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Chem. Biodiversity

Novel aminomethyl derivatives of 4-methyl-2-prenylphenol: synthesis and antioxidant properties

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4-Methyl-2-prenylphenol (**1**) was synthesized from *para*-cresol and prenol, natural alcohol under the conditions of heterogeneous catalysis. A series of nine new aminomethyl derivatives with secondary and tertiary amino groups were obtained on the basis of compound **1**. A comparative evaluation of their antioxidant properties was carried out using *in vitro* models. It was established that Mannich base with *n*-octylaminomethyl group has radical scavenging activity, high Fe^{2+}-chelation ability as well as the ability to inhibit oxidative hemolysis of red blood cells.

Keywords: alkylation o Mannich bases o antioxidants o red blood cells o oxidative hemolysis

Introduction

Prenylphenol moiety is the base for skeleton or is a part of structural backbone in many natural metabolites[1] that have a wide range of biological properties.[1 – 6] The presence of *C*-prenyl groups in the phenol molecule increases a compound's lipophilicity and its affinity to biological membranes.[7] The presence of activated reaction centers of the aromatic system in the molecules of prenylphenol derivatives opens up potential for their further functionalization using the reaction of electrophilic substitution, e.g. for aminomethylation.[8] The introduction of an aminomethyl group is often used in drug design and medicinal chemistry.[9] This structural fragment can be formed using the Mannich reaction,[8] as well as using other synthetic approaches: via reduction of Schiff bases,[10] by the interaction of bromomethyl derivatives with amines,[11] through Rh-catalyzed C– H functionalization,[12] etc. There are various examples of the influence of aminomethyl substituents on the biological properties of prenylphenol compounds (Fig. 1). Thus, Mannich bases obtained from the antibiotic novobiocin were characterized by reduced antibacterial activity,[13] while aminomethyl derivatives of the flavonoid icaritin isolated from *Epimedium Genius* had a greater cytotoxicity against human cancer cells in a several cases.[14] For Mannich bases derived from prenylated xanthones α- and γ-mangostins isolated from *Garcinia mangostana* L., an increase in antioxidant (AO) and membrane-protective (MP) properties and a significant decrease in hemolytic activity was shown in most cases.[15][16]

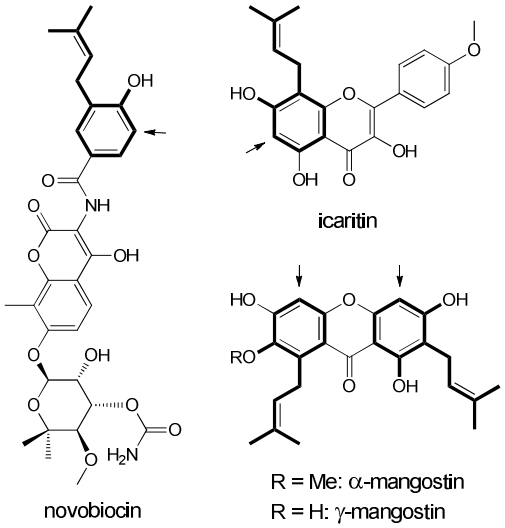
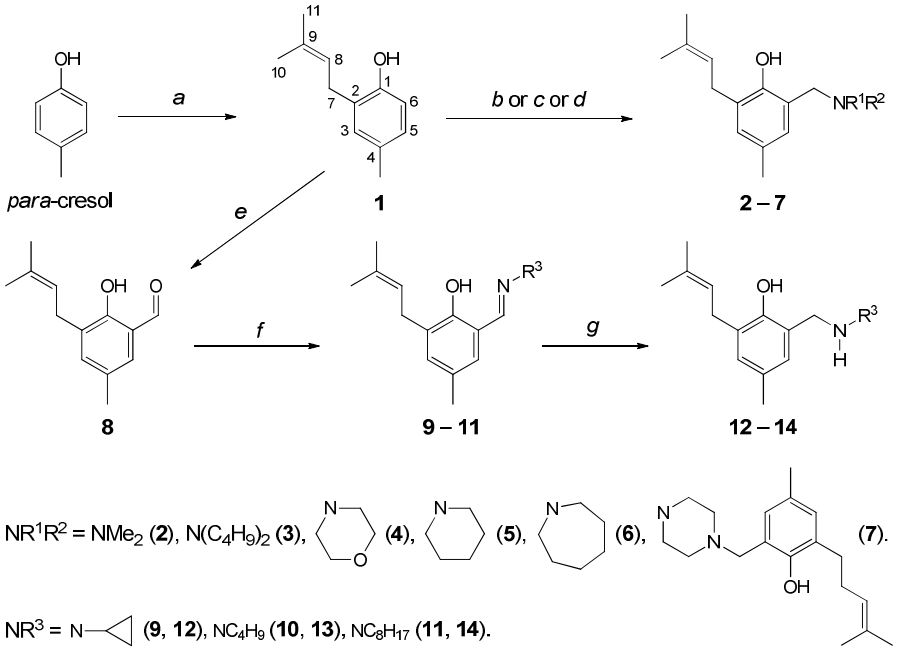


Figure 1. Examples of naturally occurring compounds with prenylphenol moieties used in the Mannich reaction. Arrows indicate positions for aminomethylation.

The aim of this work was to synthesize new aminomethyl derivatives containing an *ortho*-prenylphenol moiety, and to assess the compounds obtained as inhibitors of oxidative processes *in vitro*.

Results and Discussion

As the initial backbone structure we used 4-methyl-2-prenylphenol (**1**), which was obtained by alkylation of *para*-cresol with prenol (3-methylbut-2-en-1-ol) under the conditions of heterogeneous catalysis using montmorillonite KSF clay (Scheme 1, path *a*).[1] Aminomethyl derivatives of the compound **1** containing a tertiary amino group **2** – **7** were synthesized by the Mannich reaction using various conditions (Scheme 1, paths *b* – *d*): for the synthesis of amine **2**, aqueous solutions of formaldehyde and dimethylamine were used, amines **3** – **6** were obtained using HCHO and the corresponding secondary amines (di-*n*-butylamine, morpholine, piperidine, and azepane), and 1,4-disubstituted piperazine **7** was synthesized using aminomethyl reagent in the presence of $CaCl_2$ under solvent-free conditions.[17] Aldehyde **8** was obtained by the Casiraghi reaction[18] from cresol **1** (Scheme 1, path *e*), and imines **9** – **11** were synthesized (Scheme 1, path *f*). Mannich bases with cyclopropylamine **12**, *n*-butylamine **13**, and *n*-octylamine **14** groups were obtained as a result of reduction reaction of the corresponding Schiff bases **9** – **11** (Scheme 1, path *g*).



