Comparative evaluation of the antioxidant activity of some *ortho*-substituted mono- and dialkylphenols with the *para*-positioned hydroxymethyl group*

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The *para*-hydroxymethyl derivatives of 2,6-di-*tert*-butylphenol, 2,6-diisobornylphenol, 2-isobornyl-6-*tert*-butylphenol, 2-isobornyl-6-methylphenol, and 2-isobornylphenol were synthesized. A comparative evaluation of the antioxidant properties of the synthesized compounds was carried out in *in vitro* models. The activity of derivatives is predetermined by the number and bulkiness of the substituents at the *ortho* positions relative to the phenolic OH group and is consistent with the relationships previously identified by us for other phenolic antioxidants.

Keywords: phenols, alkylphenols, terpenephenols, hydroxymethyl derivatives, antioxidant activity, membrane-protective activities, red blood cells, oxidative hemolysis.

It is known that the most common antioxidants are the phenolic derivatives with the sterically hindered OH group (sterically hindered phenols).[1] Similarly to alkylphenols, terpenephenols[2] and their derivatives, *viz.* phenolic compounds bearing the terpene substituents,[3] are capable of inhibiting oxidative processes.[4—8] For example, it was demonstrated that some *para*-alkoxymethyl terpenephenol derivatives have *in vitro* antioxidant activity,[5] *p*-hydroxymethylphenol derivative bearing two isobornyl substituents is efficient *in vivo* against benign prostatic hyperplasia in male rats,[9] and its parent compound, 2,6-diisobornyl-4-methylphenol, is very active in the model of experimental pathospermia in rats increasing the antioxidant potential of spermatozoa and reducing the percentage of degenerative forms of spermatozoa.[10]

Nevertheless, it is still challenging to study the effects of the alkyl and/or terpene substituents positioned *ortho* to the phenolic OH group on biological activity of the *para*-hydroxymethyl derivatives. Such research requires increasing the range of the compounds by including new analogs based on available alkyl- and terpenephenols and an *in vitro* comparative evaluation of the new compounds as inhibitors of the oxidative processes, which was the aim of this work.

Results and Discussion

The known aldehydes **1**—**5** were subjected to the sodium borohydride reduction to give hydroxymethyl derivatives **6**—**10** (Scheme 1). The ^{1}H and ^{13}C NMR spectral data, IR spectral data, and elemental analysis data of products **6**, **8**, and **10** confirm expectations on their structure. The spectral properties of compounds **7** and **9** are in accord with those described earlier.[11,12] The ^{1}H and ^{13}C NMR spectra of derivatives **6**—**10** show signals of the hydroxymethyl substituent at the *para* position to the phenolic group along with the signals of 2-mono- or 2,6-disubstituted phenolic unit.

The radical scavenging activity (RSA) of compounds **6**—**10** was evaluated using DPPH assay, antioxidant activity (AOA) was examined using the substrates containing natural lipids (mouse brain and testicular homogenates), cytotoxicity, AOA, and membrane protective properties were evaluated using mammalian red blood cells. A phenolic antioxidant 2,6-di-*tert*-butyl-4-methylphenol (BHT) was used as a reference. Most of the above-mentioned test systems were used previously for comparative evaluations of AOA of different types of phenolic compounds.[5—7,13—15] To obtain the wider data coverage on AOA of the synthesized compounds we used not only the mouse brain homogenate but also the mouse testicular homogenate as a substrate. The use of the latter is of the interest since the spermatozoa and hormone-producing Leydig cells contain high level of polyunsaturated fatty acid and, therefore, are

