Full Articles

Comparative evaluation of antioxidant activity of 2-alkyl-4-methylphenols and their 6-*n*-octylaminomethyl derivatives*

E. V. Buravlev,[a]★ I. V. Fedorova,[a] and O. G. Shevchenko[b]

[a]*Institute of Chemistry, Komi Scientific Center, Ural Branch of the Russian Academy of Sciences, 48 ul. Pervomaiskaya, 167000 Syktyvkar, Russian Federation. Fax: +7 (8212) 21 9916. E-mail: eugeneburavlev@gmail.com*
[b]*Institute of Biology, Komi Scientific Center, Ural Branch of the Russian Academy of Sciences, 28 ul. Kommunisticheskaya, 167982 Syktyvkar, Russian Federation. Fax: +7 (8212) 24 0163*

A series of 2-alkyl-4-methyl-6-*n*-octylaminomethylphenols (where alkyl is methyl or *tert*-butyl group, or terpene substituent) was synthesized. A comparative evaluation of the antioxidant properties of the starting alkyl- and terpenylphenols and their Mannich bases was carried out using *in vitro* assays. Structural features providing high antioxidant activity of these compounds were revealed.

Key words: Schiff bases, Mannich bases, chelation ability, antioxidant activity, membrane-protective activity, red blood cells, oxidative hemolysis.

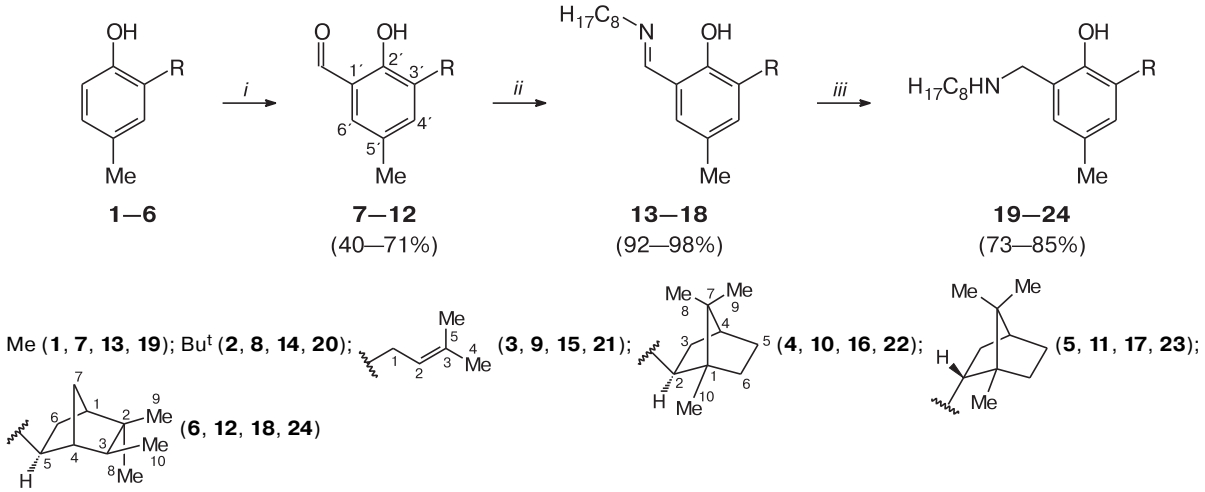
Natural and synthetic antioxidants (AOs) are widely used in modern medicine, but the mechanism of action of these compounds in living cells is not so unambiguous as it was considered fifty years ago and cannot be explained by radical scavenging only. The most abundant class of AOs is presented by phenol compounds, and the derivatives with the screened hydroxy group (sterically hindered phenols) are often used among the synthetic representatives of the phenol compounds.[1] In addition to traditional alkylphenols, terpenylphenols can serve as the starting compounds for the synthesis of new AOs. They represent a special class of natural and semisynthetic compounds, whose structures contain fragments with the hydrophilic (phenol moiety) and lipophilic (isoprene moiety) properties.[2] The use of these compounds can be substantiated by a broad range of biological activity exhibited by terpenylphenols with the isobornyl substituent.[3—7] It should be mentioned that the activity of 2,6-diisobornyl-4-methylphenol in various model systems exceeds[8—10] that of the known phenol antioxidant 2,6-di-*tert*-butyl-4-methylphenol (BHT).[1]

A convenient method for the modification of phenol compounds is the introduction of the aminomethyl group, which is often applied in the design of drugs and in medicinal chemistry.[11] This structural fragment can be formed

* Dedicated to Corresponding Member of the Russian Academy of Sciences A. V. Kutchin on the occasion of his 70th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 5, pp. 0985—0992, May, 2019.

Scheme 1*



Reagents and conditions: *i*. HCOH, $SnCl_4$, $Bu^n{}_3N$, toluene, reflux, 10 h[16]; *ii*. $C_8H_{17}NH_2$, benzene, molecular sieves 4 Å, reflux, 3.5 h; *iii*. $NaBH_4$, EtOH, reflux, 30 min.

* The presented numbering of C atoms is used for convenience of interpretation of the NMR spectra, the numberings of the C atoms of the bornyl and isobornyl structures coincide. Compounds **4** and **6** and their derivatives **10**, **12**, **16**, **18**, **22**, and **24** are racemates for which the structures of one of enantiomers are shown in Scheme 1.

using diverse synthetic approaches: *via* the Mannich reaction,[12] by the reduction of Schiff bases,[13] the reaction of the bromomethyl derivatives with amines,[14] *etc.* We have recently reported that among the *N*- and *O*-containing derivatives of isobornylphenols the Mannich base with the secondary amino group has a pronounced antioxidant activity (AOA) on *in vitro* models.[15] For detailed analysis of the influence of the structures of the alkyl and terpene substituents in the *ortho*-position to the hydroxy group on the AOA, the range of the aminomethyl derivatives should be extended by new analogs based on accessible alkyl- and terpenylphenols and their antioxidant activity should be evaluated by different method, which is the purpose of the present study.

Results and Discussion

Two commercially available compounds served as the starting compounds: 2,4-dimethylphenol (**1**) and 2-*tert*-butyl-4-methylphenol (**2**). In addition, 4-methyl-2-prenylphenol (**3**) synthesized by the alkylation of 4-methylphenol with prenol in the presence of montmorillonite KSF clay** was used. Previously described 4-methylphenols **4—6** with various structures of the bicyclic terpene substituent, *i.e.* isobornyl, bornyl, and isocamphyl fragments, were also used in the synthesis. Salicylaldehydes **7—12** were obtained from compounds **1—6** using a known procedure,[16] and Schiff bases **13—18** were synthesized from aldehydes by the condensation with *n*-octylamine. The reduction of imines afforded Mannich bases **19—24**. The synthesis of the target compounds is shown in Scheme 1.

The data of ^1H and ^{13}C NMR spectroscopy, IR spectroscopy, and elemental analysis for new products **9**, **13—18**, **20**, and **21** correspond to the expected structures, and the characteristics of the other compounds are consistent with published values.[13,17—22] Imines **13—18** have the *E*-configuration of the substituents relative to the C=N bond: the NOESY experiments for these compounds show cross-peaks between the proton of the N=CH group (δ_H 8.26—8.28) and protons of the NCH_2 group (δ_H 3.40—3.71), as well as with the H(6′) proton (δ_H 6.86—6.90), indicating their spatial proximity.