Scheme 1. Synthesis of compounds **1** – **14**. Reagents and conditions: *a*. prenol, montmorillonite KSF, CH_2Cl_2, 40 °C, 2 h; *b*. HCHO (aq.), Me_2NH (aq.), MeOH, r.t., 24 h; *c*. HCHO, di-*n*-butylamine, morpholine, piperidine or azepane, benzene, reflux, 6 – 12 h; *d*. HCHO, piperazine, $CaCl_2$, 110 °C, 35 min; *e*. HCHO, $SnCl_4$, tri-*n*-butylamine, toluene, reflux, 10 h;[18] *f*. cyclopropylamine, *n*-butylamine or *n*-octylamine, molecular sieves (4 Å), benzene, reflux, 3.5 h; *g*. $NaBH_4$, EtOH, reflux, 30 min.

The results of ^{1}H-, ^{13}C-NMR, IR-spectroscopy and elemental analysis of novel products **2** – **14** were consistent with the expected structures. The spectral characteristics of compound **1** are consistent with those previously described.[19] In the ^{1}H- and ^{13}C-NMR spectra of the obtained compounds, signals of additional substituents in the *ortho*-position relative to the phenolic hydroxyl group were observed in addition to the signals of the prenylcresol skeleton. Schiff bases **9** – **11** had the *E*-configuration of substituents relative to the C=N bond: the NOESY experiment for these compounds showed interactions of the protons of N=CH group (δ_H 8.3 – 8.4 ppm) with the protons of C(3)H (δ_H 6.9 ppm) and the protons of NCH fragments (δ_H 2.9 – 3.0 ppm for imine **9**, see Fig. 2) or NCH_2 fragments (δ_H 3.6 ppm for imines **10** and **11**[2]), evidencing their spatial convergence.

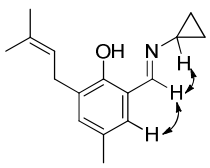


Figure 2. NOE-interactions of imine **9** that show *E*-configuration.

[1] A separate paper will be devoted to this alkylation reaction.

[2] See Fig. S9 (Supporting information).

Design and synthesis of new compounds with potential use in pharmacology should be accompanied by a rigorous study of the mechanics of their biological activity. In particular, for the phenols it is important to study their radical scavenging activity (RSA).[20] A study of toxicity of the obtained compounds using various *in vitro* tests is also an important part.[21]

For aminomethyl derivatives **2** – **7**, **12** – **14**, RSA (Fig. 3), AO activity (AOA) were assessed on a substrate obtained from the brain of laboratory mice; Fe^{2+}-chelation ability (Table 1), as well as hemolytic activity (cytotoxicity), AO and MP properties with the use of red blood cells (RBCs) were also assessed (Table 2) in the work. The above approaches have been previously successfully used by us to assess the AO properties of prenylated xanthones,[15][16] aminomethhylated terpenylphenols,[11] sulfur-containing terpenoids,[22] and non-steroidal anti-inflammatory drugs.[23] 4-Methyl-2-prenylphenol (**1**) and the known antioxidant 2,6-di-*tert*-buthyl-4-methylphenol (BHT) were used as reference compounds.

Study in non-cellular model systems (Fig. 3, Table 1) showed that compounds **1**, **2**, **13**, and **14** at a concentration of 100 μM had a moderate ability to neutralize the stable radical 2,2-diphenyl-1-picrylhydrazyl (DPPH), which was comparable to BHT, while derivatives **3**, **6**, and **12** were significantly superior in the RSA to the original cresol **1** and BHT (Fig. 3). The increase in the Fe^{2+}-chelation ability of derivatives **2** – **7**, **12** – **14** compared with BHT and compound **1**, can be explained by the presence of aminomethyl groups, which cause an increase in the coordination properties in the structures of these derivatives. High Fe^{2+}-chelation ability in phenols containing an aminomethyl fragment in the *ortho*-position is also known from the literature.[8] All the synthesized compounds, with the exception of tertiary amines **3** and **7**, inhibited Fe^{2+}/ascorbate-initiated accumulation of secondary lipid peroxidation (LPO) products to a level substantially below the spontaneous one and were not inferior in the activity to BHT (Table 1).

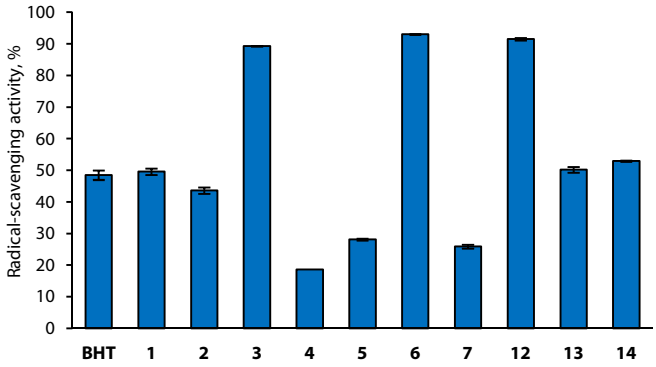


Figure 3. Comparative evaluation of RSA (test with DPPH) of the derivatives at a concentration of 100 μM.

Table 1. Comparative evaluation of Fe^{2+}-chelation ability (test with FerroZine™ Iron Reagent) and AOA (test on the substrate from brain)[a] of the derivatives at a concentration of 100 μM

Compound	Fe^{2+}-chelation ability (%)	TBA-RS (nmol/mL)
BHT	6.1 ± 1.0	5.4 ± 0.2
1	8.6 ± 1.9	5.0 ± 0.2
2	47.3 ± 2.1	5.1 ± 0.2
3	43.8 ± 1.0	10.2 ± 0.1
4	37.1 ± 1.5	6.7 ± 0.2
5	42.7 ± 1.7	5.3 ± 0.1
6	48.3 ± 1.0	5.5 ± 0.1
7	31.8 ± 0.5	20.0 ± 0.3
12	44.1 ± 1.8	5.0 ± 0.1
13	71.5 ± 0.9	4.9 ± 0.1
14	73.2 ± 0.9	4.8 ± 0.1

[a] The ability to inhibit the accumulation of secondary LPO products reacting with 2-thiobarbituric acid (thiobarbituric acid reactive substances, TBA-RS) in an organic substrate 1 h after initiating LPO with Fe^{2+}/ascorbate was assessed. TBA-RS concentration in the control (without the compounds) and intact (without oxidation initiated) samples was 40.5 ± 0.3 and 17.2 ± 0.1 nmol/mL, respectively

Assessment of hemolytic activity showed that the studied compounds at a concentration of 10 μM did not have significant cytotoxicity against RBCs (cell survival during 5 h of incubation was >90%). Despite the high RSA of most of the obtained Mannich bases, only secondary amine **14** at a concentration of 1 μM effectively protected living cells under the conditions of acute H_2O_2-induced oxidative stress. Compound **14** was not only significantly superior to BHT in its ability to inhibit hemolysis of RBCs, but also reduced the content of secondary LPO products in them (Table 2).

