DOI 10.1007/s10600-017-2150-9
Chemistry of Natural Compounds, Vol. 53, No. 5, September, 2017

SYNTHESIS AND ANTIOXIDANT ACTIVITY OF MYRTANYLTHIOTRIAZOLES

Yu. V. Gyrdymova,[1] M. Ya. Demakova,[1] O. G. Shevchenko,[2] D. V. Sudarikov,[1*] L. L. Frolova,[1] S. A. Rubtsova,[1] and A. V. Kuchin[1]

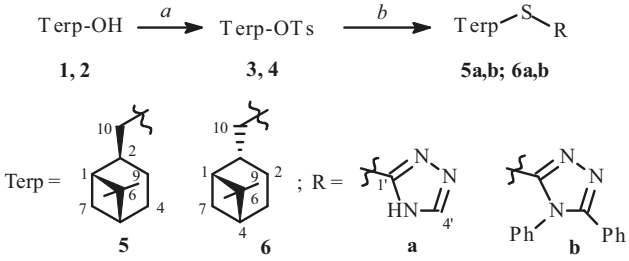
*Thio-derivatives of triazole-substituted myrtanols were synthesized in 78–95% yields and were demonstrated to have membrane-protective and antioxidant properties based on their ability to inhibit H_2O_2-induced hemolysis of erythrocytes and LPO processes in brain lipids (*in vitro*).*

Keywords: *cis*- and *trans*-myrtanols, triazoles, antioxidants, membrane-protective properties, erythrocytes, oxidative hemolysis, lipid peroxidation (LPO).

Cis- and *trans*-myrtanols occur in essential oils of plants in the family Lamiaceae and possess antibacterial properties [1]. Compounds containing triazoles are known to exhibit broad spectra of biological activity, e.g., anti-inflammatory, analgesic [2], antitumor [3], antihelminthic [4], antifungal [5], antibacterial [6, 7], antiviral [8, 9], anticonvulsant [10], and antioxidant [11–16]. Individual monoterpenoid derivatives also exhibit high antioxidant activity [17–19]. Therefore, the synthesis and characterization of the antioxidant properties of triazole-containing myrtanol derivatives are highly crucial.

Herein, syntheses of monoterpenoids containing triazoles from *cis*- and *trans*-myrtanols (**1**, **2**) are reported.

Myrtanylthiotriazoles **5a**,**b** and **6a**,**b** were prepared from monoterpenol *p*-toluenesulfonates (**3** and **4**) and heterocyclic thiols. Tosylates **3** and **4** were synthesized from *cis*-(**1**) and *trans*-myrtanols (**2**) by the published procedure (Scheme 1) [20].



a. TsCl, Py; *b*. RSH, Cs_2CO_3, TBAI, EtOH (DMF), reflux, 8 h

Scheme 1

The formation of sulfides **5a**,**b** and **6a**,**b** was consistent with IR absorption bands for C=N at 1516–1560, 1470, and 1360 cm^{-1}; N–H, 3110; and N–N, 1270 (**5a** and **6a**) of the heterocyclic moiety and C–H absorption bands for the terpene moieties (2870–2980 cm^{-1}).

PMR and ^{13}C NMR spectra of **5a**,**b** and **6a**,**b** contained resonances for the terpene and triazole fragments. The triazole-ring C–S resonances were observed in ^{13}C NMR spectra at 154–157 ppm. Resonances of myrtanyl C-10 appeared at 39–41 ppm and were characteristic of C–S bonds.

1) Institute of Chemistry, Komi Scientific Center, Ural Branch, Russian Academy of Sciences, 48 Pervomaiskaya, Syktyvkar, 167982, e-mail: sudarikov-dv@chemi.komisc.ru; 2) Institute of Biology, Komi Scientific Center, 28 Kommunisticheskaya, Syktyvkar, 167982. Translated from *Khimiya Prirodnykh Soedinenii*, No. 5, September–October, 2017, pp. 762–766. Original article submitted December 2, 2016.