The following parameters were estimated for the starting alkyl- and terpenylphenols **1—6** and synthesized Mannich bases **19—24**: radical scavenging activity (RSA) in test with 2,2-diphenyl-1-picrylhydrazyl (DPPH), AOA on the substrate obtained from the brain of laboratory mice, Fe^{2+}-chelation ability (CA) in test with FerroZine™ Iron Reagent, hemolytic activity (cytotoxicity), and antioxidant and membrane-protective (MP) properties using erythrocytes of the laboratory mice blood. These model systems were applied by us earlier when studying isobornylphenols,[14,15,21—27] xanthones,[28,29] flavonoids,[30] and sulfur-containing compounds.[27,31] The reference compound was BHT. The earlier synthesized analog of compound **22**, *i.e.*, racemic 2-*n*-hexylaminomethyl-6-isobornyl-4-methylphenol (**25**), was also used in a series of experiments.[15,22]

** This alkylation reaction will be considered in detail elsewhere.

Table 1. Comparative estimation of the RSA (test with DPPH), CA (test with FerroZine™ Iron Reagent), and AOA (test on the substrate from the brain of laboratory animals)* for derivatives **1**—**6**, **19**—**25**, and BHT

Compound	RSA (% inhibition)		CA (%)	TBA-RS/nmol mL^{-1}	
	c = 100 μmol L^{-1}	c = 10 μmol L^{-1}	c = 100 μmol L^{-1}	c = 100 μmol L^{-1}	c = 10 μmol L^{-1}
BHT	—	11.3±1.1	3.0±0.3	3.7±0.2	5.9±0.7
1	46.5±0.7	12.5±0.5	6.0±1.7	18.8±0.5	59.5±0.5
2	27.9±1.2	4.7±0.5	7.0±1.5	3.9±0.2	31.3±0.1
3	47.8±0.9	11.4±0.6	6.0±1.0	3.0±0.1	34.8±0.4
4	56.9±1.1	12.6±0.7	5.9±1.8	4.7±1.3	4.8±0.1
5	46.4±0.8	10.8±0.9	8.0±1.3	4.7±0.1	11.8±0.3
6	62.1±1.4	16.3±1.0	3.0±0.8	3.2±0.1	44.4±0.4
19	42.9±1.3	8.6±0.6	79.6±0.5	4.0±0.2	58.6±0.2
20	59.4±0.9	15.3±0.9	42.4±1.1	6.6±0.1	59.1±0.1
21	47.9±1.8	11.1±0.6	74.5±0.6	4.0±0.2	50.4±0.6
22	62.2±1.7	16.1±1.1	57.4±1.3	5.0±0.1	49.0±0.6
23	64.2±1.6	16.8±1.1	73.5±0.9	4.7±0.1	48.7±0.4
24	56.5±1.4	12.3±0.9	66.8±1.4	5.5±0.1	58.3±0.6
25	64.1±0.8	16.0±1.1	56.5±1.3	5.0±0.1	49.2±0.5

* The ability of the studied compounds to inhibit the accumulation of products of lipid peroxidation (LPO) reacting with 2-thiobarbituric acid (TBA-reactive substances, TBA-RS) was estimated in the substrate obtained from the mice brain (1 h after the Fe^{2+}/ascorbate initiation of LPO). The concentration of TBA-RS in the control (without compounds) and in intact (without initiated oxidation) samples was 85.0±3.1 and 41.3±2.6 nmol mL^{-1}, respectively.

The results of studies on the non-cellular model systems (Table 1) allow us to conclude that at the concentrations 100 and 10 μmol L^{-1} the starting 4-methylphenols **1**—**6** and corresponding Mannich bases **19**—**25** are characterized by the RSA, which is comparable with that of BHT at the concentration of the compounds equal to 10 μmol L^{-1}. Much more substantial differences in activity between 4-methylphenols **1**—**6** and their derivatives **19**—**25** were revealed when the CA was estimated: the introduction of the aminomethyl group enhances the effect by 6.0—22.6 times. The high CA of phenols containing the aminomethyl fragment in the *ortho*-position is also known.[12]

The results of studying the AOA of the derivatives on the model containing an emulsion of animal lipids showed that at a concentration of 100 μmol L^{-1} all synthesized compounds, except for 2,4-dimethylphenol (**1**), can inhibit the Fe^{2+}/ascorbate-initiated accumulation of the secondary lipid peroxidation (LPO) products to the level substantially lower than the spontaneous one and are not inferior to BHT in activity. Only 2-isobornyl-4-methylphenol (**4**) retained high activity in this test system when the concentration of the compounds was decreased by an order of magnitude (down to 10 μmol L^{-1}). The exclusively high AOA of this compound and its nearest analog, 2,4-dimethyl-6-isobornylphenol, was demonstrated earlier.[15] Note that the introduction of the aminomethyl group into the *ortho*-position of 4-methylphenols **1**—**6** did not provide the enhancement of the AOA of the products in the considered test system. On the contrary, in the most part of experiments, Mannich bases **19**—**24** inhibited the Fe^{2+}/ascorbate-initiated LPO substantially more weakly than the corresponding 4-methylphenols **1**—**6** (see Table 1). A similar dependence was observed for the initiation of LPO by H_2O_2 (the data in Table 1 are omitted). It is known that the introduction of the aminomethyl group with the secondary amine fragment increases the polarity of the compounds and, possibly, the effect observed is caused by the so-called antioxidant polar paradox, according to which in lipid emulsions the nonpolar AOs are more active than the polar AOs.[32,33]

No relation between the RSA of the BHT derivatives of various structures (test with DPPH) and their ability to inhibit the Fe^{2+}-initiated LPO in the heterogeneous medium (evaluation of the accumulation of the 2-thiobarbituric acid reactive substances (TBA-RS) in an emulsion based on vitellus) was observed previously.[34] This confirms that various methods should be applied to study the AO properties of compounds.[35,36]

The estimation of the hemolytic activity showed that the studied compounds had no substantial cytotoxicity against erythrocytes, and an insignificant hemolytic activity that did not exceed 9% was revealed only for some products in a concentration of 10 μmol L^{-1}.

An analysis of the MP properties and AOA studied using erythrocytes of laboratory mice (Tables 2 and 3) showed that the presence at the *ortho*-position of the phenol fragment of the bicyclic terpene substituents and its steric structure exerted a substantial effect on the ability of compounds to protect living cells from the toxic

Table 2. Comparative estimation of the MPA and AOA for derivatives **1**—**6** and **19**—**24** at concentration of 1 μmol L^{-1} using erythrocytes of laboratory mice

Compound	MPA (% hemolysis)			TBA-RS /nmol mL^{-1}
	1 h	3 h	5 h	
Control	17.3±0.4	43.2±0.8	50.2±0.9	2.13±0.03
1	9.7±0.4	35.8±1.1	45.7±1.2	2.21±0.13
2	9.3±0.9	26.7±0.8	37.0±0.9	1.25±0.07
3	12.1±1.6	36.8±0.4	45.1±0.5	1.72±0.19
4	2.9±0.3	12.9±0.3	20.6±0.5	0.98±0.03
5	3.3±0.2	18.5±1.3	31.7±1.4	0.99±0.02
6	3.9±0.5	15.5±1.7	26.1±0.6	0.94±0.05
19	8.4±1.0	26.4±0.8	39.5±0.6	0.86±0.03
20	6.0±1.4	21.0±0.7	36.3±0.2	0.82±0.03
21	1.9±0.1	5.5±0.3	12.9±0.7	0.67±0.03
22	1.9±0.1	4.8±0.1	9.5±0.5	0.64±0.01
23	2.0±0.1	5.3±0.2	11.3±0.5	0.60±0.02
24	1.8±0.0	5.1±0.1	10.4±0.2	0.59±0.02

action of H_2O_2. At a concentration of 1 μmol L^{-1} (see Table 2), compound **4** with the isobornyl fragment exhibited the maximum activity among the starting 4-methylphenols **1**—**6**. Note that in this model system biological activity of the derivatives also depends on the presence of the *n*-alkylaminomethyl substituent in the molecule: the ability to prevent the oxidative hemolysis of erythrocytes and accumulation of the secondary LPO products are substantially higher for Mannich bases **19**—**24** than those for their precursors **1**—**6**, which is likely caused by a high CA of the latter (*cf.* data in Tables 1 and 2).