In addition, there was a decrease in the methemoglobin/oxyhemoglobin and ferrylhemoglobin/oxyhemoglobin ratios by 1.9 and 1.6 times, respectively (data not shown in the Table 2). It should be noted, that differences in activity between compounds **13** and **14** containing *n*-butylaminomethyl and *n*-octylaminomethyl groups were only found in these studies on living cells. Thus, the high AOA of the Mannich base with *n*-octylaminomethyl fragment **14** in the cellular model system may be due to the combination of several functional groups in the molecule – the phenol hydroxyl group providing RSA, the secondary amino group, which causes high chelation ability, and, finally, two lipophilic (prenyl and *n*-octylaminomethyl) fragments, which appear to contribute to the optimal interaction of compound **14** with the biomembrane.

Table 2. Comparative evaluation of MPA and AOA of the derivatives at a concentration of 1 μM on the model of RBCs oxidative hemolysis

Compound	Membrane-protective activity (hemolysis, %)			TBA-RS (nmol/mL)
	1 h	3 h	5 h	
Control	18.0 ± 1.6	44.9 ± 1.6	55.0 ± 1.4	1.67 ± 0.06
BHT	2.9 ± 0.3	13.9 ± 0.8	20.9 ± 0.8	0.94 ± 0.09
1	14.6 ± 1.6	38.0 ± 1.9	49.9 ± 1.8	1.21 ± 0.09
2	9.4 ± 0.9	32.2 ± 0.8	45.7 ± 0.6	0.98 ± 0.06
3	24.0 ± 1.6	39.2 ± 0.4	52.0 ± 0.6	1.02 ± 0.02
4	13.4 ± 0.3	38.6 ± 1.0	48.9 ± 0.9	1.06 ± 0.01
5	10.9 ± 0.8	35.9 ± 0.5	49.0 ± 1.1	1.11 ± 0.03
6	12.2 ± 0.2	49.3 ± 1.0	65.5 ± 0.3	1.16 ± 0.06
7	13.0 ± 1.5	31.1 ± 2.5	42.7 ± 3.5	1.29 ± 0.13
12	28.0 ± 2.2	60.0 ± 1.8	66.0 ± 1.5	1.79 ± 0.04
13	11.0 ± 0.6	24.9 ± 0.4	39.5 ± 0.4	1.17 ± 0.03
14	1.4 ± 0.4	3.3 ± 0.1	10.1 ± 0.4	1.10 ± 0.03

Conclusions

Thus, in this work, 4-methyl-2-prenylphenol (**1**) was obtained and a series of nine novel Mannich bases containing tertiary and secondary amino groups was synthesized using simple transformations. For the synthesized derivatives **2** – **7**, **12** – **14** radical scavenging activity and antioxidant activity were assessed on an organic substrate containing animal lipids, as well as Fe^{2+}-chelation ability, antioxidant, and membrane-protective properties using RBCs. It was shown that with respect to a set of indicators characterizing the studied compounds as inhibitors of oxidative processes, the most optimal bio-antioxidant was Mannich base **14** with *n*-octylaminomethyl fragment.

Experimental Section

General

The spectral data were obtained using the equipment of the Centre of Collective Usage 'Chemistry', Institute of Chemistry, Komi Scientific Centre, Ural Branch of the RAS. The IR spectra were recorded on a 'Shimadzu IR Prestige 21' FT-IR spectrometer. The ^{1}H-, ^{13}C-NMR spectra were recorded on a 'Bruker Avance II 300' instrument. The chemical shifts were referenced to the residual signals of $CHCl_3$ (δ_H = 7.26 ppm, δ_C = 77.00 ± 0.42 ppm). The signals of carbon atoms were assigned using NMR ^{13}C spectra in *J*-modulation mode; some assignments were made using NOESY, HSQC, and HMBC experiments. The melting points were measured on a 'Sanyo Gallenkamp MPD 350' instrument and were not corrected. The 'Elementar vario MICRO cube' instrument was employed for elemental analysis.

The course of reactions was monitored by thin-layer chromatography (TLC) on a 'Sorbfil' plates. To detect the components, the plates were exposed to $KMnO_4$ solution (15.0 g of $KMnO_4$, 300 mL of H_2O, 0.5 mL of concentrated H_2SO_4). Silica gel 60 ('Alfa Aesar', 0.06 – 0.2 mm) was used for column chromatography.

Commercially available *para*-cresol, prenol, montmorillonite KSF, piperidine, azepane, anhydrous piperazine, $SnCl_4$, tri-*n*-butylamine, cyclopropylamine, *n*-octylamine, BHT, DPPH ('Alfa Aesar'), dimethylamine (40% aq. solution), FerroZine™ Iron Reagent ('Sigma-Aldrich'), di-*n*-butylamine, morpholine, *n*-butylamine ('Acros Organics'), formaldehyde (37% aq. solution), and paraform (reagent-grade quality) were used without additional purification. Petroleum ether (PE) with b.p. 65 – 70 °C was used freshly distilled. Molecular sieves (4 Å) were used after heating for 3 h at 140 °C.

The *in vitro* assays were done using the equipment of the Centre of Collective Usage 'Molecular Biology', Institute of Biology, Komi Scientific Centre, Ural Branch of the RAS. The mice from the scientific collection of experimental animals of Institute of Biology, Komi Scientific Centre, Ural Branch of the RAS (http://www.ckp-rf.ru/usu/471933/) were used in the work. The optical density was measured on a spectrophotometer 'Thermo Spectronic Genesys 20'; the absorption spectra of hemolysates were analyzed using 'Fluorat-02-Panorama' spectrofluorimeter. Incubation of brain homogenates and mice erythrocytes were carried out in thermostated 'Biosan ES-20' shaker. Compounds **1** – **7**, **12** – **14**, and BHT were dissolved in an acetone for the *in vitro* experiments.