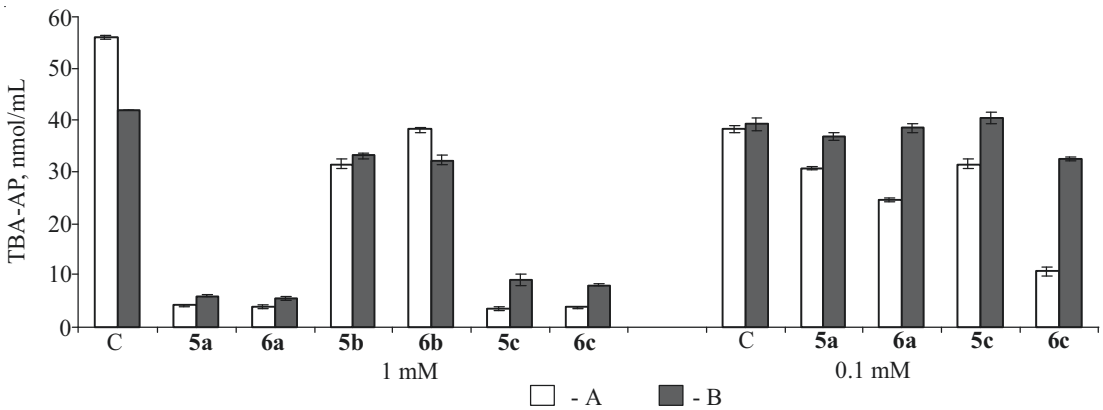
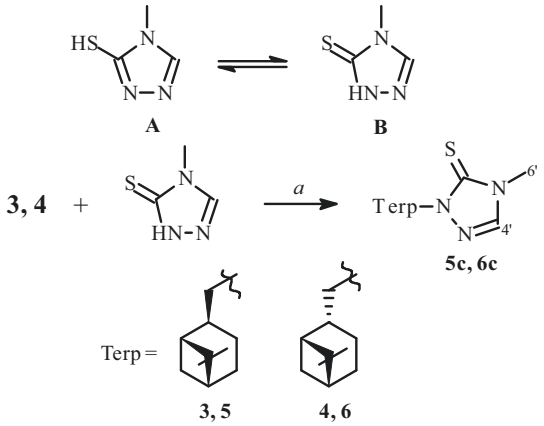


Fig. 1. Effects of myrtanylthiotriazoles at concentrations of 1 and 0.1 mM on TBA-AP content in brain homogenate 1 h after LPO initiation (initiators: A, ascorbate/Fe^{2+}; B, H_2O_2). C is the control sample without the studied compounds.

3-Mercapto-1,2,4-triazole is known to exist in two tautomeric forms, i.e., thiol (**A**) and thione (**B**) (Scheme 2) with the latter dominating [21]. Thus, reaction of tosylates **3** and **4** with thione form **B** formed thioamides **5c** and **6c** in yields of 89 and 95%, respectively (Scheme 2).



a. TsCl, Py; *b*. RSH, Cs_2CO_3, TBAI, EtOH (DMF), reflux, 8 h

Scheme 2

Formation of the thioamides was confirmed by IR and NMR spectral data. Thus, IR spectra of conjugates **5c** and **6c** showed absorption bands characteristic of C=S vibrations at 1090 cm^{-1}. ^{13}C NMR spectra of these same compounds exhibited resonances for the heterocyclic-ring C=S at 167 ppm and for myrtanyl C-10 at 53–55 ppm that were characteristic of C–N bonds.

Antioxidant activity (AOA) of synthesized myrtanylthiotriazoles **5a**–**c** and **6a**–**c** was studied in extracellular and cellular model systems (*in vitro*).

Mammal blood erythrocytes are convenient subjects for testing the AOA of various compounds and plant extracts [22]. Brain lipids of laboratory animals are widely used as an extracellular model for assessing AOA [23–25].