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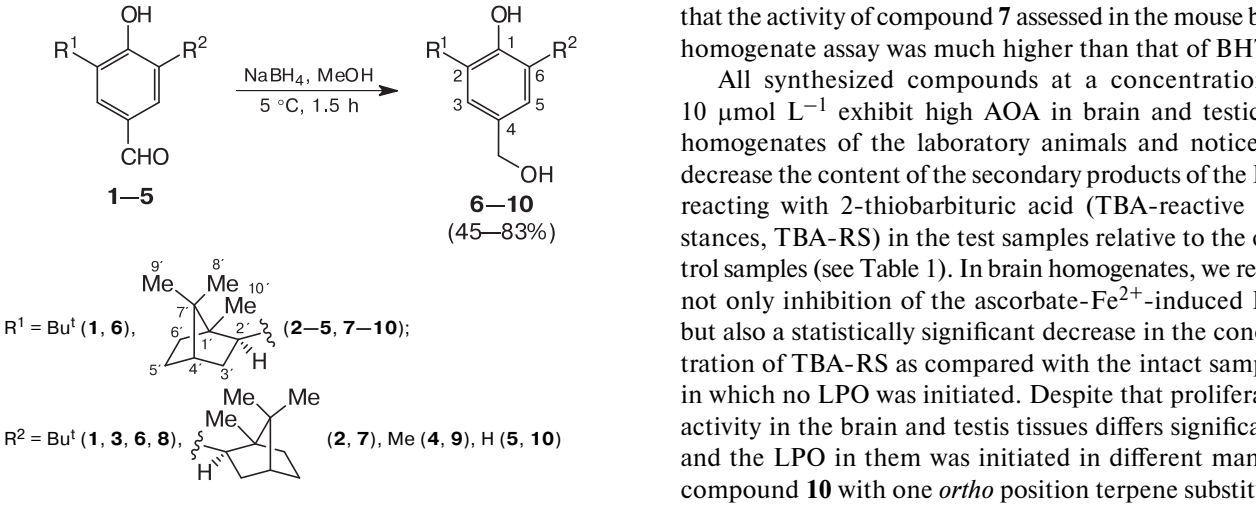
Scheme 1*



* *Note*. The numbering scheme for the carbon atoms is used for the interpretation of the NMR spectra and may not correspond to the IUPAC nomenclature. Compounds **2** and **7** are *meso* stereoisomers, compounds **3**—**5** and **8**—**10** are racemates. Scheme 1 shows the structures of one of the enantiomers.

very sensitive to reactive oxygen species.[16—18] It was experimentally demonstrated that some antioxidants, for instance, melatonin and α-tocopherol, can suppress the ascorbate-Fe^{2+}-induced lipid peroxidation (LPO) in microsomes and mitochondria of the rat testicles and protect the polyunsaturated fatty acids from oxidation.[16,17].

We found that RSA of the studied compounds is determined by the number and bulkiness of the substituents at the *ortho* positions to the phenolic OH group. Thus, compound **10** with one terpene substituent was the least active, while, *para*-hydroxymethyl derivative **7** bearing two isobornyl units was the most active (Table 1). Note that the activity of compound **7** assessed in the mouse brain homogenate assay was much higher than that of BHT.

All synthesized compounds at a concentration of 10 μmol L^{-1} exhibit high AOA in brain and testicular homogenates of the laboratory animals and noticeably decrease the content of the secondary products of the LPO reacting with 2-thiobarbituric acid (TBA-reactive substances, TBA-RS) in the test samples relative to the control samples (see Table 1). In brain homogenates, we record not only inhibition of the ascorbate-Fe^{2+}-induced LPO but also a statistically significant decrease in the concentration of TBA-RS as compared with the intact samples, in which no LPO was initiated. Despite that proliferative activity in the brain and testis tissues differs significantly and the LPO in them was initiated in different manner, compound **10** with one *ortho* position terpene substituent was the least active in both cases. When concentration of the compounds was decreased to 1 μmol L^{-1}, low activity was detected not only for compound **10** but also for derivative **6** with two *tert*-butyl groups. Thus, AOA of the *para*-hydroxymethyl derivatives in the above test systems is determined by the number and bulkiness of the substituents at the *ortho* position relative to the phenolic OH group.

Hemolytic activity measurements using red blood cells isolated from mice show that neither of the synthesized compounds has the pronounced activity at a concentration of 10 μmol L^{-1}. Five hours after incubation with compounds **6**—**10**, the hemolysis level of the mouse red blood cells does not exceed 6.9±0.2%.