On the whole, the high MP and AO activities of the studied compounds in the cellular model system are provided by a combination of the terpene fragment and aminomethyl group, which follows from an analysis of the data of the experiment performed at the concentration of the compounds equal to 0.1 μmol L^{-1} (see Table 3). It was found that even at such a low concentration derivatives **22**—**25** efficiently protected erythrocytes from decay and prevented the accumulation of the secondary LPO products, oxidation of native hemoglobin, and oxidative degradation of the heme. These derivatives substantially exceeded the BHT reference by the majority of parameters.

Thus, we pioneered in the comparative evaluation of the antioxidant properties of 2-alkyl-4-methylphenols and their 6-*n*-alkylaminomethyl derivatives. It is shown that the studied compounds are characterized by high antioxidant activity in diverse model systems. It is revealed that the chelation ability of the compounds is mainly determined by the presence of the aminomethyl substituent in the molecule, whereas the antioxidant and membrane-protective activities in the cellular model system depend substantially also on the structure of the alkyl/terpene fragment. According to all parameters characterizing the compounds as inhibitors of oxidation processes, the most active are substituted 4-methylphenols **22**—**25**, whose structures contain the bicyclic terpene fragment and *n*-alkylaminomethyl substituent, and the length of the alkyl group at the nitrogen atom (C_6H_{13} and C_8H_{17} for derivatives **25** and **22**, respectively) exerts an insignificant effect on the antioxidant properties in the considered test systems. Thus, the high antioxidant activity of the Mannich bases with *n*-alkyl fragments **22**—**25** in the cellular model system can be due to the presence of several functional groups in the molecule: the phenol hydroxy group providing radical scavenging activity, the secondary amino group in the *ortho*-position providing high chelation ability, and finally, two lipophilic fragments (terpene and *n*-octylaminomethyl) favoring, most likely, the optimum interaction of these compounds with the biomembrane.

Experimental

The course of the reactions was monitored by TLC on the Sorbfil plates (LLC IMID). The reaction products were detected by the treatment of the plates with a $KMnO_4$ solution (15 g of $KMnO_4$, 300 mL of H_2O, and 0.5 mL of concentrated H_2SO_4).

Table 3. Comparative estimation of the MPA and AOA for derivatives **21**—**25** and BHT at a concentration of 0.1 μmol L^{-1} using erythrocytes of laboratory mice

Compound	MPA (% hemolysis)			TBA-RS / nmol mL^{-1}	metHb /oxyHb*	I_{fl} /arb. units**
	1 h	3 h	5 h			
Control	14.9±0.3	33.9±0.4	41.9±0.4	1.57±0.04	1.156±0.051	10.11±0.42
BHT	7.4±0.6	23.3±0.1	31.1±0.2	1.15±0.03	0.935±0.039	7.67±0.81
21	7.1±0.6	26.0±0.3	36.7±0.3	1.08±0.03	1.163±0.049	8.43±0.60
22	3.2±0.5	5.9±0.8	9.3±0.2	0.78±0.04	0.682±0.037	8.21±0.49
23	2.9±0.4	5.7±0.2	9.0±0.4	0.65±0.03	0.560±0.026	7.25±0.07
24	2.9±0.3	5.3±0.2	8.9±0.2	0.71±0.02	0.707±0.048	7.41±0.36
25	3.0±0.4	6.0±0.2	11.4±0.2	0.69±0.01	0.811±0.021	8.24±0.33

* metHb is methemoglobin, and oxyHb is oxyhemoglobin.

** The fluorescence intensity (I_{fl}) in the intact sample was 5.42±0.19 arb. units.

The ^{1}H and ^{13}C NMR spectra of the obtained compounds were recorded on a Bruker Avance II 300 spectrometer (300.17 (^{1}H) and 75.5 (^{13}C) MHz) at room temperature. Signal assignment was performed using the ^{13}C NMR spectra recorded on the *J*-modulation mode and the HSQC, HMBC, and NOESY experiments. Diffuse reflectance IR spectra were recorded on a Shimadzu IR Prestige 21 FT-IR spectrometer in KBr pellets for solid compounds and neat for liquid compounds. Melting points were determined on a Sanyo Gallenkamp MPD 350 instrument and were not corrected. The following reagents were used without additional purification: montmorillonite KSF, 4-methylphenol, 2,4-dimethylphenol (**1**), prenol, *n*-octylamine, 2-*tert*-butyl-4-methylphenol (**2**), BHT, DPPH (Alfa Aesar), and FerroZine™ Iron Reagent (sodium 5,6-diphenyl-3-(2-pyridyl)-1,2,4-triazine-4′,4″-disulfonic acid hydrate) (Sigma-Aldrich). 2-Isobornyl-4-methylphenol (**4**),[20] 2-isocamphyl-4-methylphenol (**6**),[37] and an enantioenriched sample of (+)-2-bornyl-4-methylphenol (**5**) ($[\alpha]_D^{25}$ +29.1 (*c* 0.3, $CHCl_3$); according to the chiral HPLC data, *ee* >99%) were used in the syntheses. According to the data of GLC and ^{1}H NMR spectroscopy, the purity of the compounds was >97%. Molecular sieves 4 Å were calcined for 3 h at 140 °C. Silica gel 0.06—0.2 mm (Alfa Aesar) was used for column chromatography.

Analyses of the synthesized compounds were partially carried out using the equipment of the Center for Collective Use "Chemistry" of the Institute of Chemistry (Komi Scientific Center, Ural Branch of the Russian Academy of Sciences). The activities of the compounds were studied using the equipment of the Center for Collective Use "Molecular Biology" of the Institute of Biology (Komi Scientific Center, Ural Branch of the Russian Academy of Sciences). Animals of the scientific collection of experimental animals of the Institute of Biology (Komi Scientific Center, Ural Branch of the Russian Academy of Sciences) were used (http://www.ckp-rf.ru/usu/471933/).