Studies of the AOA of the synthesized thiotriazoles in the extracellular model system showed that all compounds without phenyls (**5a**, **6a**, **5c**, **6c**) were highly active at a concentration of 1 mM (Fig. 1).

Thioamide **6c** exhibited the greatest inhibitory activity if the concentrations were reduced by an order of magnitude (0.1 mM).

The antioxidant and membrane-protective activities of the synthesized compounds in the cellular model system were studied for all compounds except **6b** and **6c**, which were highly cytotoxic even at a concentration of 0.1 mM according to preliminary investigations.

Figure 2 shows results for the membrane-protective activity of myrtanylthiotriazoles **5a**–**c** and **6a** in an erythrocyte oxidative hemolysis model.

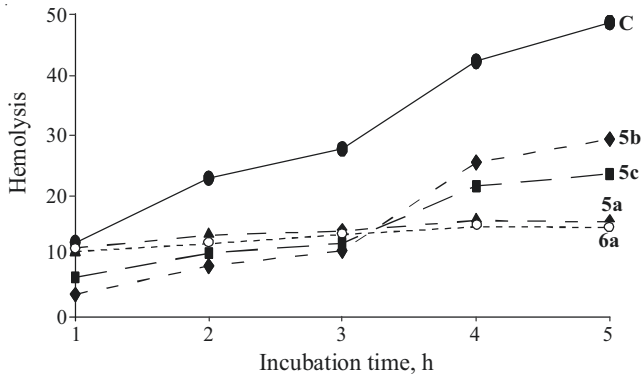


Fig. 2. Effect of myrtanylthiotriazoles (**5a**–**c** and **6a**) at a concentration of 0.1 mM on degree of H_2O_2-induced hemolysis of erythrocytes after incubation for 1–5 h.

All studied compounds exhibited membrane-protective activity. However, sulfanyltriazoles **5a** and **6a** with unsubstituted triazoles in their structures possessed the greatest ability to inhibit H_2O_2-induced hemolysis during the whole incubation period.

The ability of the myrtanylthiotriazoles to prevent oxidation of hemoglobin and lipids in the cellular model confirmed that they had antioxidant activity. Thus, compounds **5a**, **6a**, and **5c** slowed the conversion rate of oxyhemoglobin to methemoglobin by 1.5–1.6 times whereas **6a** and **5c** decreased the accumulation rate of LPO secondary products by 1.3–1.4 times.

Thus, myrtanylthiotriazoles of various structures were synthesized. Myrtanylsulfanyl-1*H*-triazoles **5a** and **6a** possessed the greatest antioxidant activity for H_2O_2-induced oxidative stress according to a mammal blood erythrocyte test system, possibly because the triazole contained a free H that was susceptible to hemolytic cleavage to form a resonance-stabilized electron-saturated triazole radical that probably trapped free radicals in the system. Thiotriazoles **6b** and **6c** were cytotoxic because of the *trans*-myrtanyl moiety in their structures. Studies of the antioxidant activity in a non-cellular model system with substrate obtained from brain tissue showed that all thiotriazoles without phenyl substituents were active regardless of the myrtanyl isomer.

Myrtanylsulfanyltriazoles **5a** and **6a** were most promising for further research according to the comprehensive study of antioxidant activity in the two model test systems.

EXPERIMENTAL

IR spectra were recorded from thin films or KBr pellets on a Shimadzu IR Prestige 21 FTIR spectrometer. PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using solvent resonances as internal standards on a Bruker Avance-300 spectrometer (300.17 MHz for ^1H and 75.48 MHz for ^{13}C). ^{13}C NMR spectra were recorded in *J*-modulation mode. Resonances of ^1H and ^{13}C were fully assigned using two-dimensional homo- (^1H–^1H COSY, ^1H–^1H NOESY) and heteronuclear experiments (^1H–^{13}C HSQC, ^1H–^{13}C HMBC). Mass spectra were recorded on a Shimadzu GCMS-QP 2010 Plus instrument at ion-source temperature 200°C in mass scan range *m*/*z* 2–400 with electron-impact ionization at 70 eV. Optical rotation angles were measured on an Optical Activity PolAAr 3001 automated digital polarimeter (England). TLC used Sorbfil plates, $CHCl_3$ solvent, and phosphomolybdic acid developer. Column chromatography used Alfa Aesar silica gel (0.06–0.2 mm) and eluents petroleum ether–EtOAc (5:1, 1:1), $CHCl_3$–Et_2O (10:1), $CHCl_3$–*i*-PrOH (5:1), and petroleum ether–Et_2O (5:1, 50:1).

