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SYNTHESIS AND ANTIOXIDANT ACTIVITY OF QUERCETIN ETHERS

E. R. Karimova,[1] L. A. Baltina,[2*] L. V. Spirikhin,[2]
R. M. Kondratenko,[3] R. R. Farkhutdinov,[3] and I. V. Petrova[3]

*Quercetin (Q) methyl ethers were synthesized from CH_3I under various conditions. The principal products from the reactions of Q with alkylhalides (CH_3I, C_4H_9Br) in DMF were 3,7,4′-tri-*O*-alkyl ethers. The structures of the products were confirmed by PMR and ^{13}C NMR spectra. The antioxidant activity of Q tetra- and tri-*O*-methyl ethers was demonstrated by chemiluminescence in model systems generating active oxygen species and promoting lipid peroxidation.*

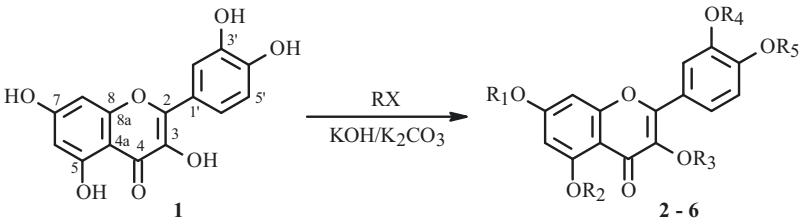
Keywords: quercetin, flavonoids, ethers, antioxidant activity, chemiluminescence.

Quercetin (Q) (**1**) and its glycoside rutin are bioflavonoids with known P-vitamin activity that are used in medicine to prevent and treat various diseases associated with disruption of capillary-wall permeability and also as antioxidant, hepatoprotective, anti-inflammatory, and antiulcer agents [1–4].

Q, rutin, and flavonoids related to them are difficultly soluble in organic solvents and aqueous media. Therefore, they have low bioavailability. Chemical modification of Q at the phenolic hydroxyls via alkylation or acylation is interesting for designing of the compounds with greater solubility. Several Q ethers that are natural antioxidants, e.g., rhamnetin (7-*O*-methylquercetin), isorhamnetin (3′-*O*-methylquercetin), tamaraxetin (4′-*O*-methylquercetin), and azaleatin (5-*O*-methylquercetin) in addition to various di- and tri-*O*-substituted Q methyl ethers were synthesized via sequential protection and deprotection of different phenolic hydroxyls [5–8]. It was shown that methylation of Q by diazomethane produced exclusively Q 3,7,3′,4′-tetra-*O*-methyl ether [9]. This ether also resulted from heating Q with dimethylsulfate and KOH in MeOH [10] or dimethylsulfate and K_2CO_3 in Me_2CO [11]. Methylation of Q tetra-*O*-methyl ether by dimethylsulfate and NaOH [11] or CH_3I and K_2CO_3 formed Q penta-*O*-methyl ether [12]. Several fully substituted Q esters in addition to tetra-*O*-substituted esters with free 5-OH and 7-OH groups were synthesized [7].

Herein, we present results on the synthesis, identification by NMR spectra, and *in vitro* assessment of the antioxidant activity of several fully or partially substituted Q ethers.

Compound **1** was methylated by CH_3I in DMSO in the presence of powdered KOH using a Q–CH_3I ratio of 1:10 and 1:5 or in DMF in the presence of K_2CO_3 using a Q–CH_3I ratio of 1:7 at ambient temperature (22–24°C).