4-Methyl-2-(3-methylbut-2-en-1-yl)phenol (3). Prenol (0.94 mL, 9.25 mmol) and montmorillonite KSF (0.5 g) were added to a solution of 4-methylphenol (0.5 g, 4.6 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at 40 °C for 2 h. After the completion of the reaction, the clay was filtered off and washed with CH_2Cl_2, the solvent was removed under reduced pressure, and the product was isolated by column chromatography using a petroleum ether—Et_2O (5 : 1 → 3 : 1) system as an eluent. Light yellow oil. The yield was 0.51 g (62%). The spectral characteristics of compound **3** correspond to those published earlier.[17]

Aldehydes 7—12 were synthesized from cresols **1**—**6** using a known procedure.[16]

2-Hydroxy-3,5-dimethylbenzaldehyde (7). Yellow oil. The yield was 49%. The spectral characteristics of compound **7** correspond to those published earlier.[18]

3-*tert*-Butyl-2-hydroxy-5-methylbenzaldehyde (8). Yellow powder, m.p. 73—74 °C. The yield was 42%. The spectral characteristics of compound **8** correspond to those published earlier.[19]

2-Hydroxy-5-methyl-3-(3-methylbut-2-en-1-yl)benzaldehyde (9). Yellow oil. The yield was 55%. Found (%): C, 76.58; H, 7.78. $C_{13}H_{16}O_2$. Calculated (%): C, 76.44; H, 7.90. IR (neat), ν/cm^{-1}: 3264, 3142 (OH); 2970, 2918, 2855, 1458 (CH_3, CH_2); 1651 (C=O); 1261 (C—O); 1213 ($C(CH_3)_2$); 864, 793 (=C—H). ^{1}H NMR ($CDCl_3$), δ: 1.73 (s, 3 H, C(5)H$_3$); 1.76 (s, 3 H, C(4)H$_3$); 2.31 (s, 3 H, C(5′)CH$_3$); 3.34 (d, 2 H, C(1)H, *J* = 7.3 Hz); 5.30 (br.t, 1 H, C(2)H, *J* ≈ 7.2 Hz); 7.18 (s, 1 H, H(6′)); 7.20 (s, 1 H, H(4′)); 9.83 (s, 1 H, CH=O); 11.11 (s, 1 H, OH). ^{13}C NMR ($CDCl_3$), δ: 17.77 (C(5)); 20.32 (C(5′)$\underline{C}H_3$); 25.77 (C(4)); 27.29 (C(1)); 119.94 (C(1′)); 121.50 (C(2)); 128.67 (C(5′)); 130.08 (C(3′)); 131.04 (C(6′)); 133.34 (C(3)); 137.81 (C(4′)); 157.52 (C(2′)); 196.67 (CH=O).

2-Hydroxy-5-methyl-3-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)benzaldehyde (10). Yellow powder, m.p. 100—101 °C. The yield was 68%. The spectral characteristics of the compound correspond to those published earlier.[20]

2-Hydroxy-5-methyl-3-{(1*R*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl}benzaldehyde (11). The yield was 40%. Colorless powder, m.p. 121—123 °C (methanol). $[\alpha]_D^{22}$ +99.0 (*c* 0.31, $CHCl_3$). The spectral characteristics of the compound correspond to those published earlier.[13]

2-Hydroxy-5-methyl-3-(2,2,3-trimethylbicyclo[2.2.1]hept-*exo*-5-yl)benzaldehyde (12). Light yellow oil. The yield was 71%. The spectral characteristics of the compound correspond to those published earlier.[20]

Synthesis of imines 13—18 (general procedure). Molecular sieves 4 Å (four weights of aldehyde) and *n*-octylamine (0.25 mL, 1.5 mmol) were added to a solution of aldehyde **7**—**12** (1.5 mmol) in anhydrous benzene (6 mL). The reaction mixture was refluxed for 3.5 h under argon. After the completion of the reaction, molecular sieves were filtered off and washed with $CHCl_3$, and the solvents were removed under reduced pressure.

(*E*)-2,4-Dimethyl-6-*n*-octyliminomethylphenol (13). Yellow-brown oil. The yield was 0.376 g (96%). Found (%): C, 78.01; H, 10.50; N, 5.51. $C_{17}H_{27}NO$. Calculated (%): C, 78.11; H, 10.41; N, 5.36. IR (neat), ν/cm^{-1}: 3453 (OH); 2926, 2855, 1474 (CH_3, CH_2); 1634 (C=N); 1271 (C—O); 856, 781 (=C—H). ^{1}H NMR ($CDCl_3$), δ: 0.89 (t, 3 H, $NCH_2(CH_2)_6C\underline{H}_3$, *J* = 6.1 Hz); 1.16—1.48 (m, 10 H, $N(CH_2)_2(C\underline{H}_2)_5CH_3$); 1.62—1.76 (m, 2 H, $NCH_2C\underline{H}_2(CH_2)_5CH_3$); 2.26 (s, 6 H, C(3′)CH$_3$, C(5′)CH$_3$); 3.57 (t, 2 H, $NC\underline{H}_2(CH_2)_6CH_3$, *J* = 6.7 Hz); 6.88 (s, 1 H, C(6′)H); 7.00 (s, 1 H, C(4′)H); 8.27 (s, 1 H, CH=N); 13.69 (s, 1 H, OH). ^{13}C NMR ($CDCl_3$), δ: 14.07 ($NCH_2(CH_2)_6\underline{C}H_3$); 15.41 (C(3′)$\underline{C}H_3$); 20.31 (C(5′)$\underline{C}H_3$); 22.64, 27.19, 29.21, 29.33, 30.92, 31.83 ($NCH_2(\underline{C}H_2)_6CH_3$); 59.51 ($N\underline{C}H_2(CH_2)_6CH_3$); 117.69 (C(1′)); 125.62,126.81 (C(3′), C(5′)); 128.64 (C(6′)); 133.99 (C(4′)); 157.39 (C(2′)); 164.53 (CH=N).

(*E*)-2-*tert*-Butyl-4-methyl-6-*n*-octyliminomethylphenol (14). Yellow-brown oil. The yield was 0.437 g (96%). Found (%): C, 79.08; H, 11.11; N, 4.73. $C_{20}H_{33}NO$. Calculated (%): C, 79.15; H, 10.96; N, 4.62. IR (neat), ν/cm^{-1}: 3254 (OH); 2955, 2926, 2857, 1462 (CH_3, CH_2); 1634 (C=N); 1267 (C—O); 860, 781 (=C—H). ^{1}H NMR ($CDCl_3$), δ: 0.89 (t, 3 H, $NCH_2(CH_2)_6C\underline{H}_3$, *J* = 6.1 Hz); 1.19—1.49 (m, 10 H, $N(CH_2)_2(C\underline{H}_2)_5CH_3$); 1.44 (s, 9 H, $C(CH_3)_3$); 1.61—1.79 (m, 2 H, $NCH_2C\underline{H}_2(CH_2)_5CH_3$); 2.29 (s, 3 H, C(5′)CH$_3$); 3.56 (t, 2 H, $NC\underline{H}_2(CH_2)_6CH_3$, *J* = 6.9 Hz); 6.90 (s, 1 H, C(6′)H); 7.12 (s, 1 H, C(4′)H); 8.28 (s, 1 H, CH=N); 13.97 (s, 1 H, OH). ^{13}C NMR ($CDCl_3$), δ: 14.09 ($NCH_2(CH_2)_6\underline{C}H_3$); 20.66 (C(5′)$\underline{C}H_3$); 22.65, 27.21, 29.21, 29.32, 30.91, 31.84 ($NCH_2(\underline{C}H_2)_6CH_3$); 29.39 ($C(\underline{C}H_3)_3$); 34.72 ($\underline{C}(CH_3)_3$); 59.62 ($N\underline{C}H_2(CH_2)_6CH_3$); 118.40 (C(1′)); 126.29 (C(5′)); 129.29 (C(6′)); 130.15 (C(4′)); 137.12 (C(3′)); 158.31 (C(2′)); 165.08 (CH=N).