Cis- and *trans*-myrtanols were synthesized from commercially available (–)-*β*-pinene (Alfa Aesar), $[\alpha]_D^{20}$ –27.9° (neat). Sulfides were synthesized using 3-mercapto-1,2,4-triazole, 3-mercapto-4-methyl-1,2,4-triazole, and 3-mercapto-2,4-diphenyl-1,2,4-triazole (Alfa Aesar).

(–)-*cis*-Myrtanol, (1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptane-2-methanol (2) was prepared by the literature method [26], $[\alpha]_D^{20}$ –20.5° (*c* 1.9, $CHCl_3$), lit. $[\alpha]_D^{20}$ –20.9° (*c* 4.0, $CHCl_3$) [26]. The spectral characteristics agreed with those published [27].

(–)-*trans*-Myrtanol, (1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptane-2-methanol (3) was prepared by the literature method [27], $[\alpha]_D^{20}$ –27.9° (*c* 1.9, $CHCl_3$), lit. $[\alpha]_D^{20}$ –28.5° (*c* 4.0, $CHCl_3$) [27]. The spectral characteristics agreed with those in the literature [27].

Tosylates of (–)-*cis*- (3) and (–)-*trans*-myrtanols (4) were synthesized as before [28].

General Method for Synthesizing Thio-derivatives. Thiol (1.5 mmol) was dissolved in DMF (5 mL), treated with Cs_2CO_3 (1 mmol) and TBAI (1 mmol), stirred for 5 min, and treated with a solution of tosylate **3** or **4** (1 mmol) in DMF. The syntheses were carried out with constant stirring and refluxing for 8 h. The reaction was monitored by TLC. When the reaction was finished, the solvent was distilled off. The residue was extracted with EtOAc. The extract was washed with saturated $KHCO_3$ solution. The combined organic fractions were combined and dried over Na_2SO_4. The target sulfides were isolated by column chromatography over silica gel.

2-[(1*R*,2*S*,5*R*)-(1,2,4-Triazolylsulfanyl)methyl]-6,6-dimethylbicyclo[3.1.1]heptane (5a). Yield 91%, yellow oily liquid, R_f 0.11 ($CHCl_3$–Et_2O, 10:1), $[\alpha]_D^{20}$ –23.4° (*c* 1.18, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 3110 (N–H), 2980–2870 (C–H), 1516–1560, 1470, 1360 (C=N), 1270 (N–N). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 237.20 (70) $[M^+]$. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.88 (1H, d, J = 9.7, H-7α), 1.02 (3H, s, H-8), 1.18 (3H, s, H-9), 1.49–1.65 (1H, m, H-3α), 1.73–2.14 (5H, m, H-1, 3β, 4α, 4β, 5), 2.28–2.42 (2H, m, H-2, 7β), 3.28 (2H, dd, J = 7.7, 6.7, H-10), 8.13 (1H, s, H-4′), 11.96 (1H, br.s, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 21.77 (C-3), 23.16 (C-8), 26.02 (C-4), 27.88 (C-9), 33.23 (C-7), 39.63 (C-10), 41.02 (C-2), 41.15 (C-5), 44.64 (C-6), 45.31 (C-1), 148.03 (C-4′), 156.96 (C-1′).