1 **2 - 6**

RX = CH_3I, C_4H_9Br, C_6H_5COCl

2: $R_1 = R_2 = R_3 = R_4 = R_5 = CH_3$; **3:** $R_1 = R_3 = R_4 = R_5 = CH_3$, $R_2 = H$
4: $R_1 = R_3 = R_5 = CH_3$, $R_2 = R_4 = H$; **5:** $R_1 = R_3 = R_5 = C_4H_9$, $R_2 = R_4 = H$
6: $R_1 = R_2 = R_3 = R_4 = R_5 = C_6H_5CO$

1) Higher Professional Education Institute, Bashkir State University, 450076, Ufa, Ul. Zaki Validi, 32, Russian Federation; 2) Ufa Chemistry Institute, Russian Academy of Sciences, 450054, Ufa, Prosp. Oktyabrya, 71, fax: +7 (347) 235 60 66, e-mail: baltina@anrb.ru; 3) Higher Professional Education Institute, Bashkir State Medical University, Russian Federation Ministry of Health, 450000, Ufa, Ul. Lenina, 3. Translated from *Khimiya Prirodnykh Soedinenii*, No. 5, September–October, 2015, pp. 731–735. Original article submitted January 30, 2015.

The reaction of Q with an excess of CH_3I in DMSO (1:10) in the presence of KOH formed a mixture of Q 3,5,7,3′,4′-penta-*O*-methyl ether (**2**) (40%) and 3,7,3′,4′-tetra-*O*-methyl ether (**3**) (55%) that was separated by column chromatography over silica gel.

The PMR spectrum of **2** had resonances for five methoxy groups at 3.9–4.2 ppm and for five aromatic protons of Q at weak field (6.7–8.7 ppm). The ^{13}C NMR spectrum of **2** showed five new resonances for the CH_3O C atoms (55.6–59.6 ppm).

The IR spectrum of **3** contained an absorption maximum for OH at 3200 cm^{-1}. Its PMR spectrum displayed resonances for four groups of OCH_3 protons (δ 3.7–3.9 ppm) and for 5-OH (δ 12.63 ppm). The ^{13}C NMR spectrum contained resonances for CH_3O C atoms in the range 55.8–60.2 ppm. The proton with chemical shift (CS) δ 6.33 ppm in the ^1H–^{13}C HMBC spectrum gave cross peaks with C atoms with CS δ 165.4, 162.0, 106.0, and 92.2 whereas the proton with CS δ 6.43 ppm correlated with C atoms with CS δ 165.4, 97.8, 156.7, and 106.0. Thus, the resonance in the ^{13}C NMR spectrum at δ 165.4 ppm corresponded to C-7; 97.8, C-8; 162.0, C-8a; 106.0, C-4a; 156.7, C-5; and 92.2, C-6. Two doublets for protons with δ 6.97 ppm (J = 8.5 Hz) and 7.73 (J = 8.5 Hz) in the HSQC spectrum correlated with C atoms C-5′ (δ 110.8 ppm) and C-6′ (δ 122.2). Proton H-5′ gave cross peaks in the HMBC spectrum with C atoms C-6′, C-3′, and C-4′. Proton H-2′ correlated with C-1′ (122.8 ppm), C-3′ (148.7), C-4′ (151.4), and C-2 (155.8 ppm) whereas H-6′ correlated with C-5′, C-1′, C-4′, and C-2.

Alkylation of **1** by CH_3I in DMSO with a reagent ratio of 1:5 produced a mixture of products, the principal one of which was Q tetra-*O*-methyl ether **3** (42%). Q 3,7,4′-trimethyl ether (ayanin) (**4**) [8] (6%) was identified in a more polar fraction. The PMR spectrum of **4** exhibited three OCH_3 resonances (δ 3.78, 3.80, 3.84 ppm) and singlets for two OH groups (δ 12.63 and 9.45 ppm). Resonances for aromatic protons were observed as two doublets at δ 7.57 and 7.09 (J = 8.9 Hz).and three singlets (δ 6.36, 6.72, 7.56 ppm). The CS of OCH_3, methine, and quaternary C atoms were found in ^{13}C NMR spectra using full proton decoupling and DEPT 90. Protons with δ 6.36 and 6.72 ppm in the HMBC spectrum gave cross peaks with resonances for C atoms with δ 92.8, 161.4, 105.7, and 165.6 ppm (former) and 92.3, 165.6, 156.8, and 109.7 ppm (latter). Thus, the resonance with δ 105.7 corresponded to C-4a; 161.4, C-8a; 98.3, C-8; 165.6, C-7; and 92.8 ppm, C-6. Doublets in the PMR spectrum belonged to H-5′ and H-6′ because the proton with δ 7.09 ppm that was bonded to the C atom with CS 112.4 correlated in the HMBC spectrum with C atoms C-1′ (δ 122.6 ppm), C-4′ (δ 150.8), and C-3′ (δ 146.8). The proton with CS 7.57 ppm correlated with C-2′ (δ 115.5) and C-4′ (δ 150.8 ppm). In turn, H-2′ gave cross peaks with C-6′, C-3′, and C-2 (δ 156.1 ppm). Thus, the resonances with CS 138.7 and 178.6 ppm belonged to quaternary C atoms C-3 and C-4, respectively. Protons of the C-4′ OCH_3 group correlated in the NOESY spectrum with H-5′; of the C-7 OCH_3 group, with H-6 and H-8.

