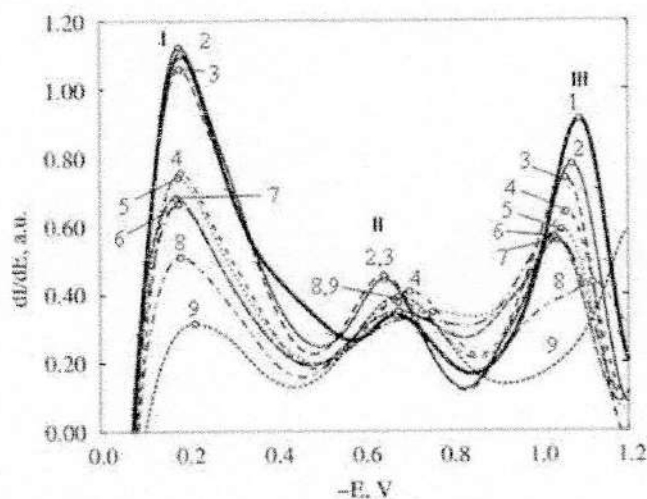


Figure 5. The differential voltammograms of the oxygen reduction on copper in different concentrations (2-6) of 2i: 1 - background: 0,1 M NaCl; 2 - 0,19; 3 - 0,38; 4 - 0,60;
 5 - 0,74; 6 - 0,90; 7 - 1,07; 8 - 1,23;
 9 - 1,37 mM.

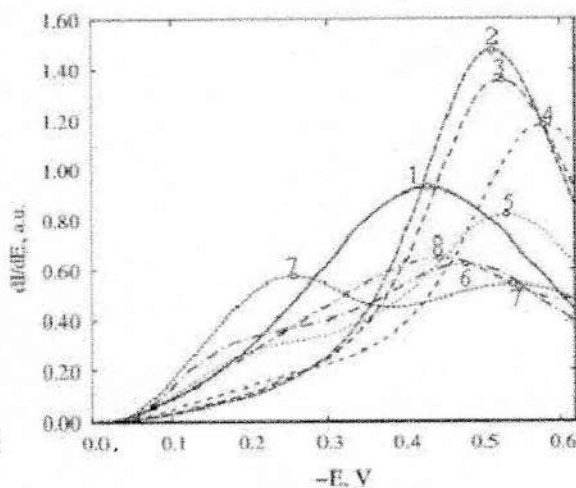


Figure 6. The differential voltammograms for the oxygen reduction on platinum in the background electrolyte 0,1 M NaCl in water (1), containing the ions Fe^{2+} (2 - 2,42), with the different concentrations of 2i: 3 - 0,09;
 4 - 0,20; 5 - 0,38; 6 - 0,57; 7 - 0,74;
 8 - 0,91 mM.

The voltammetric investigation of the influence of 2i on Fe^{2+} oxidation peak shows that it may also be considered a preventive antioxidant (Fig. 6).

Even in the lowest concentration ($C=0,19 \cdot 10^{-3} \text{ mol l}^{-1}$) of 3c, containing an amino group, the height of the peaks I and III reduces significantly, yet the height of II is highly

enhanced and remains on the same level in all the investigated concentration range (Fig. 7). The maximal decrease of the peak I is observed in the concentration of $0,38 \cdot 10^{-3} \text{ mol l}^{-1}$. The peak III is reduced if the concentration of the compound increases to $0,60 \cdot 10^{-3} \text{ mol l}^{-1}$; yet the further increase of the concentration of the compound makes the peak III disappear.

The differential voltammogram obtained on the platinum electrode (Fig. 8) shows that the compound 3c reduces the Fe^{2+} oxidation peak proportionally to its concentration. At the same time, the wave potential is shifted to more cathodic potential values. If the concentration is equal to $0,57 \cdot 10^{-3} \text{ mol l}^{-1}$, a peak of Fe^{3+} appears and increases. So, the compound 3c may be considered a preventive antioxidant.