2-{[(1*R*,2*S*,5*R*)-(1,5-Diphenyl-1*H*-1,2,4-triazolyl)sulfanyl]methyl}-6,6-dimethylbicyclo[3.1.1]heptane (5b). Yield 78%. White powder, mp 246–247°C, R_f 0.10 ($CHCl_3$–*i*-PrOH, 5:1), $[\alpha]_D^{26}$ +35.2° (*c* 0.4, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 2980–2860 (C–H), 1560–1516 (C=N), 1622, 1494 (C_6H_5), 1470, 1360 (C=N), 1270 (N–N). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 391.20 (73) $[M]^+$, 392.20 (24) $[M + 1]^+$. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 0.80 (3H, s, H-8), 1.19 (3H, s, H-9), 1.30–1.46 (2H, m, H-3α, 7α), 1.72–1.98 (5H, m, H-1, 3β, 4α, 4β, 5), 2.01–2.14 (1H, m, H-7β), 2.26–2.40 (1H, m, H-2), 7.19–7.61 (10H, m, 2 C_6H_5).^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 20.09 (C-8), 21.87 (C-3), 23.72 (C-7), 24.16 (C-4), 26.61 (C-9), 34.84 (C-2), 38.66 (C-10), 39.50 (C-6), 40.73 (C-5), 44.89 (C-1), 126.71 (C-6′), 127.39, 128.13, 128.42, 129.56, 129.75, 128.86 (C-7′–11′, 13′–17′), 134.40 (C-12′), 153.16 (C-4′), 154.67 (C-1′).

2-(1*R*,2*S*,5*R*)-(4-Methyl-2,4-dihydro-3-thione-1,2,4-triazolyl)-6,6-dimethylbicyclo[3.1.1]heptane (5c). Yield 89%, white powder, mp 112–113°C, R_f 0.27 ($CHCl_3$–Et_2O, 10:1), $[\alpha]_D^{27}$ –8.1° (*c* 0.3, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 2980–2870 (C–H), 1560–1516, 1470, 1360 (C=N), 1270 (N–N). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 251.05 (21) $[M^+]$. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90 (1H, d, J = 9.9, H-7α), 1.19 (6H, d, H-8, 9), 1.59–1.73 (1H, m, H-3α), 1.76–2.06 (5H, m, H-1, 3β, 4α, 4β, 5), 2.28–2.41 (1H, m, H-7), 2.68–2.83 (1H, m, H-2), 3.56 (3H, s, H-6′), 4.20 (2H, t, J = 8.07, H-10), 7.74 (1H, s, H-4′). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 18.93 (C-3), 23.08 (C-8), 25.84 (C-4), 27.20 (C-9), 32.69 (C-6′), 32.91 (C-7), 38.65 (C-6), 39.82 (C-2), 41.20 (C-5), 43.26 (C-1), 54.41 (C-10), 138.70 (C-1′), 162.01 (C-4′).

2-[(1*R*,2*S*,5*R*)-(1,2,4-Triazolylsulfanyl)methyl]-6,6-dimethylbicyclo[3.1.1]heptane (6a). Yield 90%. oily liquid, R_f 0.18 ($CHCl_3$–Et_2O, 1:1). IR spectrum (KBr, ν, cm^{-1}): 3109 (NH), 2978–2871 (C–H), 1560–1516, 1470, 1360 (C=N), 1270 (N–N). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 237.15 (80) $[M^+]$. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.77 (3H, s, H-8), 1.18 (3H, s, H-9), 1.32 (2H, d, J = 10.2, H-3α, 7α), 1.70–1.82 (3H, m, H-3β, 4α, 4β), 1.85–1.93 (2H, m, H-1, 5), 2.00–2.10 (1H, m, H-7β), 2.19–2.32 (1H, m, H-2), 3.01–3.17 (2H, m, H-10), 8.15 (1H, s, H-4′), 13.13 (1H, br.s, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 20.00 (C-8), 21.83 (C-3), 23.27 (C-7), 24.10 (C-4), 26.56 (C-9), 34.99 (C-2), 38.91 (C-10), 39.44 (C-6), 40.68 (C-5), 44.83 (C-1), 147.90 (C-1′), 156.47 (C-4′).