The UV spectrum of **4** in EtOH was characterized by two strong absorption maxima at 257 and 355 nm that persisted in alcoholic NaOAc solution (0.01%). This indicated that the phenolic OH groups in the 7- and 4′-positions were substituted [9]. A bathochromic shift of the long-wavelength maximum by 26 nm in alcoholic NaOEt solution (0.01%) confirmed that the 3′-OH was free [13].

Alkylation of **1** by CH_3I in DMF in the presence of powdered K_2CO_3 with a reagent ratio of 1:7 occurred primarily at the 3-, 7-, and 4′-positions to give ether **4** (44%) whereas treatment with C_4H_9Br afforded 3,7,4′-tri-*O*-butyl ether **5** in 43% yield. The PMR spectrum (300 MHz) of **5** exhibited a multiplet for the CH_3, CH_2, and C_4H_9 groups at strong field with δ 1.0–2.2 ppm. The ^{13}C NMR spectrum showed additional resonances for three $\underline{C}H_2O$ groups at δ 72.7, 68.8, and 68.4 and a set of resonances for CH_3- and CH_2- groups at 13.8–32.1 ppm.

Refluxing Q with an excess of benzoylchloride in Py produced the known penta-*O*-benzoate **6** [7] in 92% yield. The PMR spectrum of **6** had strong multiplets for the aromatic protons at weak field (7.8–8.3 ppm). The ^{13}C NMR spectrum contained resonances for aromatic C atoms at 134.4–126.7 ppm.

Chemiluminescence (CL) was used to study the antioxidant activity of ethers **3**, **4** and **6** in *in vitro* free-radical oxidation (FRO) for a model generating active oxygen species (AOS) (system 1) and in a model promoting lipid peroxidation (LPO) (system 2) [14] with Q used as the reference. Table 1 presents the experimental results.

System 1 showed that ethers **3** and **4** exhibited the greatest antioxidant activity and changed the CL parameter by decreasing spontaneous emission and rapid luminescence in a dose-dependent manner (Table 1). Ether **4** at a concentration of 0.1 mg/mL was the most active inhibitor of AOS generation and was comparable to Q (Fig. 1).

System 2 indicated that ethers **3** and **4** also suppressed spontaneous emission by decreasing the luminescence and CL light sum. Tri-*O*-methyl ether **4** at a concentration of 0.1 mg/mL again turned out to be the most active (Table 1) (activity similar to Q). Thus, ethers **3** and **4** could suppress AOS and LPO in the model systems. This suggested that their antioxidant properties depended on the number of free phenolic OH groups and the concentration. Penta-*O*-benzoate **6** did not exhibit antioxidant activity in the model systems.