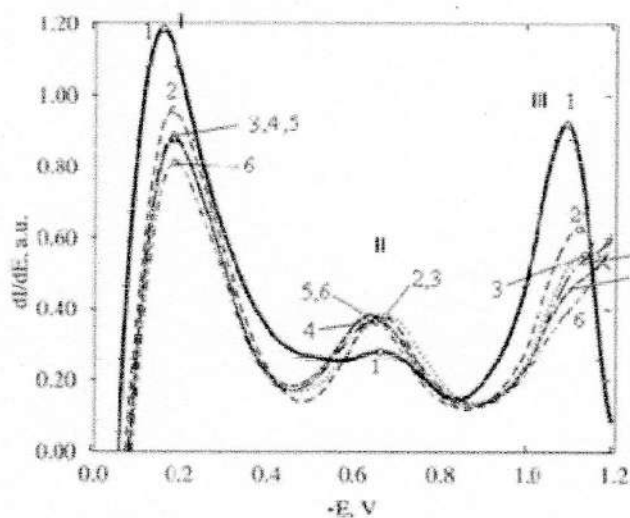


Figure 7. Differential voltammograms of oxygen reduction on copper in the presence of different concentrations (2-6) of 3c:

1 – background 0,1 M NaCl; 2 – 0,19;
3 – 0,38; 4 – 0,57; 5 – 0,74; 6 – 0,90 mM.

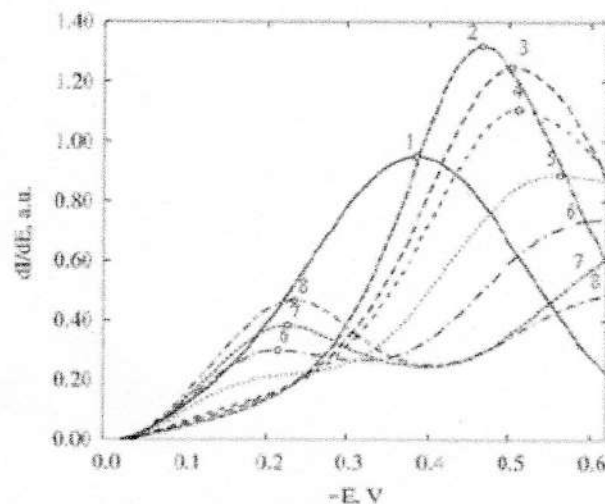


Figure 8. The differential voltammograms of the oxygen reduction on platinum in the background of 0,1 M NaCl in water (1), containing Fe^{2+} (2 – 2,42), with different concentrations of 3c: 3 – 0,09; 4 – 0,20; 5 – 0,38; 6 – 0,57; 7 – 0,74; 8 – 0,91 mM.

Analyzing the influences of the concentrations of all of the mentioned compounds on the electrochemical behavior, represented by voltammograms, we may make the next observations:

The compound 3c is more effective in the hydroxyl radical suppression in lower concentrations $0,19\text{-}0,38 \cdot 10^{-3} \text{ mol l}^{-1}$, yet the compounds 1i and 2i act with higher concentrations.

The oxygen reduction (peak II) in all concentration range is facilitated efficiently by 3c, yet the compound 2i is most efficient only in the concentration range of $0,19\text{-}0,38 \cdot 10^{-3} \text{ mol l}^{-1}$.

The 3c compound is the most effective e in the reduction of the peak III (hydrogen peroxide formation); the compounds 1i and 2i also have an antioxidant effect, but they influence the peak nearly equally.

4. Conclusions

From the antioxidant activity spectrochemical and electrochemical test of three novel quinolinic derivatives, it was possible to conclude that: The compounds manifest significant antioxidant activity, and their activity, in low concentration, is higher than that of the reference compound – cysteamine; The antioxidant activity investigation by impulse voltammetry confirmed the high antioxidant activity of the investigated compounds. They are considered preventive antioxidants; The compound 3c was the most efficient antioxidant, acting with all

the peaks of reacting oxygen species generation; It confirms the availability of the tested compounds as efficient radioprotectors.

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Conflicts of Interest

The authors declare no conflict of interest.

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