Synthesis of compound **1**

Prenol (3.76 mL, 37.0 mmol) and montmorillonite KSF (2.0 g) were added to the solution of *para*-cresol (2.0 g, 18.5 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was heated for 2 h with stirring at 40 °C. At the end of the reaction, the clay was separated by filtration, washed with CH_2Cl_2, the solvent was removed under reduced pressure, the product was isolated by column chromatography (PE/Et_2O 5:1 → 3:1).

4-Methyl-2-(3-methylbut-2-en-yl)phenol (1). Light yellow oil. Yield 2.0 g (61%). R_f = 0.52 (PE/Et_2O 5:1). The spectral characteristics of the compound are consistent with those presented in the work.[19]

Synthesis of compound **2**

Formaldehyde (37% aq. solution, 0.11 mL, 1.5 mmol) and dimethylamine (40% aq. solution, 0.19 mL, 1.5 mmol) were added to the solution of cresol **1** (0.22 g, 1.25 mmol) in MeOH (1 mL). The reaction mixture was stirred for 24 h at r.t. At the end of the reaction, the solvent was removed under reduced pressure, the product was isolated by column chromatography (PE/Et_2O 20:1 → 3:1).

2-((Dimethylamino)methyl)-4-methyl-6-(3-methylbut-2-en-1-yl)phenol (2). Colorless oil. Yield 0.218 g (75%). R_f = 0.31 (PE/Et_2O 5:1). Anal. calc. for $C_{15}H_{23}NO$ (233.36): C 77.21, H 9.94, N 6.00; found: C 76.98, H 10.12, N 6.06. IR (thin layer): 2959, 2928, 2866, 2818, 2735, 1476, (CH_3, CH_2); 1611 (C–H); 1248, 1150 (C–O); 858, 785 (=C–H). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.74 (*s*, 3 H, C(11)H_3); 1.75 (*s*, 3 H, C(10)H_3); 2.23 (*s*, 3 H, ArCH_3); 2.31 (*s*, 6 H, N(CH_3)$_2$); 3.31 (*d*, 2 H, *J* = 7.2, C(7)H_2); 3.58 (*s*, 2 H, ArCH_2N); 5.35 (*br. t*, 1 H, *J* = 7.5, C(8)H); 6.63 (*s*, 1 H, C(5)H); 6.85 (*s*, 1 H, C(3)H); 10.71 (*br. s*, 1 H, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.77 (C(11)); 20.51 (ArCH_3); 25.79 (C(10)); 28.04 (C(7)); 44.42 (N(CH_3)$_2$); 62.94 (ArCH_2N); 121.16 (C(6)); 123.00 (C(8)); 126.50 (C(5)); 127.47, 128.05 (C(2), C(4)); 129.06 (C(3)); 131.97 (C(9)); 153.31 (C(1)).

Synthesis of compounds **3** – **6**

Paraform (0.075 g, 2.5 mmol) and amine (2.5 mmol) were added to the solution of cresol **1** (0.22 g, 1.25 mmoL) in anhydrous benzene (5 mL). The reaction mixture was refluxed for 6 h (piperidine, azepane) or 12 h (di-*n*-butylamine, morpholine). At the end of the reaction, the solvent was removed under reduced pressure, the product was isolated by column chromatography (PE/Et_2O, with an increase in the fraction of the latter).

2-((Di-*n*-buthylamino)methyl)-4-methyl-6-(3-methylbut-2-en-1-yl)phenol (3). Colorless oil. Yield 0.358 g (90%). R_f = 0.86 (PE/Et_2O 5:1). Anal. calc. for $C_{21}H_{35}NO$ (317.52): C 79.44, H 11.11, N 5.04; found: C 79.57, H 11.01, N 5.01. IR (thin layer): 2978, 2953, 2914, 2858, 2826, 2781, 1476 (CH_3, CH_2); 1611 (C–H); 1250, 1146 (C–O); 864, 783 (=C–H). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.90 (*t*, 3 H, *J* = 7.3, N($CH_2CH_2CH_2CH_3$)$_2$); 1.21 – 1.39 (*m*, 4 H, N($CH_2CH_2CH_2CH_3$)$_2$); 1.43 – 1.60 (*m*, 4 H, N($CH_2CH_2CH_2CH_3$)$_2$); 1.72 (*s*, 3 H, C(11)H_3); 1.74 (*s*, 3 H, C(10)H_3); 2.22 (*s*, 3 H, ArCH_3); 2.42 – 2.53 (*m*, 4 H, N($CH_2CH_2CH_2CH_3$)$_2$); 3.34 (*d*, 2 H, *J* = 7.2, C(7)H_2); 3.69 (*s*, 2 H, ArCH_2N); 5.36 (*br. t*, 1 H, *J* = 6.8, C(8)H); 6.62 (*s*, 1 H, C(5)H); 6.83 (*s*, 1 H, C(3)H); 11.07 (*br. s*, 1 H, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): 13.96 (N($CH_2CH_2CH_2CH_3$)$_2$); 17.77 (C(11)); 20.57 (N($CH_2CH_2CH_2CH_3$)$_2$); 20.57 (ArCH_3); 25.80 (C(10)); 27.97 (C(7)); 28.46 (N($CH_2CH_2CH_2CH_3$)$_2$); 53.07 (N($CH_2CH_2CH_2CH_3$)$_2$); 58.27 (ArCH_2N); 121.54 (C(6)); 123.01 (C(8)); 126.60 (C(5)); 127.36, 128.04 (C(2), C(4)); 128.78 (C(3)); 131.93 (C(9)); 153.35 (C(1)).