TABLE 1. Change of Light Sum and Maximum CL Intensity of a Model System Generating AOS and Imitating LPO after Adding the Synthesized Compounds,[a] %

Compound	Concentration, mg/mL	AOS model		LPO model	
		LS	I_{max}	LS	I_{max}
1	1.0	0.53*	0.87*	0.37*	0.88*
	0.1	3.99*	5.51*	0.47*	0.97*
	0.01	14.20*	15.23*	0.34*	1.05*
6	1.0	99.82	98.00	7.97*	7.84*
	0.1	81.54	88.53	31.83*	15.85*
	0.01	73.26	76.63	20.39*	35.89*
3	1.0	33.51*	42.30*	6.74*	10.55*
	0.1	34.44*	49.73*	0.64*	74.98
	0.01	57.08	67.33	132.52	113.49
4	1.0	13.30*	12.43*	0.23*	0.73*
	0.1	22.44*	21.43*	0.79*	1.75*
	0.01	40.23*	40.40*	3.57*	6.03*

[a]Emission intensity of models without adding the synthesized compounds was taken as 100%; averages of 10 measurements are given ($p < 0.05$); *statistically significant differences; LS, light sum; I_{max}, maximum luminosity.

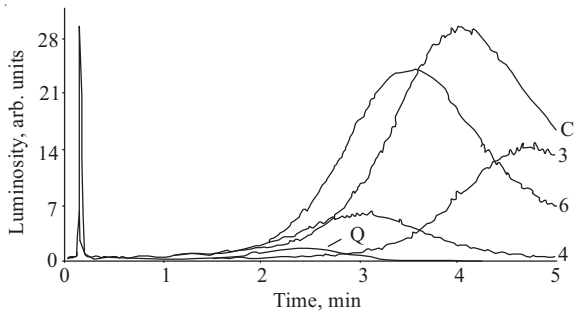


Fig. 1. Influence of methyl ethers **3** and **4** and ester **6** (0.1 mg/mL) on FRO in AOS model system; C = control.

EXPERIMENTAL

General. PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with TMS internal standard on Bruker Avance-III (500 MHz) at operating frequency 500.13 (^1H) and 125.47 MHz (^{13}C) and Bruker AMX-300 (300 and 75.5 MHz, respectively) spectrometers. Resonances in ^{13}C NMR spectra were assigned based on 2D spectra and literature data for Q and its derivatives [15]. IR spectra were taken from mineral-oil mulls on an IR Prestige-21 spectrophotometer (Shimadzu). UV spectra were obtained on a UF-400 spectrophotometer (Carl Zeiss). Molecular ions were determined by liquid chromatography/mass spectrometry (LC/MS) on an LCMS-2010 instrument (Shimadzu) using chemical ionization at atmospheric pressure. Melting points were measured on a Boetius apparatus.

TLC was performed on Sorbfil plates (Sorbpolimer, Russia) using $CHCl_3$–EtOH (20:1). Spots were detected by H_2SO_4 solution (5%) in EtOH with heating at 110–120°C for 2–3 min. Compounds were separated by column chromatography over KSK silica gel (SG) (50–150 μm) (Sorbpolimer). Pharmacopoeial Q (Farmstandart, Ufa VITA) was used.

Methylation of Q by CH_3I (1:10) in DMSO. A solution of **1** (0.30 g, 1 mmol) in DMSO (10 mL) was treated with powdered KOH (0.56 g, 10 mmol), stirred for 30 min, treated dropwise with CH_3I (0.62 mL, 10 mmol), and stirred for 4 h with TLC monitoring. The resulting solution was poured into H_2O and acidified (pH 2–3) with HCl. The precipitate was filtered off, rinsed with H_2O until neutral, and dried. The dry product (0.37 g) was chromatographed over a column of SG with elution by C_6H_6 and a C_6H_6–EtOH gradient (100:0.1→50:1, v/v). Homogeneous TLC fractions were combined and evaporated to afford two principal fractions with R_f 0.77 and 0.73 that were recrystallized from EtOH. The first fraction was identified as penta-*O*-methyl ether **2** (0.15 g, 40% yield). The second fraction turned out to be tetra-*O*-methyl ether **3** (0.20 g, 55% yield).