2-{[(1*R*,2*S*,5*R*)-(1,5-Diphenyl-1*H*-1,2,4-triazolyl)sulfanyl]methyl}-6,6-dimethylbicyclo[3.1.1]heptane (6b). Yield 89%. White powder, mp 155–156°C. R_f 0.20 (petroleum ether–Et_2O, 5:1), $[\alpha]_D^{27}$ –7.4° (*c* 0.5, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 3026 (NH), 2980–2870 (C–H), 1595 (C_6H_5), 1560–1515 (C=N), 1270 (N–N), 644 (C–S). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 389.20 (20) $[M^+]$, 390.20 (24) $[M + 1]^+$. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.87 (3H, s, H-8), 1.20 (3H, s, H-9), 1.30–1.40 (2H, m, H-3α, 7α), 1.72–1.83 (3H, m, H-3β, 4α, 4β), 1.88 (2H, d, J = 5.8, H-1, 5), 5.00–5.12 (1H, m, H-7β), 2.26–2.40 (1H, m, H-2), 3.14–3.33 (2H, m, H-10), 7.19–7.56 (10H, m, 2C_6H_5). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 20.07 (C-8), 21.84 (C-3), 23.30 (C-7), 24.13 (C-4), 26.58 (C-9), 34.79 (C-2), 38.62 (C-10), 39.47 (C-6), 40.68 (C-5), 44.84 (C-1), 126.63 (C-6′), 127.35, 128.11, 128.40, 129.56, 129.74, 128.84 (C-7′–11′, 13′–17′), 134.34 (C-12′), 153.53 (C-4′), 154.70 (C-1′).

2-(1*R*,2*R*,5*R*)-(4-Methyl-2,4-dihydro-3-thione-1,2,4-triazolyl)-6,6-dimethylbicyclo[3.1.1]heptane (6c). Yield 95%, yellowish powder, mp 88–89°C, R_f 0.43 ($CHCl_3$–Et_2O, 10:1), $[\alpha]_D^{26}$ –24.5° (*c* 0.8, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}):

2980–2870 (C–H), 1560–1516, 1470, 1360 (C=N), 1270 (N–N). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 251.15 (35) [M^+], 252.15 (23) [M + 1]$^+$. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 0.17 (3H, s, H-8), 0.57 (3H, s, H-9), 0.71–0.86 (2H, m, H-3α, 7α), 0.86–1.04 (1H, m, H-3β), 1.06–1.19 (3H, m, H-1, 4α, 5), 1.19–1.30 (1H, m, H-4β), 1.42–1.53 (1H, m, 7β), 3.37 (2H, m, H-10), 7.36 (1H, s, H-4′). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 18.72 (C-3), 19.74 (C-8), 23.18 (C-7), 23.62 (C-4), 26.33 (C-9), 32.33 (C-6′), 33.96 (C-2), 38.88 (C-6), 40.43 (C-5), 42.34 (C-1), 53.30 (C-10), 162.22 (C-4′), 166.50 (C-1′).

Antioxidant activity of the myrtanylthiotriazoles was assessed from the ability to inhibit lipid peroxidation (LPO) processes in brain lipids of laboratory mice [23–25]. Excised brain was homogenized (10%) in normal saline (pH 7.4) and centrifuged for 10 min. Then, the supernatant (S1) containing H_2O, proteins, DNA, RNA, and lipids (cholesterol, galactolipids, individual phospholipids, and gangliosides) was collected. The studied compounds were added to S1 as Me_2CO solutions (final concentration 0.1 and 1 mM). After 30 min, LPO was initiated by adding freshly prepared $FeSO_4$ (3 μM) and ascorbic acid (300 μM). Then, the test samples were incubated for 1 h at 37°C with gentle stirring. The contents of LPO secondary products that reacted with 2-thiobarbituric acid (TBA-AP) were determined by spectrophotometry at λ = 532 nm using a Thermo Genesys Spectronic 20 spectrophotometer (USA) [23–25, 29].