4-Methyl-2-(3-methylbut-2-en-1-yl)-6-(morpholinomethyl)phenol (4). Colorless oil. Yield 0.308 g (90%). R_f = 0.28 (PE/Et_2O 5:1). Anal. calc. for $C_{17}H_{25}NO_2$ (275.39): C 74.14, H 9.15, N 5.09; found: C 74.31, H 8.99, N 5.06. $C_{17}H_{25}NO_2$. IR (thin layer): 3455 (OH); 2963, 2914, 2853, 2822, 1478, 1452 (CH_3, CH_2); 1612 (C–H); 1246, 1119 (C–O); 864, 783 (=C–H). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.73 (*s*, 3 H, C(11)H_3); 1.75 (*s*, 3 H, C(10)H_3); 2.22 (*s*, 3 H, ArCH_3); 2.40 – 2.72 (*m*, 4 H, N(CH_2CH_2)$_2$O); 3.30 (*d*, 2 H, *J* = 7.1, C(7)H_2); 3.60 – 3.90 (*m*, 4 H, N(CH_2CH_2)$_2$O); 3.65 (*s*, 2 H, ArCH_2N); 5.33 (*br. t*, 1 H, *J* = 6.9, C(8)H); 6.65 (*s*, 1 H, C(5)H); 6.86 (*s*, 1 H, C(3)H); 10.54 (*br. s*, 1 H, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.78 (C(11)); 20.48 (ArCH_3); 25.78 (C(10)); 28.02 (C(7)); 52.89 (N(CH_2CH_2)$_2$O); 61.96 (ArCH_2N); 66.78 (N(CH_2CH_2)$_2$O); 119.87 (C(6)); 122.77 (C(8)); 127.01 (C(5)); 127.93, 128.22 (C(2), C(4)); 129.38 (C(3)); 132.27 (C(9)); 152.77 (C(1)).

4-Methyl-2-(3-methylbut-2-en-1-yl)-6-(piperidin-1-ylmethyl)phenol (5). Colorless oil. Yield 0.311 g (91%). R_f = 0.62 (PE/Et_2O 5:1). Anal. calc. for $C_{18}H_{27}NO$ (273.42): C 79.07, H 9.95, N 5.12; found: C 79.20, H 9.91, N 5.18. IR (thin layer): 2934, 2857, 2804, 2756, 1476, 1445 (CH_3, CH_2); 1611 (C–H); 1248, 1111 (C–O); 860, 785 (=C–H). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.29 – 1.71 (*m*, 2 H, N(CH_2CH_2)$_2$$CH_2$); 1.56 – 1.71 (*m*, 4 H, N(CH_2CH_2)$_2$$CH_2$); 1.74 (*s*, 3 H, C(11)$H_3$);

1.75 (*s*, 3 H, C(10)H_3); 2.22 (*s*, 3 H, ArCH_3); 2.19 – 2.80 (*m*, 4 H, N(CH_2CH_2)$_2$CH_2); 3.31 (*d*, 2 H, *J* = 7.1, C(7)H_2); 3.61 (*s*, 2 H, ArCH_2N); 5.36 (*br. t*, 1 H, C(8)H, *J* = 6.9); 6.62 (*s*, 1 H, C(5)H); 6.84 (*s*, 1 H, C(3)H); 10.71 (*br. s*, 1 H, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.79 (C(11)); 20.51 (ArCH_3); 24.05 (N(CH_2CH_2)$_2$CH_2); 25.80 (C(10)); 25.82 (N(CH_2CH_2)$_2$CH_2); 28.03 (C(7)); 53.85 (N(CH_2CH_2)$_2$CH_2); 62.25 (ArCH_2N); 120.86 (C(6)); 122.96 (C(8)); 126.67 (C(5)); 127.42, 128.02 (C(2), C(4)); 128.86 (C(3)); 132.03 (C(9)); 153.34 (C(1)).

2-(Azepan-1-ylmethyl)-4-methyl-6-(3-methylbut-2-en-1-yl)phenol (6). Colorless oil. Yield 0.305 g (85%). R_f = 0.62 (PE/Et_2O 5:1). Anal. calc. for $C_{19}H_{29}NO$ (287.45): C 79.39, H 10.17, N 4.87; found: C 79.53, H 10.24, N 4.90. IR (thin layer): 2924, 2857, 2735, 1476, 1447 (CH_3, CH_2); 1611 (C–H); 1250, 1144 (C–O); 864, 783 (=C–H). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.46 – 1.86 (*m*, 8 H, N(CH_2CH_2CH_2)$_2$); 1.74 (*s*, 3 H, C(11)H_3); 1.75 (*s*, 3 H, C(10)H_3); 2.22 (*s*, 3 H, ArCH_3); 2.55 – 2.83 (*m*, 4 H, N(CH_2CH_2CH_2)$_2$); 3.32 (*d*, 2 H, *J* = 6.9, C(7)H_2); 3.72 (*s*, 2 H, ArCH_2N); 5.36 (*br. t*, 1 H, *J* = 6.7, C(8)H); 6.62 (*s*, 1 H, C(5)H); 6.85 (*s*, 1 H, C(3)H); 10.47 (*br. s*, 1 H, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.79 (C(11)); 20.53 (ArCH_3), 25.80 (C(10)); 26.69, 27.71 (N(CH_2CH_2CH_2)$_2$); 28.01 (C(7)); 55.17 (N(CH_2CH_2CH_2)$_2$); 62.09 (ArCH_2N); 121.60 (C(6)); 122.97 (C(8)); 126.57 (C(5)); 127.35, 128.14 (C(2), C(4)); 128.92 (C(3)); 131.98 (C(9)); 153.63 (C(1)).

Synthesis of compound **7**

It was obtained by the described method[17] with minor modifications. Calcium chloride (0.5 g, 4.5 mmol) was ground in a mortar with 0.043 g (0.5 mmol) of anhydrous piperazine and 0.035 g (1.2 mmol) of paraform. The powder was transferred to a round bottom flask, then cresol **1** (0.176 g, 1.0 mmol) was added, and the resulting mixture was heated for 35 min at 110 °C. At the end of the reaction, the mixture was cooled to r.t., $CHCl_3$ (10 mL) was added, $CaCl_2$ was separated by filtration, washed with $CHCl_3$ (2 × 7 mL), the solvent was removed under reduced pressure, the final product was precipitated from MeOH.