(*E*)-4-Methyl-2-(3-methylbut-2-en-1-yl)-6-*n*-octyliminomethylphenol (15). Yellow-brown oil. The yield was 0.463 g (98%). Found (%): C, 80.08; H, 10.31; N, 4.50. $C_{21}H_{33}NO$. Calculated (%): C, 79.95; H, 10.54; N, 4.44. IR (neat), ν/cm^{-1}: 3455 (OH); 2957, 2926, 2855, 1464 (CH_3, CH_2); 1632 (C=N);

1269 (C—O); 855, 793 (=C—H). ^{1}H NMR ($CDCl_3$), δ: 0.89 (t, 3 H, $NCH_2(CH_2)_6C\underline{H}_3$, J = 6.0 Hz); 1.17—1.47 (m, 10 H, $N(CH_2)_2(C\underline{H}_2)_5CH_3$); 1.58—1.79 (m, 2 H, $NCH_2C\underline{H}_2(CH_2)_5CH_3$); 1.74 (s, 3 H, C(5)$H_3$); 1.76 (s, 3 H, C(4)$H_3$); 2.27 (s, 3 H, C(5′)$CH_3$); 3.37 (d, 2 H, C(1)H, J = 7.1 Hz); 3.57 (t, 2 H, $NC\underline{H}_2(CH_2)_6CH_3$, J = 6.7 Hz); 5.30 (br.t, 1 H, C(2)H, J ≈ 7.0 Hz); 6.89 (s, 1 H, C(6′)H); 6.99 (s, 1 H, C(4′)H); 8.28 (s, 1 H, CH=N); 13.73 (s, 1 H, OH). ^{13}C NMR ($CDCl_3$), δ: 14.07 ($NCH_2(CH_2)_6\underline{C}H_3$); 17.79 (C(5)); 20.44 (C(5′)$\underline{C}H_3$); 22.64, 27.78, 29.21, 29.33, 30.91, 31.83 ($NCH_2(\underline{C}H_2)_6CH_3$); 25.81 (C(4)); 27.19 (C(1)); 57.54 ($N\underline{C}H_2(CH_2)_6CH_3$); 117.88 (C(1′)); 122.42 (C(2)); 126.93 (C(5′)); 128.80 (C(6′)); 129.18, 132.55 (C(3), (C(3′)); 132.69 (C(4′)); 157.01 (C(2′)); 164.56 (CH=N).

(*E*)-4-Methyl-2-*n*-octyliminomethyl-6-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol (16). Yellow-brown oil. The yield was 0.531 g (92%). Found (%): C, 81.12; H, 10.98; N, 3.72. $C_{26}H_{41}NO$. Calculated (%): C, 81.41; H, 10.77; N, 3.65. IR (neat), ν/cm^{-1}: 3431 (OH); 2951, 2928, 2874, 2859, 1458 (CH_3, CH_2); 1634 (C=N); 1263 (C—O); 860, 770 (=C—H). ^{1}H NMR ($CDCl_3$), δ: 0.80 (s, 3 H, C(10)H_3); 0.85 (s, 3 H, C(8)H_3); 0.89 (t, 3 H, $NCH_2(CH_2)_6C\underline{H}_3$, overlapped with the adjacent signals); 0.91 (s, 3 H, C(9)H_3); 1.16—1.44, 1.47—1.75 (both m, 10 H, 6 H, 1 H(3), 1 H(5), H(6), $NCH_2(C\underline{H}_2)_6CH_3$); 1.76—1.96 (m, 2 H, C(4)H, 1 C(5)H); 2.05—2.24 (m, 1 H, 1 C(3)H); 2.29 (s, 3 H, C(5′)CH_3); 3.36 (t, 1 H, C(2)H, J = 8.9 Hz); 3.42—3.56, 3.56—3.71 (both m, 1 H each, $NC\underline{H}_2(CH_2)_6CH_3$); 6.87 (s, 1 H, C(6′)H); 7.17 (s, 1 H, C(4′)H); 8.27 (s, 1 H, CH=N); 13.83 (s, 1 H, OH). ^{13}C NMR ($CDCl_3$), δ: 12.29 (C(10)); 14.08 ($NCH_2(CH_2)_6\underline{C}H_3$); 20.44 (C(9)); 20.81 (C(5′)$\underline{C}H_3$); 21.46 (C(8)); 22.65, 27.18, 29.20, 29.32, 30.91, 31.83 ($NCH_2(\underline{C}H_2)_6CH_3$); 27.54 (C(5)); 34.06 (C(3)); 39.72 (C(6)); 44.56 (C(2)); 45.78 (C(4)); 47.97 (C(7)); 49.85 (C(1)); 59.53 ($N\underline{C}H_2(CH_2)_6CH_3$); 117.58 (C(1′)); 126.01 (C(5′)); 128.48 (C(6′)); 131.52 (C(4′)); 131.64 (C(3′)); 158.60 (C(2′)); 164.76 (CH=N).

(*E*)-4-Methyl-2-*n*-octyliminomethyl-6-{(1*R*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl}phenol (17). Yellow-brown oil. The yield was 0.575 g (95%). $[\alpha]_D^{22}$ +102.0 (*c* 0.3, $CHCl_3$). Found (%): C, 81.63; H, 10.89; N, 3.49. $C_{26}H_{41}NO$. Calculated (%): C, 81.41; H, 10.77; N, 3.65. IR (neat), ν/cm^{-1}: 3455 (OH); 2953, 2928, 2878, 2857, 1458 (CH_3, CH_2); 1634 (C=N); 1265 (C—O); 862, 760 (=C—H). ^{1}H NMR ($CDCl_3$), δ: 0.78 (s, 3 H, C(10)H_3); 0.88 (t, 3 H, $NCH_2(CH_2)_6C\underline{H}_3$, J = 6.2 Hz); 0.94 (s, 3 H, C(8)H_3); 1.11 (s, 3 H, C(9)H_3); 1.12—1.46, 1.47—1.92 (both m, 13 H, 5 H, 1 C(3)H, C(4)H, C(5)H, C(6)H, $NCH_2(C\underline{H}_2)_6CH_3$); 2.17 (br.tt, 1 H, 1 C(3)H, J ≈ 12.4 Hz, J ≈ 3.9 Hz); 2.33 (s, 3 H, C(5′)CH_3); 3.40—3.55, 3.55—3.71 (both m, 1 H each, $NC\underline{H}_2(CH_2)_6CH_3$); 3.83 (br.ddd, 1 H, C(2)H, J ≈ 11.6 Hz, J ≈ 5.3 Hz, J ≈ 1.8 Hz); 6.90 (s, 1 H, C(6′)H); 7.12 (s, 1 H, C(4′)H); 8.28 (s, 1 H, CH=N); 13.71 (s, 1 H, OH). ^{13}C NMR ($CDCl_3$), δ: 14.08 ($NCH_2(CH_2)_6\underline{C}H_3$); 14.83 (C(10)); 18.81 (C(9)); 19.88 (C(8)); 20.81 (C(5′)$\underline{C}H_3$); 22.64, 27.17, 29.20, 29.31, 30.89, 31.82 ($NCH_2(\underline{C}H_2)_6CH_3$); 28.56 (C(5)); 29.03 (C(6)); 34.96 (C(3)); 40.21 (C(2)); 45.72 (C(4)); 50.36, 50.55 (C(1), C(7)); 59.59 ($N\underline{C}H_2(CH_2)_6CH_3$); 117.81 (C(1′)); 126.07 (C(5′)); 128.93 (C(6′)); 130.48 (C(3′)); 133.07 (C(4′)); 158.14 (C(2′)); 164.77 (CH=N).