Methylation of Q by CH_3I (1:5) in DMSO was carried out in the same manner as above. Two principal fractions were isolated and crystallized from EtOH. The mp, TLC, and NMR spectra of the first fraction agreed with those of tetra-*O*-methyl ether **3** (0.15 g, 42% yield). The second fraction was identified as tri-*O*-methyl ether **4** (0.02 g, 6% yield).

Methylation of Q by CH_3I (1:7) in DMF was carried out in the same manner as above. The obtained yellowish-green precipitate was filtered off, rinsed with H_2O, dried, and chromatographed over a column of SG with elution by C_6H_6–EtOH (200:1, 100:1, 100:2, 100:3, v/v). The principal fraction was isolated and identified as tri-*O*-methyl ether **4** (0.15 g, 44% yield). The other fractions contained inseparable product mixtures.

Alkylation of Q by Butylbromide (1:7) in DMF. The obtained product was rinsed with H_2O by decantation, dried, and chromatographed over a column of SG with elution by C_6H_6–MeOH (300:1, 200:1, 100:1, 50:1, v/v). Fractions that were homogeneous according to TLC were combined and evaporated. The principal fraction was isolated and identified as 3,4′,7-tri-*O*-butyl ether **6** (0.2 g, 43% yield).

Quercetin 3,5,7,3′,4′-penta-*O*-methyl ether (2), mp 152–154°C, lit. 151–152°C (EtOH) [9], 151°C (EtOH) [12]. IR spectrum (ν_{max}, cm^{-1}): 1645, 1632, 1609, 1580, 1520, 1271, 1250. UV spectrum (EtOH, λ_{max}, nm) (log ε): 250 (5.7), 340 (5.6). ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 3.95, 3.99, 4.04, 4.04, 4.23 (15H, all s, $5OC\underline{H}_3$), 6.70 (1H, s, H-8), 6.98 (1H, s, H-6), 7.25 (1H, d, J = 9, H-5′), 8.06 (1H, d, J = 9, H-6′), 8.72 (1H, s, H-2′). ^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 173.2 (C-4), 164.2 (C-7), 161.1 (C-8a), 158.9 (C-5), 152.5 (C-2), 151.5 (C-4), 148.2 (C-3′), 141.4 (C-3), 123.6 (C-1′), 122.0 (C-6′), 111.9 (C-2′), 111.6 (C-5′), 109.7 (C-4a), 96.1(C-6), 93.1 (C-8); $5OCH_3$: 55.6, 55.7, 55.8, 56.0, 59.6; MS: *m/z* 373, $[M + H]^+$. $C_{20}H_{20}O_7$. [M] 372.4.

Quercetin 3,7,3′,4′-tetra-*O*-methyl ether (3), mp 157–159°C (MeOH–Et_2O) (yellow needles), lit. 159–160°C (anhydr. EtOH) [9], 159°C (EtOH) [10]. IR spectrum (ν_{max}, cm^{-1}): 3215 (OH), 1650, 1603, 1589, 1512. UV spectrum (EtOH, λ_{max}, nm) (log ε): 254 (5.5), 353 (5.5). ^1H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm): 3.85, 3.86, 3.95, 3.96 (12H, all s, $4OC\underline{H}_3$), 6.33 (1H, s, H-8), 6.43 (1H, s, H-6), 6.97 (1H, d, J = 8.5, H-5′), 7.67 (1H, s, H-2′), 7.73 (1H, d, J = 8.5, H-6′), 12.63 (1H, s, OH). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): 178.8 (C-4), 165.4 (C-7), 162.0 (C-8a), 156.7 (C-5), 155.8 (C-2), 151.4 (C-4′), 148.7 (C-3′), 139.0 (C-3), 122.9 (C-1′), 122.2 (C-6′), 111.3 (C-2′), 110.8 (C-5′), 106.0 (C-4a), 97.8 (C-6), 92.2 (C-8); 4 OCH_3: 55.8, 55.9, 56.0, 60.2. MS: *m/z* 359, $[M + H]^+$, 357 $[M - H]^-$. $C_{19}H_{22}O_7$. [M] 358.4.