6,6'-(Piperazine-1,4-diylbis(methylene))bis(4-methyl-2-(3-methylbut-2-en-1-yl)phenol) (7). Colorless powder. M.p. 170 – 172 °C. Yield 0.131 g (57%). R_f = 0.33 (PE/Et_2O 5:1). Anal. calc. for $C_{30}H_{42}N_2O_2$ (462.68): C 77.88, H 9.15, N 6.05; found: C 78.02, H 9.12, N 5.99. IR (KBr): 2953, 2918, 2868, 2818, 1470 (CH_3, CH_2); 1254 (C–O); 856, 785 (=C–H). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.74 (*s*, 6 H, 2×C(11)H_3); 1.75 (*s*, 6 H, 2×C(10)H_3); 2.01 – 3.20 (*m*, 8 H, N(CH_2CH_2)$_2$N); 2.22 (*s*, 6 H, 2×ArCH_3); 3.31 (*d*, 4 H, *J* = 7.1, 2×C(7)H_2); 3.68 (*s*, 4 H, 2×ArCH_2N); 5.34 (*br. t*, 2 H, *J* = 6.7, 2×C(8)H); 6.65 (*s*, 2 H, 2×C(5)H); 6.86 (*s*, 2 H, 2×C(3)H); 10.55 (*br. s*, 2 H, 2×OH). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.79 (2×C(11)); 20.49 (2×ArCH_3); 25.79 (2×C(10)); 28.04 (2×C(7)); 52.31 (N(CH_2CH_2)$_2$N); 61.35 (2×ArCH_2N); 120.07 (2×C(6)); 122.79 (2×C(8)); 126.94 (2×C(5)); 127.95, 128.22 (2×C(2), 2×C(4)); 129.36 (2×C(3)); 132.18 (2×C(9)); 152.84 (2×C(1)).

Synthesis of compound **8**

Aldehyde **8** was synthesized from cresol **1** by the known method.[18]

2-Hydroxy-5-methyl-3-(3-methylbut-2-en-1-yl)benzaldehyde (8). Yellow oil. Yield 0.35 g (55%). R_f = 0.77 (PE/Et_2O 5:1). Anal. calc. for $C_{13}H_{16}O$ (204.27): C 76.44, H 7.90; found: C, 76.58; H, 7.78. IR (thin layer): 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 (300 MHz, $CDCl_3$): 1.73 (*s*, 3 H, C(11)H_3); 1.76 (*s*, 3 H, C(10)H_3); 2.31 (*s*, 3 H, ArCH_3); 3.34 (*d*, 2 H, *J* = 7.3, C(7)H_2); 5.30 (*br. t*, 1 H, *J* = 7.7, C(8)H); 7.18 (*s*, 1 H, C(5)H); 7.20 (*s*, 1 H, C(3)H); 9.83 (*s*, 1 H, CH=O); 11.11 (*s*, 1 H, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): 17.77 (C(11)); 20.32 (ArCH_3); 25.77 (C(10)); 27.29 (C(7)); 119.94 (C(6)); 121.50 (C(8)); 128.66 (C(4)); 130.08 (C(2)); 131.03 (C(5)); 133.34 (C(9)); 137.81 (C(3)); 157.52 (C(1)); 196.65 (CH=O).

Synthesis of compounds **9** – **11**

Molecular sieves (4 Å, 0.4 g) and amine (0.5 mmol) were added to the solution of aldehyde **8** (0.102 g, 0.5 mmol) in anhydrous benzene (3 mL). The reaction mixture was refluxed under an argon atmosphere for 3.5 h. At the end of the reaction, the molecular sieves were separated by filtration, washed with $CHCl_3$, the solvents were removed under reduced pressure.

(*E*)-2-((Cyclopropylimino)methyl)-4-methyl-6-(3-methylbut-2-en-1-yl)phenol (9). Yellow waxy mass. Yield 0.119 g (98%). R_f = 0.85 (PE/Et_2O 5:1). Anal. calc. for $C_{16}H_{21}NO$ (243.35): C 78.97, H 8.70, N 5.76; found: C 80.08, H 10.31, N 4.50. IR (thin layer): 3240 (OH); 3007, 2970, 2916, 2872, 1462 (CH_3, CH_2); 1624 (C=N); 1265 (C–O); 864, 792 (=C–H). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.82 – 1.02 (*m*, 4 H, NCH(CH_2)$_2$); 1.73 (*s*, 3 H, C(11)H_3); 1.75 (*s*, 3 H, C(10)H_3); 2.27 (*s*, 3 H, ArCH_3); 2.89 – 3.00 (*m*, 1 H, NC*H*(CH_2)$_2$); 3.34 (*d*, 2 H, *J* = 7.1, C(7)H_2); 5.30 (*br. t*, 1 H, *J* = 6.5, C(8)H); 6.87 (*s*, 1 H, C(5)H); 6.96 (*s*, 1 H, C(3)H); 8.43 (*s*, 1 H, CH=N); 12.83 (*s*, 1 H, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.20 (NCH(*C*H_2)$_2$); 17.78 (C(11)); 20.44 (ArCH_3); 25.77 (C(10)); 27.81 (C(7)); 40.18 (N*C*H(CH$_2$)$_2$); 118.21 (C(6)); 122.44 (C(8)); 127.26 (C(4)); 128.44 (C(5)); 128.93, 132.50 (C(2), C(9)); 132.31 (C(3)); 155.90 (C(1)); 162.14 (CH=N).

(*E*)-2-((*n*-Butylimino)methyl)-4-methyl-6-(3-methylbut-2-en-1-yl)phenol (10). Yellow brown oil. Yield 0.122 g (94%). R_f = 0.85 (PE/Et_2O 5:1). Anal. calc. for $C_{17}H_{25}NO$ (259.39): C 78.72, H 9.71, N 5.40; found: C 78.80, H 9.62, N 5.33. IR (thin layer): 3254 (OH); 2959, 2926, 2864, 1464 (CH_3, CH_2); 1632 (C=N); 1267 (C–O); 856, 791 (=C–H). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.95 (*t*, 3 H, *J* = 7.3, NCH$_2$CH$_2$CH$_2$C*H*$_3$); 1.32 – 1.50 (*m*, 2 H, NCH$_2$CH$_2$C*H*$_2$CH$_3$); 1.58 – 1.77 (*m*, 2 H, NCH$_2$C*H*$_2$CH$_2$CH$_3$); 1.74 (*s*, 3 H, C(11)H_3); 1.76 (*s*, 3 H, C(10)H_3); 2.27 (*s*, 3 H, ArCH_3); 3.37 (*d*, 2 H, *J* = 7.2, C(7)H_2); 3.58 (*t*, 2 H, *J* = 6.8, NC*H*$_2$CH$_2$CH$_2$CH$_3$); 5.36 (*br. t*, 1 H, *J* = 7.4, C(8)H); 6.89 (*s*, 1 H, C(5)H); 6.99 (*s*, 1 H, C(3)H); 8.28 (*s*, 1 H, CH=N); 13.71 (*s*, 1 H, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): 13.77 (NCH$_2$CH$_2$CH$_2$CH$_3$); 17.79 (C(11)); 20.29 (NCH$_2$CH$_2$*C*H$_2$CH$_3$); 20.44 (ArCH_3); 25.80 (C(10)); 27.79 (C(7)H$_2$); 32.97 (NCH$_2$CH$_2$CH$_2$CH$_3$); 59.17 (NCH$_2$CH$_2$CH$_2$CH$_3$); 117.90 (C(6)); 122.44 (C(8)); 126.94 (C(4)); 128.81 (C(5)); 129.19, 132.53 (C(2), C(9)); 132.71 (C(3)); 157.01 (C(1)); 164.61 (CH=N).