Toxicity and antioxidant and membrane-protective activities of the compounds were studied using a suspension (0.5%, v/v) of laboratory-mouse erythrocytes in phosphate-buffered saline (PBS, pH 7.4). Toxicity of the compounds was assessed (*in vitro*) from their ability to induce hemolysis. Solutions of the compounds were added to erythrocyte suspension and incubated at 37°C for 5 h in a Bioscan ES-20 thermostatted shaker (Latvia). Cytotoxicity was assessed from the degree of erythrocyte hemolysis after incubation for 1, 3, and 5 h. Membrane-protective and antioxidant activities were determined from the degrees of inhibition of H_2O_2-induced hemolysis, suppression of accumulation of LPO secondary products, and oxidation of oxyhemoglobin in erythrocytes. For this, hemolysis was initiated by adding H_2O_2 solution (0.006%) to Me_2CO suspensions of erythrocytes 30 min after the studied compounds were added. Then, the reaction mixtures were incubated in a thermostatted shaker at 37°C with gentle mixing for 5 h. Aliquots of the incubation mixture were taken every hour and centrifuged for 5 min (1,600 g). Hemolysis was determined at λ = 524 nm from the hemoglobin content in the supernatant on a Thermo Spectronic Genesys 20 spectrophotometer (USA). The percent hemolysis was calculated from the ratio to total hemolysis of the sample. The content of LPO secondary products that reacted with TBA-AP was determined spectrophotometrically [29]. Accumulation of hemoglobin oxidation products after the incubation was assessed by total hemolysis of an aliquot of erythrocyte suspension, centrifugation to precipitate erythrocyte particulates, and analysis of the absorption spectrum in the range 540–630 nm using a Fluorat-02-Panorama spectrofluorimeter (Lumex, St. Petersburg). The contents of various hemoglobin species (oxyHb and ferrylHb) were calculated considering the corresponding extinction coefficients [30].

Each experiment was performed in 4–5 repetitions. Results were processed statistically using Microsoft Office Excel 2007 software.

Antioxidant and membrane-protective activity were studied at the Molecular Biology Center for Collective Use, Inst. Biol., Komi SC, UB, RAS. Animals from the scientific collection of experimental animals of the Inst. Biol., Komi SC, UB, RAS, were used in the work (http://www.ckp-rf.ru/usu/471933/).

ACKNOWLEDGMENT

The work was supported financially in part by the RFBR (Project 16-53-00171 Bel_a) using equipment at the Khimiya Center for Collective Use, Inst. Chem., Komi SC, UB, RAS.

REFERENCES

1. J.-Y. Yang, H.-W. Lee, and H.-S. Lee, *Food Sci. Biotechnol.*, **24**, 169 (2015).
2. G. Chawla, U. Kumar, S. Bawa, and J. Kumar, *J. Enzyme Inhib. Med. Chem.*, **27**, 658 (2012).
3. D. A. Ibrahim, *Eur. J. Med. Chem.*, **44**, 2776 (2009).
4. S. M. el-Khawass, M. A. Khalil, A. A. Hazzaa, H. A. Bassiouny, and N. F. Loutfy, *Farmaco (Soc. Chim. Ital.)*, **44**, 703 (1989).
5. T. Karabasanagouda, A. V. Adhikari, and N. S. Shetty, *Eur. J. Med. Chem.*, **42**, 521 (2007).