(*E*)-4-Methyl-2-*n*-octyliminomethyl-6-(2,2,3-trimethylbicyclo[2.2.1]hept-*exo*-5-yl)phenol (18). Yellow-brown oil. The yield was 0.553 g (96%). Found (%): C, 81.54; H, 10.65; N, 3.73. $C_{26}H_{41}NO$. Calculated (%): C, 81.41; H, 10.77; N, 3.65. IR (neat), ν/cm^{-1}: 3439 (OH); 2957, 2928, 2859, 1458 (CH_3, CH_2); 1634 (C=N); 1265 (C—O); 858, 771 (=C—H). ^{1}H NMR ($CDCl_3$), δ: 0.81—0.99 (m, 9 H, C(8)H_3, C(10)H_3, $NCH_2(CH_2)_6C\underline{H}_3$); 1.08 (s, 3 H, C(9)$H_3$); 1.17—1.51, 1.55—1.84 (both m, 13 H, 4 H, C(1)H, C(3)H, 1 C(6)H, C(7)H, $NCH_2(C\underline{H}_2)_6CH_3$); 1.94 (s, 1 H, 1 C(4)H); 2.24—2.36 (m, 1 H, 1 C(6)H); 2.29 (s, 3 H, C(5′)CH_3); 3.08 (t, 1 H, C(5)H, J = 7.4 Hz); 3.56 (t, 2 H, $NC\underline{H}_2(CH_2)_6CH_3$, J = 6.8 Hz); 6.86 (s, 1 H, C(6′)H); 7.04 (s, 1 H, C(4′)H); 8.26 (s, 1 H, CH=N); 13.78 (s, 1 H, OH). ^{13}C NMR ($CDCl_3$), δ: 14.07 ($NCH_2(CH_2)_6\underline{C}H_3$); 16.30, 24.87 (C(8), C(10)); 20.71 (C(5′)$\underline{C}H_3$); 22.64, 27.19, 29.20, 29.32, 30.90, 31.83 ($NCH_2(\underline{C}H_2)_6CH_3$); 27.65 (C(9)); 32.80 (C(6)); 33.62 (C(7)); 39.58 (C(2)); 40.22 (C(5)); 48.84 (C(1)); 49.86 (C(3)); 51.13 (C(4)); 59.54 ($N\underline{C}H_2(CH_2)_6CH_3$); 117.71 (C(1′)); 126.44 (C(5′)); 128.15 (C(6′)); 129.17 (C(4′)); 135.12 (C(3′)); 157.20 (C(2′)); 164.67 (CH=N).

Synthesis of amines 19—24 (general procedure). To a solution of imine **13—18** (1.2 mmol) in anhydrous EtOH (40 mL) $NaBH_4$ (0.23 g, 6.0 mmol) was added with stirring. The reaction mixture was refluxed for 30 min. After the completion of the reaction, the mixture was cooled to room temperature, and 2 *M* aqueous solution of NaOH (10 mL) was added. The mixture was stirred for 5 min, diethyl ether (30 mL) was added, and stirring was continued for 15 min. The organic layer was washed with 2 *M* aqueous solution of NaCl (4×25 mL) to pH ≈ 7.0 and dried with anhydrous K_2CO_3, the solvent was removed under reduced pressure, and the product was isolated by column chromatography using a petroleum ether—Et_2O (100 : 1→10 : 1) system as an eluent.

2,4-Dimethyl-6-*n*-octylaminomethylphenol (19). Pale beige oil. The yield was 0.256 g (81%). The spectral characteristics of compound **19** correspond to those published earlier.[21]

2-*tert*-Butyl-4-methyl-6-*n*-octylaminomethylphenol (20). Pale beige oil. The yield was 0.286 g (78%). Found (%): C, 78.91; H, 11.67; N, 4.64. $C_{20}H_{35}NO$. Calculated (%): C, 78.63; H, 11.55; N, 4.58. IR (neat), ν/cm^{-1}: 3314, 3295 (NH, OH); 2994, 2953, 2924, 2855, 1464 (CH_3, CH_2); 1242 (C—O); 860, 770 (=C—H). ^{1}H NMR ($CDCl_3$), δ: 0.89 (t, 3 H, $NCH_2(CH_2)_6C\underline{H}_3$, J = 6.3 Hz); 1.17—1.40 (m, 10 H, $N(CH_2)_2(C\underline{H}_2)_5CH_3$); 1.42 (s, 9 H, $C(CH_3)_3$); 1.44—1.59 (m, 2 H, $NCH_2C\underline{H}_2(CH_2)_5CH_3$); 2.25 (s, 3 H, C(5′)$CH_3$); 2.65 (t, 2 H, $NC\underline{H}_2(CH_2)_6CH_3$), J = 6.9 Hz); 3.93 (s, 2 H, $ArC\underline{H}_2N$), 6.69 (s, 1 H, C(6′)H); 6.99 (s, 1 H, C(4′)H). ^{13}C NMR ($CDCl_3$), δ: 14.06 ($NCH_2(CH_2)_6\underline{C}H_3$); 20.74 (C(5′)$\underline{C}H_3$); 22.63, 27.12, 29.19, 29.37, 29.56, 31.79 ($NCH_2(\underline{C}H_2)_6CH_3$); 29.56 ($C(\underline{C}H_3)_3$); 34.57 ($\underline{C}(CH_3)_3$); 48.62 ($N\underline{C}H_2(CH_2)_6CH_3$); 53.12 ($Ar\underline{C}H_2N$); 122.83 (C(1′)); 126.44 (C(4′)); 126.82 (C(5′)); 126.84 (C(6′)); 136.50 (C(3′)); 154.91 (C(2′)).

4-Methyl-2-(3-methyl-2-en-1-yl)-6-*n*-octylaminomethylphenol (21). Pale beige oil. The yield was 0.324 g (85%). Found (%): C, 79.51; H, 11.02; N, 4.28. $C_{21}H_{35}NO$. Calculated (%): C, 79.44; H, 11.11; N, 4.41. IR (neat), ν/cm^{-1}: 3316, 3292 (NH, OH); 2957, 2924, 2855, 1474 (CH_3, CH_2); 1250 (C—O); 858, 785 (=C—H). ^{1}H NMR ($CDCl_3$), δ: 0.89 (t, 3 H, $NCH_2(CH_2)_6C\underline{H}_3$, J = 6.3 Hz); 1.18—1.40 (m, 10 H, $N(CH_2)_2(C\underline{H}_2)_5CH_3$); 1.43—1.61 (m, 2 H, $NCH_2C\underline{H}_2(CH_2)_5CH_3$); 1.74 (s, 3 H, C(5)$H_3$); 1.75 (s, 3 H, C(4)$H_3$); 2.22 (s, 3 H, C(5′)$CH_3$); 2.66 (t, 2 H, $NC\underline{H}_2(CH_2)_6CH_3$), J = 7.0 Hz); 3.32 (d, 2 H, C(1)H, J = 7.1 Hz); 3.93 (s, 2 H, $ArC\underline{H}_2N$); 5.35 (br.t, 1 H, C(2)H, J ≈ 6.8 Hz); 6.66 (s, 1 H, C(6′)H); 6.85 (s, 1 H, C(4′)H). ^{13}C NMR ($CDCl_3$), δ: 14.06 ($NCH_2(CH_2)_6\underline{C}H_3$); 17.77 (C(5)); 20.51 (C(5′)$\underline{C}H_3$); 22.63, 28.02, 29.19, 29.39, 29.59, 31.79 ($NCH_2(\underline{C}H_2)_6CH_3$);

25.80 (C(4)); 27.13 (C(1)); 48.82 ($N\underline{C}H_2(CH_2)_6CH_3$); 52.85 ($Ar\underline{C}H_2N$); 121.95 (C(1′)); 122.98 (C(2)); 126.41 (C(6′)); 127.47, 128.42 (C(3′); C(5′)); 128.98 (C(4′)); 132.00 (C(3); 153.59 (C(2′)).