Quercetin 3,7,4′-tri-*O*-methyl ether (4), mp 168–170°C (EtOH) (yellow needles), lit. 169°C (Me_2CO–MeOH) [8]. IR spectrum (ν_{max}, cm^{-1}): 3398 (OH), 1651, 1625, 1517. UV spectrum (EtOH, λ_{max}, nm) (log ε): 256 (5.4), 357 (5.3). UV spectrum (0.01% NaOAc, λ_{max}, nm) (log ε): 257 (5.5), 356 (5.4). UV spectrum (0.01% NaOEt, λ_{max}, nm) (log ε): 273 (5.4), 383 (5.0). ^1H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm): 3.78, 3.80, 3.85 (15H, all s, $3OC\underline{H}_3$), 6.36 (1H, s, H-8), 6.72 (1H, s, H-6), 7.56 (1H, s, H-2′), 7.09 (1H, d, J = 8.9, H-5′), 7.57 (1H, d, J = 8.9, H-6′), 8.29. ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ, ppm): 178.6 (C-4), 165.6 (C-7), 161.4 (C-9), 156.1 (C-2), 156.8 (C-5), 150.8 (C-4′), 146.8 (C-3′), 138.7 (C-3), 122.6 (C-1′), 120.9 (C-6′), 115.5 (C-2′), 112.4 (C-5′), 105.7 (C-10), 98.3 (C-6), 92.8 (C-8); $3OCH_3$: 56.1, 56.5, 60.2. MS: *m/z* 345, $[M + H]^+$, 343 $[M - H]^-$. $C_{18}H_{16}O_7$. [M] 344.3.

Quercetin 3,4′,7-tri-*O*-butyl ether (5), amorphous compound. IR spectrum (ν_{max}, cm^{-1}): 3406, 1732, 1605, 1510. ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.03–2.19 (9H, m, $3CH_3CH_2CH_2CH_2$), 3.99–4.16 (18H, m, $3CH_3CH_2CH_2CH_2$), 5.75 (1H, s, H-8), 6.35 (1H, s, H-6), 6.97 (1H, d, J = 9, H-5′), 7.28 (1H, s, H-2′), 7.71 (1H, d, J = 9, H-6′). ^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 179.0 (C-4), 165.0 (C-7), 161.9 (C-9), 156.8 (C-5), 155.8 (C-2), 148.1 (C-4′), 145.5 (C-3′), 138.3 (C-3), 123.6 (C-1′), 121.6 (C-6′), 114.4 (C-2′), 110.9 (C-5′), 105.9 (C-4a), 98.2 (C-8), 92.5 (C-6); $3CH_2O$, $3CH_2$, $3CH_3$: 72.7, 68.8, 68.4, 32.1, 31.1, 31.0, 19.2, 18.9, 13.8. $C_{27}H_{34}O_7$. [M] 470.5.

Quercetin 3,3′,4′,5,7-Penta-*O*-benzoate (6) [9]. Compound **1** (0.30 g, 1 mmol) was dissolved in anhydrous Py (20 mL), treated with benzoylchloride (1.15 mL, 10 mmol), refluxed for 4 h, left overnight at 22–24°C, and diluted on the following day with cold H_2O. The resulting precipitate (0.92 g) was filtered off, dried, and recrystallized from $CHCl_3$–MeOH. Yield 0.76 g (92%), mp 170–172°C. IR spectrum (ν_{max}, cm^{-1}): 3472, 1742, 1582, 1506. ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 7.18–7.54 (17H, m, $3C_6\underline{H}_5CO$, H-8, 6), 7.88–8.15 (13H, m, $2C_6\underline{H}_5CO$, H-6′, 5′, 2′). ^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 169.8 (C-4), 164.9 (C-7), 163.8, 163.4, 157.0, 154.5, 153.6, 150.7, 145.0, 142.8, 134.4, 134.2, 133.8, 133.5, 130.7, 130.4, 130.2, 129.2, 128.8, 128.5, 128.0, 126.7, 124.0, 123.7, 115.3, 114.4, 109.4. MS: *m/z* 823 $[M + H]^+$. $C_{50}H_{30}O_{12}$. [M] 822.8.