6. I. Ledeti, V. Bercean, A. Alexa, C. Soica, L.-M. Suta, C. Dehelean, C. Trandafirescu, D. Muntean, M. Licker, and A. Fulias, *J. Chem.*, **1**, 2015 (2015).
7. P. Zoumpoulakis, C. Camoutsis, G. Pairas, M. Sokovic, J. Glamoclija, C. Potamitis, and A. Pitsas, *Bioorg. Med. Chem.*, **20**, 1569 (2012).
8. M. Kritsanida, A. Mouroutsou, P. Marakos, N. Pouli, S. Papakonstantinou-Garoufalias, C. Pannecouque, M. Witvrouw, and E. De Clercq, *Il Farmaco*, **57**, 253 (2002).
9. Z. Li, Y. Cao, P. Zhan, C. Pannecouque, J. Balzarini, E. Clercq, Y. Shen, and X. Liu, *Med. Chem.*, **9**, 968 (2013).
10. X.-Q. Deng, M.-X. Song, Y. Zheng, and Z.-S. Quan, *Eur. J. Med. Chem.*, **73**, 217 (2014).
11. A. Cetin and I. Gecibesler, *J. Appl. Pharm. Sci.*, 120 (2015).
12. S.-F. Barbuceanu, D. Ilies, G. Saramet, V. Uivarosi, C. Draghici, and V. Radulescu, *Int. J. Mol. Sci.*, **15**, 10908 (2014).
13. L. Savegnago, M. do Sacramento, L. M. P. Brod, M. G. Fronza, N. Seus, E. J. Lenardao, M. W. Paixao, and D. Alves, *RSC Adv.*, **6**, 8021 (2016).
14. D. Hussain, *Orient. J. Chem.*, **32**, 539 (2016).
15. A. A. Hameed and F. Hassan, *Int. J. Appl. Sci. Technol.*, **4**, No. 2, 202 (2014).
16. R. Nimal, S. Aftab, U. A. Rana, A. Lashin, S. U.-D. Khan, S. Ali, H.-B. Kraatz, and A. Shah, *J. Electrochem. Soc.*, **163**, H871 (2016).
17. L. Nikitina, N. Artemova, and V. Startseva, *Natural and Thiomodified Monoterpenoids: Synthesis and Biological Activity of Thioterpenoids* [in Russian], LAP Lambert Academic Publishing, 2012.
18. E. V. Buravlev, I. Y. Chukicheva, O. V. Sukrusheva, O. G. Shevchenko, and A. V. Kutchin, *Russ. Chem. Bull.*, **64**, 1406 (2015).
19. E. S. Izmest′ev, D. V. Sudarikov, O. G. Shevchenko, S. A. Rubtsova, and A. V. Kutchin, *Russ. J. Bioorg. Chem.*, **41**, 77 (2015).
20. A. W. Snow and E. E. Foos, *Synthesis*, 0509 (2003).
21. J. K. Shneine and Y. H. Alaraji, *Int. J. Sci. Res. (IJSR)*, **5** (3), 1411 (2016).
22. O. G. Shevchenko and L. N. Shishkina, *Usp. Sovrem. Biol.*, **134**, 133 (2014).
23. C. I. Acker, R. Brandao, A. R. Rosario, and C. W. Nogueira, *Environ. Toxicol. Pharmacol.*, **28**, 280 (2009).
24. . J.-S. Kim, *Food Nutr. Sci.*, **4**, 177 (2013).
25. S. T. Stefanello, A. S. Prestes, T. Ogunmoyole, S. M. Salman, R. S. Schwab, C. R. Brender, L. Dornelles, J. B. T. Rocha, and F. A. A. Soares, *Toxicology in Vitro*, **27** (5), 1433 (2013).
26. G. Zweifel and H. C. Brown, *J. Am. Chem. Soc.*, **86**, 393 (1964).
27. M. J. P. Ferreira, V. Emerenciano, G. A. Linia, P. Romoff, P. A. Macari, and G. Rodrigues, *Prog. Nucl. Magn. Res. Spectrosc.*, **33**, 153 (1998).
28. A. Banach, J. Scianowski, and P. Ozimek, *Phosphorus Sulfur Silicon Relat. Elem.*, **189**, 274 (2014).
29. T. Asakawa and S. Matsushita, *Lipids*, **15**, 137 (1980).
30. J. J. M. Van den Berg, J. A. F. Opden Kamp, B. H. Lubin, B. Roelofsen, and F. A. Kuypers, *Free Radical Biol. Med.*, **12**, 487 (1992).