(*E*)-4-Methyl-2-(3-methylbut-2-en-1-yl)-6-((octylimino)methyl)phenol (11). Yellow brown oil. Yield 0.154 g (98%). R_f = 0.85 (PE/Et_2O 5:1). Anal. calc. for $C_{21}H_{33}NO$ (315.50): C 79.95, H 10.54, N 4.44; found: C 80.08, H 10.31, N 4.50. IR (thin layer): 3455 (OH); 2957, 2926, 2855, 1464 (CH_3, CH_2); 1632 (C=N); 1269 (C–O); 855, 793 (=C–H). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.89 (*t*, 3 H, *J* = 6.3, $NCH_2(CH_2)_6CH_3$); 1.17 – 1.47 (*m*, 10 H, $N(CH_2)_2(CH_2)_5CH_3$); 1.58 – 1.79 (*m*, 2 H, $NCH_2CH_2(CH_2)_5CH_3$); 1.74 (*s*, 3H, C(11)H_3); 1.76 (*s*, 3 H, C(10)H_3); 2.27 (*s*, 3 H, $ArCH_3$); 3.37 (*d*, 2 H, *J* = 7.2, C(7)H_2); 3.57 (*t*, 2 H, *J* = 6.8, $NCH_2(CH_2)_6CH_3$); 5.36 (*br. t*, 1 H, *J* = 7.1, C(8)H); 6.89 (*s*, 1 H, C(5)H); 6.99 (*s*, 1 H, C(3)H); 8.27 (*s*, 1 H, CH=N), 13.73 (*s*, 1 H, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.07 ($NCH_2(CH_2)_6CH_3$); 17.79 (C(11)H_3); 20.44 ($ArCH_3$); 22.64, 27.78, 29.21, 29.33, 30.91, 31.83 ($NCH_2(CH_2)_6CH_3$); 25.80 (C(10)H_3); 27.19 (C(7)H_2); 59.54 ($NCH_2(CH_2)_6CH_3$); 117.87 (C(6)H); 122.41 (C(8)H); 126.92 (C(4)); 128.80 (C(5)); 129.18, 132.55 (C(2), C(9)); 132.68 (C(3)); 157.01 (C(1)); 164.56 (CH=N).

Synthesis of compounds **12** – **14**

Sodium borohydride (0.076 g 2.0 mmol) was added to the solution of imine **9** – **11** in anhydrous EtOH (4 mL) while stirring. The reaction mixture was heated under reflux for 30 min. At the end of the reaction, the mixture was cooled to r.t., 3.5 mL of 2 *N* aqueous NaOH solution were added, stirred for 5 min, 10 mL of Et_2O were added, and stirring was continued for 15 min. Next, the organic layer was washed with 2 *N* aqueous NaCl solution (4×8 mL) to pH 7.0, dried with anhydrous K_2CO_3, the solvent was removed under reduced pressure, the product was isolated by column chromatography (PE/Et_2O with an increase in the fraction of the latter).

2-((Cyclopropylamino)methyl)-4-methyl-6-(3-methylbut-2-en-1-yl)phenol (12). Colorless oil. Yield 0.071 g (72%). R_f = 0.47 (PE/Et_2O 3:1). Anal. calc. for $C_{16}H_{23}NO$ (245.37): C 78.32, H 9.45, N 5.71; found: C 78.11, H 9.66, N 5.75. IR (thin layer): 3292 (NH, OH); 2965, 2916, 2855, 1477 (CH_3, CH_2); 1246 (C–O); 858, 783 (=C–H). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.45 – 0.60 (*m*, 4 H, $NCH(CH_2)_2$); 1.73 (*s*, 3 H, C(11)H_3); 1.75 (*s*, 3 H, C(10)H_3); 2.15 – 2.29 (*m*, 1 H, $NCH(CH_2)_2$); 2.23 (*s*, 3 H, $ArCH_3$); 3.29 (*d*, 2 H, *J* = 7.2, C(7)H_2); 3.99 (*s*, 2 H, $ArCH_2N$); 5.33 (*br. t*, 1 H, *J* = 7.3, C(8)H); 6.68 (*s*, 1 H, C(5)H); 6.84 (*s*, 1 H, C(3)H). ^{13}C-NMR (75 MHz, $CDCl_3$): 6.04 ($NCH(CH_2)_2$); 17.77 (C(11)); 20.51 ($ArCH_3$); 25.78 (C(10)); 28.02 (C(7)); 30.53 ($NCH(CH_2)_2$); 52.81 ($ArCH_2N$); 122.32 (C(6)); 122.91 (C(8)); 126.41 (C(5)); 127.74, 128.46 (C(2), C(4)); 129.12 (C(3)); 132.06 (C(9)); 153.15 (C(1)).

2-((*n*-Butylamino)methyl)-4-methyl-6-(3-methylbut-2-en-1-yl)phenol (13). Pale yellow oil. Yield 0.087 g (83%). R_f = 0.32 (PE/Et_2O 3:1). Anal. calc. for $C_{17}H_{27}NO$ (261.41): C 78.11, H 10.41, N 5.36; found: C 78.19, H 10.37, N 5.30. IR (thin layer): 3316, 3291 (NH, OH); 2959, 2918, 2857, 1470 (CH_3, CH_2); 1248 (C–O); 858, 785 (=C–H). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.93 (*t*, 3 H, *J* = 7.3, $NCH_2CH_2CH_2CH_3$); 1.25 – 1.46 (*m*, 2 H, $NCH_2CH_2CH_2CH_3$); 1.47 – 1.61 (*m*, 2 H, $NCH_2CH_2CH_2CH_3$); 1.74 (*s*, 3 H, C(11)H_3); 1.76 (*s*, 3 H, C(10)H_3); 2.23 (*s*, 3 H, $ArCH_3$); 2.68 (*t*, 2 H, *J* = 7.0, $NCH_2CH_2CH_2CH_3$); 3.32 (*d*, 2 H, *J* = 4.9, C(7)H_2); 3.93 (*s*, 2 H, $ArCH_2N$); 5.36 (*br. t*, 1 H, *J* = 6.9, C(8)H); 6.66 (*s*, 1 H, C(5)H); 6.85 (*s*, 1 H, C(3)H). ^{13}C-NMR (75 MHz, $CDCl_3$): 13.87 ($NCH_2CH_2CH_2CH_3$); 17.76 (C(11)); 20.28, 31.72 ($NCH_2CH_2CH_2CH_3$); 20.51 ($ArCH_3$); 25.79 (C(10)); 28.03 (C(7)); 48.50 ($NCH_2CH_2CH_2CH_3$); 52.87 ($ArCH_2N$); 121.94 (C(6)); 122.99 (C(8)); 126.41 (C(5)); 127.47, 128.42 (C(2), C(4)); 128.99 (C(3)); 131.98 (C(9)); 153.59 (C(1)).