4-Methyl-2-*n*-octylaminomethyl-6-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-5-yl)phenol (22). Pale beige oil. The yield was 0.344 g (73%). The spectral characteristics of compound **22** correspond to those published earlier.[22]

4-Methyl-2-*n*-octylaminomethyl-6-{(1*R*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl}phenol (23). Light yellow oil. The yield was 0.361 g (78%). $[\alpha]_D^{23}$ +64.6 (*c* 0.3, $CHCl_3$). The spectral characteristics of compound **23** correspond to those published earlier.[21]

4-Methyl-2-*n*-octylaminomethyl-6-(2,2,3-trimethylbicyclo-[2.2.1]hept-*exo*-5-yl)phenol (24). Light yellow oil. The yield was 0.347 g (75%). The spectral characteristics of compound **24** correspond to those published earlier.[21]

The radical scavenging activity of the compounds was estimated using a known procedure[38] by their ability to react with DPPH. The studied compounds in concentrations of 100 and 10 μmol L^{-1} were introduced into a solution of DPPH in MeOH, the mixtures were stirred, and 30 min after the absorbance of the solution was measured at λ = 517 nm on a Thermo Spectronic Genesys 20 spectrophotometer.

The chelation ability of the compounds was evaluated using described procedures.[39,40] A solution of the studied compounds in a concentration of 100 μmol L^{-1} was introduced into MeOH, and then a solution of $FeSO_4$ was added. The reaction was initiated by the addition of a solution of FerroZine™ Iron Reagent, the mixture was shaken up, and 10 min after the absorbance was measured at λ = 562 nm on a Thermo Spectronic Genesys 20 spectrophotometer.

The antioxidant activity was estimated by their ability to inhibit LPO in the substrate obtained from the brain of laboratory mice.[41,42] The brain was taken out, homogenized (10%) in a physiological solution (pH 7.4), and centrifuged for 10 min. Then the supernatant (S1)[41,43] containing water, proteins, DNA, RNA, and lipids (cholesterol, galactolipids, individual phospholipids, and gangliosides) was sampled. The studied compounds were introduced into the supernatant as solutions in acetone (final concentrations 10 and 100 μmol L^{-1}). After 30 min, LPO was initiated by the addition of freshly prepared $FeCl_2$ and ascorbic acid[44] or a solution of H_2O_2 (0.006%), and the studied samples were incubated at 37 °C for 1 h with slow stirring in a Biosan ES-20 temperature-controlled shaker. The content of TBA-RS was determined on a Thermo Spectronic Genesys 20 spectrophotometer at λ = 532 nm, and the molar absorption coefficient equal to $1.56 \cdot 10^5$ L mol^{-1} cm^{-1} was used for the calculations.[42,45]

Studies of the hemolytic activity (cytotoxicity), membrane-protective and antioxidant properties. A suspension of red blood cells of laboratory mice in a phosphate salt buffer (pH 7.4) was used for evaluation. The toxicity of the compounds was evaluated on the *in vitro* model from their ability to induce erythrocyte hemolysis. Solutions of the compounds in acetone were added to a suspension of erythrocytes in the final concentration equal to 10 μmol L^{-1}, and the samples were incubated at 37 °C for 5 h in a Biosan ES-20 temperature-controlled shaker.

The membrane-protective and antioxidant activities were determined from the degree of inhibition of induced hemolysis, inhibition of accumulation of the secondary LPO products, and oxidation of oxyhemoglobin (oxyHb) in erythrocytes. For this purpose, 30 min after introduction of solutions of the studied compounds (final concentration 1 and 0.1 μmol L^{-1}) to a suspension of red blood cells, hemolysis was initiated by the addition of a solution of H_2O_2 (0.006%). The reaction mixture was incubated at 37 °C for 5 h in a temperature-controlled shaker with slow stirring. An aliquot was taken from the incubation medium at an interval of 60 min and centrifuged for 5 min (1600 *g*). The degree of hemolysis was determined from the hemoglobin content in the supernatant on a Thermo Spectronic Genesys 20 spectrophotometer at λ = 524 nm.[46] The hemolysis percentage was calculated by the ratio to complete hemolysis of the sample. The content of TBA-RS was determined spectrophotometrically as indicated above. The absorption spectrum was examined in the range λ = 540—640 nm to estimate the accumulation of the products of hemoglobin oxidation. The contents of oxyhemoglobin (oxyHb) and methemoglobin (metHb) were calculated taking into account the corresponding molar absorption coefficients.[47] To estimate the concentration of the products of heme degradation formed by the oxidation of membrane-bound hemoglobin by active oxygen species, the fluorescence intensity (I_{fl}) at the maximum at λ = 488 nm was used (Flyuorat-02-Panorama spectrofluorimeter, excitation at λ = 321 nm, emission at λ = 400—600 nm, increment of spectrum recording 2 nm).[48—50]

Each experiment was carried out 4—8 times. Statistical data processing was performed using the Microsoft Office Excel 2007, 2010 program packages.

This work was financially supported by the Ministry of Science and Higher Education of the Russian Federation (state tasks Nos. AAAA-A18-118012490385-8 and AAAA-A18-118011120004-5).

References

1. V. K. Kolvolter, *Russ. Chem. Bull.*, 2010, **59**, 37.
2. E. V. Kuzakov, E. N. Shmidt, *Chem. Nat. Compd.*, 2000, **36**, 245.
3. M. Cirri, P. Mura, P. Corvi Mora, *Int. J. Pharm.*, 2007, **340**, 84.
4. M. B. Plotnikov, V. I. Smolyakova, I. S. Ivanov, A. V. Kuchin, I. J. Chukicheva, E. A. Krasnov, *Bull. Exp. Biol. Med.*, 2008, **145**, 328.
5. T. M. Plotnikova, G. A. Chernysheva, V. I. Smol′yakova, P. P. Shchetinin, A. V. Kuchin, I. Yu. Chukicheva, M. B. Plotnikov, *Bull. Exp. Biol. Med.*, 2014, **157**, 211.
6. G. A. Chenysheva, V. A. Smol′yakova, A. V. Kutchin, I. Yu. Chukicheva, M. B. Plotnikov, *Bull. Exp. Biol. Med.*, 2018, **166**, 15.
7. T. M. Plotnikova, G. A. Chernysheva, V. A. Smol′yakova, P. P. Shchetinin, A. V. Kuchin, I. Yu. Chukicheva, M. B. Plotnikov, *Bull. Exp. Biol. Med.*, 2018, **165**, 657.
8. I. Yu. Chukicheva, E. V. Buravlev, I. V. Fedorova, M. F. Borisenkov, A. V. Kutchin, *Russ. Chem. Bull.*, 2010, **59**, 2276.
9. O. G. Shevchenko, S. N. Plyusnina, L. N. Shishkina, I. Yu. Chukicheva, I. V. Fedorova, A. V. Kuchin, *Biochemistry* (*Moscow*) *Suppl. Ser. A: Membr. Cell Biol.*, 2013, **7**, 302.
10. O. V. Shchukina, I. Yu. Chukicheva, O. G. Shevchenko, T. A. Kolegova, K. Yu. Suponitsky, A. V. Kutchin, *Russ. J. Gen. Chem.*, 2018, **88**, 664.
11. G. Roman, *Eur. J. Med. Chem.*, 2015, **89**, 743.