Determination of Antioxidant Activity. The effect of the compounds on *in vitro* FRO was assessed using model systems generating AOS and promoting LPO and chemiluminescence on a KhLM-003 instrument (Russia). CL of the model systems was characterized by spontaneous emission, rapid luminescence, and then slow luminescence. The principal and most informative CL characteristics were the emission light sum, which was determined from the emission intensity, and the maximum emission amplitude.

The first model system that generated AOS consisted of phosphate buffer (10 mL, 20 mM KH_2PO_4, 105 mM KCl) with added luminol solution (10^{-5} M) and sodium citrate (50 mM). The pH of the prepared solution was adjusted to 7.45 by titration with saturated KOH solution. Reactions associated with AOS generation were initiated by adding a solution of Fe^{2+} salts (1 mL, 50 mM). Emission was recorded for 5 min with constant stirring.

The influence of the compounds on LPO was studied using egg-yolk lipids, which were similar in composition to blood lipids. Lipids were obtained by homogenization of egg yolk in phosphate buffer at a 1:5 ratio followed by dilution (20×). Adding a solution of Fe^{2+} (1 mL, 50 mM) initiated oxidation of unsaturated fatty acids, which was associated with CL. The LPO processes were assessed from the emission intensity.

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REFERENCES

1. G. E. Pronchenko, *Medicinal Plant Drugs* [in Russian], A. P. Arzamastsev and I. A. Samylina (eds.), GEOTAR-MED, Moscow, 2002.
2. M. D. Mashkovskii, *Drugs. Aide for Physicians* [in Russian], Vol. 2, 14th Ed., Novaya Volna, Moscow, 2000.
3. V. A. Baraboi, *Plant Phenols and Human Health* [in Russian], Nauka, Moscow, 1984.
4. E. A. Zueva, *Handbook of Bioadditives* [in Russian], Feniks, Rostov-on-Don, 2003.
5. E. E. Nifant′ev, M. P. Koroteev, G. Z. Kaziev, and I. S. Zakharova, *Zh. Obshch. Khim.*, **73**, 11 (2003).
6. B. K. Carte, S. Carr, et al., *Tetrahedron*, **47**, 1815 (1991).
7. A. Mattarei, L. Biasutto, F. Rastrelli, S. Garbisa, E. Marotta, M. Zoratti, and C. Paradisi, *Molecules*, **15**, 4722 (2010).
8. L. Jurd, *J. Org. Chem.*, **27**, 1294 (1962).
9. A. S. Gomm and M. Nierenstein, *J. Am. Chem. Soc.*, **53**, 4408 (1931).
10. H. L. Hergert, P. Coad, and A. V. Logan, *J. Org. Chem.*, **21**, 304 (1956).
11. L. Chen, T. He, Y. Han, J.-Z. Sheng, S. Jin, and M. W. Jin, *Molecules*, **16**, 5754 (2011).
12. M. Picq, A. F. Prigent, G. Nemoz, A. C. Andre, and H. Pacheco, *J. Med. Chem.*, **25**, 1192 (1982).
13. E. R. Karimova, L. V. Spirikhin, L. A. Baltina, and M. I. Abdullin, *Russ. J. Gen. Chem.*, **84**, 1711 (2014).
14. R. R. Farkhutdinov and S. I. Tevdoradze, *Methods for Assessing Antioxidant Activity of Therapeutic and Preventive Biologically Active Compounds: Collection of Works* [in Russian], E. B.Burlakova (ed.), Izd. RUDN, Moscow, 2005.
15. D. Yu. Korul′kin, Zh. A. Abilov, R. A. Muzychkina, and G. A. Tolstikov, *Natural Flavonoids* [in Russian], Teo, Novosibirsk, 2007.