4-Methyl-2-(3-methylbut-2-en-1-yl)-6-((*n*-octylamino)methyl)phenol (14). Pale beige oil. Yiled 0.108 g (85%). R_f = 0.36 (PE/Et_2O 5:1). Anal. calc. for $C_{21}H_{35}NO$ (317.52): C 79.44, H 11.11, N 4.41. IR (thin layer): 3316, 3292 (NH, OH); 2957, 2924, 2855, 1474 (CH_3, CH_2); 1250 (C–O); 858, 785 (=C–H). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.89 (*t*, 3 H, *J* = 6.3, $N(CH_2)_7CH_3$); 1.18 – 1.40 (*m*, 10 H, $N(CH_2)_2(CH_2)_5CH_3$); 1.47 – 1.61 (*m*, 2 H, $NCH_2CH_2(CH_2)_5CH_3$); 1.74 (*s*, 3 H, C(11)H_3); 1.75 (*s*, 3 H, C(10)H_3); 2.22 (*s*, 3 H, $ArCH_3$); 2.67 (*t*, 2 H, *J* = 7.0, $NCH_2(CH_2)_6CH_3$); 3.32 (*d*, 2 H, *J* = 7.2, C(7)H_2); 3.93 (*s*, 2 H, $ArCH_2N$); 5.35 (*br. t*, 1 H, *J* = 6.8, C(8)H); 6.66 (*s*, 1 H, C(5)H); 6.85 (*s*, 1 H, C(3)H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.06 ($N(CH_2)_7CH_3$); 17.77 (C(11)); 20.51 ($ArCH_3$); 22.62, 28.02, 29.19, 29.39, 29.59, 31.79 ($NCH_2(CH_2)_6CH_3$); 25.80 (C(10)); 27.13 (C(7)); 48.82 ($NCH_2(CH_2)_6CH_3$); 52.85 ($ArCH_2N$); 121.95 (C(6)); 122.98 (C(8)); 126.41 (C(5)); 127.47, 128.42 (C(2), C(4)); 128.98 (C(3)); 132.00 (C(9)); 153.59 (C(1)).

DPPH radical scavenging activity

DPPH radical scavenging activity of the compounds was assessed by their ability to interact with DPPH.[24] The studied compounds at a concentration of 100 μM were added to a DPPH solution in MeOH, stirred, and the solution absorbance was measured at λ = 517 nm after 30 min.

Fe^{2+}-chelation ability

Fe^{2+}-chelation ability of the compounds was assessed by the described methods.[25][26] A solution of the studied compounds at a concentration of 100 μM was added to MeOH, then a $FeSO_4$ solution was added. The reaction was initiated with a FerroZine™ Iron Reagent solution, the mixture was shaken, and the solution absorbance was measured at λ = 562 nm after 10 min.

Antioxidant activity (brain lipids test)

Antioxidant activity of the compounds was assessed by their ability to inhibit LPO processes in a substrate obtained from the brain of laboratory mice.[27][28] After extraction, the brain was homogenized (10%) in a saline solution (pH 7.4) and centrifuged for 10 min. Then the supernatant (S1) containing water, proteins, DNA, RNA, and lipids was collected. The studied compounds in the form of solutions in acetone (final concentration 100 μM) were added to the supernatant. After 30 min, LPO was initiated by adding freshly prepared $FeCl_2$ and ascorbic acid, the test samples were incubated in a

shaker for 1 h at 37 °C and while slow stirring. The content of thiobarbituric acid reactive substances (TBA-RS) was determined at λ = 532 nm; the extinction coefficient 1.56×10^5 M^{-1} cm^{-1} was used for the calculations.[28 – 30]

Toxicity, antioxidant activity, and membrane-protective activity (RBCs tests)

Toxicity, antioxidant and membrane-protective activity of compounds were studied in the suspension of RBCs of laboratory mice in phosphate-buffered saline (pH 7.4). The toxicity of the compounds was assessed in an *in vitro* model by their ability to induce RBCs hemolysis. Solutions of the compounds in acetone were added to the RBCs suspension at a final concentration of 10 μM and incubated for 5 h at 37 °C. Membrane-protective and antioxidant activities were determined by the degree of inhibition of induced hemolysis, inhibition of accumulation of secondary LPO and oxyhemoglobin oxidation products in RBCs. For this purpose, hemolysis was initiated with a H_2O_2 solution (0.006%) 30 min after adding solutions of the studied compounds into the RBCs suspension (final concentration of 1 μM). The reaction mixture was incubated with slow stirring for 5 h at 37 °C. Every 60 min, an aliquot was taken from the incubation medium, centrifuged for 5 min (1600 *g*), the degree of hemolysis was determined by hemoglobin content in the supernatant at λ = 524 nm.[31] Hemolysis percentage was calculated relative to the total hemolysis of the sample. The content of TBA-RS was determined using spectrophotometry as described above. Absorption spectrum in the range of λ = 540 – 640 nm was analyzed to assess the accumulation of hemoglobin oxidation products. Oxyhemoglobin and methemoglobin content was calculated taking into account the corresponding extinction coefficients.[32] Each experiment was conducted in 4 – 10 replicates. Statistical data processing was carried out using Microsoft Office Excel 2007, and 2010 software packages.

Supplementary Material

Supporting information for this article is available on the WWW under https://doi.org/10.1002/cbdv.201xxxxxx.

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Author Contribution Statement

Evgeny V. Buravlev and Irina V. Fedorova: design, synthesis, and structure elucidation; Oksana G. Shevchenko: *in vitro* activity assays; Aleksandr V. Kutchin: concept and project administration. All authors prepared, discussed, and approved the manuscript.

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