12. M. Tramontini, L. Angiolini, *Mannich Bases: Chemistry and Uses*, CRC Press, Boca Raton, 1994, 304 pp.
13. I. A. Dvornikova, E. V. Buravlev, K. Yu. Suponitskii, I. Yu. Chukicheva, A. V. Kutchin, *Russ. J. Org. Chem.*, 2015, **51**, 480.
14. E. V. Buravlev, I. Yu. Chukicheva, O. G. Schevchenko, K. Yu. Suponitskii, A. V. Kutchin, *Russ. Chem. Bull.*, 2017, **66**, 91.
15. E. V. Buravlev, O. G. Shevchenko, *Russ. Chem. Bull.*, 2019, **68**, 79.
16. G. Casiraghi, G. Casnati, G. Puglia, G. Sartori, G. Terenghi, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1862.
17. J.-J. Helesbeux, O. Duval, D. Guilet, D. Séraphin, D. Rondeau, P. Richomme, *Tetrahedron*, 2003, **59**, 5091.
18. P. D. Knight, P. N. O´Shaughnessy, I. J. Munslow, B. S. Kimberley, P. Scott, *J. Organomet. Chem.*, 2003, **683**, 103.
19. P. D. Knight, G. Clarkson, M. L. Hammond, B. S. Kimberley, P. Scott, *J. Organomet. Chem.*, 2005, **690**, 5125.
20. A. Berkessel, M. R. Vennemann, J. Lex, *Eur. J. Org. Chem.*, 2002, 2800.
21. I. Yu. Chukicheva, E. V. Buravlev, D. V. Belykh, I. S. Khudyaeva, I. V. Fedorova, O. G. Shevchenko, M. A. Maximova, L. F. Zainullina, Yu. V. Vakhitova, A. V. Kutchin, *Russ. Chem. Bull.*, 2018, **67**, 548.
22. D. V. Belykh, E. V. Buravlev, I. Yu. Chukicheva, I. S. Tarabukina, O. G. Shevchenko, S. N. Plyusnina, A. V. Kutchin, *Russ. J. Bioorg. Chem.*, 2012, **38**, 558.
23. O. G. Shevchenko, S. N. Plyusnina, E. V. Buravlev, I. Yu. Chukicheva, I. V. Fedorova, O. V. Shchukina, A. V. Kutchin, *Russ. Chem. Bull.*, 2017, **66**, 1881.
24. E. V. Buravlev, I. Yu. Chukicheva, O. V. Sukrusheva, O. G. Shevchenko, A. V. Kutchin, *Russ. Chem. Bull.*, 2015, **64**, 1406.
25. E. V. Buravlev, I. Yu. Chukicheva, O. G. Shevchenko, K. Yu. Suponitskii, A. V. Kutchin, *Russ. Chem. Bull.*, 2016, **65**, 1232.
26. E. V. Buravlev, I. Yu. Chukicheva, O. G. Shevchenko, A. V. Kutchin, *Russ. Chem. Bull.*, 2017, **66**, 297.
27. I. Yu. Chukicheva, O. A. Shumova, O. G. Shevchenko, O. V. Sukrusheva, A. V. Kutchin, *Russ. Chem. Bull.*, 2016, **65**, 721.
28. E. V. Buravlev, O. G. Shevchenko, A. V. Kutchin, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 826.
29. E. V. Buravlev, O. G. Shevchenko, A. A. Anisimov, K. Yu. Suponitsky, *Eur. J. Med. Chem.*, 2018, **152**, 10.
30. E. V. Buravlev, O. G. Shevchenko, I. Y. Chukicheva, A. V. Kutchin, *Chem. Pap.*, 2018, **72**, 201.
31. S. V. Pestova, E. S. Izmest´ev, O. G. Shevchenko, S. A. Rubtsova, A. V. Kutchin, *Russ. Chem. Bull.*, 2015, **64**, 723.
32. W. L. Porter, E. D. Black, A. M. Drolet, *J. Agric. Food. Chem.*, 1989, **37**, 615.
33. W. A. Yehye, N. A. Rahman, A. Ariffin, S. B. A. Hamid, A. A. Alhadi, F. A. Kadir, M. Yaeghoobi, *Eur. J. Med. Chem.*, 2015, **101**, 295.
34. A. Ariffin, N. A. Rahman, W. A. Yehye, A. A. Alhadi, F. A. Kadir, *Eur. J. Med. Chem.*, 2014, **87**, 564.
35. E. Niki, *Free Radical Biol. Med.*, 2010, **49**, 503.
36. B. Li, D. A. Pratt, *Free Radical Biol. Med.*, 2015, **82**, 187.
37. I. Yu. Chukicheva, I. V. Fedorova, A. V. Kutchin, *Khim. Rast. Syr´ya* [*Chemistry of Plant Raw Materials*], 2009, No. 3, 63 (in Russian).
38. K. Sevgi, B. Tepe, C. Sarikurkcu, *Food Chem. Toxicol.*, 2015, **77**, 12.
39. U. Sukatta, M. Takenaka, H. Ono, H. Okadome, I. Sotome, K. Nanayama, W. Thanapase, S. Isobe, *Biosci. Biotechnol. Biochem.*, 2013, **77**, 984.
40. J. Lin, Y. Gao, H. Li, L. Zhang, X. Li, *Adv. Pharmaceut. Bull.*, 2014, **4**, 147.
41. C. I. Acker, R. Brandao, A. R. Rosario, C. W. Nogueira, *Environ. Toxicol. Pharmacol.*, 2009, **28**, 280.
42. S. T. Stefanello, A. S. Prestes, T. Ogunmoyole, S. M. Salman, R. S. Schwab, C. R. Brender, L. Dornelles, J. B. T. Rocha, F. A. A. Soares, *Toxicol. in Vitro*, 2013, **27**, 1433.
43. N. A. V. Belle, G. D. Dalmolin, G. Fonini, M. A. Rubim, J. B. T. Rocha, *Brain Res.*, 2004, **1008**, 245.
44. R. Chawla, R. Arora, R. Kumar, A. Sharma, J. Prasad, S. Singh, R. Sagar, P. Chaudhary, S. Shukla, G. Kaur, R. K. Sharma, S. C. Puri, K. L. Dhar, G. Handa, V. K. Gupta, G. N. Qazi, *Mol. Cell. Biochem.*, 2005, **273**, 193.
45. T. Asakawa, S. Matsushita, *Lipids*, 1980, **15**, 137.
46. J. Takebayashi, J. Chen, A. A. Tai, *Methods Mol. Biol.*, 2010, **594**, 287.
47. J. J. M. Van den Berg, J. A. F. Op den Kamp, B. H. Lubin, B. Roelofsen, F. A. Kuypers, *Free Radical Biol. Med.*, 1992, **12**, 487.
48. E. Nagababu, J. M., Rifkind, *Biochem. Biophys. Res. Commun.*, 1998, **247**, 592.
49. E. Nagababu, M. E. Fabry, R. L. Nagel, J. M. Rifkind, *Blood Cells, Mol., Dis.*, 2008, **41**, 60.
50. E. Nagababu, J. G. Mohanty, S. Bhamidipaty, G. R. Ostera, J. M. Rifkind, *Life Sci.*, 2010, **86**, 133.

Received November 22, 2018;
in revised form February 21, 2019;
accepted March 11, 2019