The structure—activity relationships for derivatives **6**—**10** described above were corroborated by a comparative

Table 1. Comparative evaluation of RSA and AOA* of derivatives **6**—**10**

Compound	RSA (inhibition (%)) c = 10 μmol L^{-1}	TBA-RS/nmol mL^{-1}			
		mouse testicular homogenate		mouse brain homogenate	
		c = 10 μmol L^{-1}	c = 1 μmol L^{-1}	c = 10 μmol L^{-1}	c = 1 μmol L^{-1}
Control	—	32.0±0.4	42.7±0.2	72.7±2.1	
Intact sample	—	7.3±0.6	12.6±0.6	30.9±0.8	
BHT	5.0±0.4	8.1±0.2	36.2±0.5	7.6±0.1	86.4±0.4
6	6.9±0.2	8.8±0.2	40.6±1.5	22.7±0.1	78.7±0.4
7	14.4±0.8	8.5±0.3	33.3±0.5	7.1±0.3	60.7±0.9
8	6.5±0.5	7.4±0.2	32.0±0.5	6.9±0.3	58.5±0.1
9	9.0±0.7	7.4±0.4	32.7±0.3	7.3±0.2	65.7±0.9
10	2.5±0.2	20.1±0.1	37.0±0.5	54.1±0.2	80.6±0.3

* The ability of compounds **6**—**10** to inhibit the accumulation of the products of the lipid peroxidation (LPO) reacting with 2-thiobarbituric acid (TBA-reactive substances, TBA-RS) was estimated using the mouse testicular homogenate (3 h after the H_2O_2 initiation of the LPO) and mouse brain homogenate (1 h after the ascorbate-Fe^{2+}-initiation of the LPO). The control samples are the samples containing no test compounds, the intact samples are the samples in which oxidation was not initiated.

Table 2. Comparative evaluation of MPA of derivatives **6**—**10** at a concentration of 1 μmol L^{-1} assessed using H_2O_2-induced hemolysis of red blood cells

Compound	MPA (hemolysis (%))		
	1 h	3 h	5 h
Control	16.4±1.5	40.0±0.9	56.8±1.6
BHT	6.7±1.2	37.0±1.7	49.2±1.0
6	11.5±1.2	37.7±0.7	52.0±0.4
7	1.8±0.0	3.3±0.0	5.4±0.3
8	2.0±0.2	25.6±1.2	30.4±1.0
9	5.4±1.0	37.7±0.7	48.8±1.0
10	16.4±1.7	34.2±0.7	49.4±0.3

evaluation of the membrane-protective activity (MPA) (Table 2). Thus, compound **7** most efficiently prevented H_2O_2-induced cell death and compounds **6** and **10** were the least active. The high statistically significant AOA of derivative **7** in the biological systems was confirmed by its ability to efficiently inhibit accumulation of the secondary LPO products and hemoglobin oxidation. For instance, compound **7** induces a 1.4-times decrease in the concentration of TBA-RS and 2.8-times and 1.8-times decrease in methemoglobin/oxyhemoglobin (metHb/oxyHb) and ferrylhemoglobin/oxyhemoglobin (ferrylHb/oxyHb) ratios, respectively, as compared with the control. Finally, this compound efficiently protected the erythrocyte heme from the H_2O_2-induced damage, which was evidenced from the decrease in the fluorescence of the products of heme oxidative degradation (Table 3).

It should be emphasized that in the cell test system (red blood cells) derivatives **7** and **8** bearing the *para* position hydroxymethyl group were significantly more active than BHT; while, their advantages were not such pronounced in non-cellular bioassays (mouse lipid homogenates) (see Table 1). It is also notable that compound **7** shows the higher antioxidant power in the animal model assay than other phenolic antioxidants.[9]

In summary, in the present work we synthesized a series of mono- and dialkylphenols with the *para* position hydroxymethyl group. The *in vitro* studies indicate that the activity of the synthesized products is determined by the number and bulkiness of the substituents at the *ortho* position relative to the phenolic group, which is in agreement with the relationships found by us earlier for other phenolic antioxidants.[19—23] In terms of the set of the considered parameters, the lowest activity was observed for *para*-hydroxymethyl derivative **10** with one terpene substituent at the *ortho* position relative to the phenolic OH group and the highest activity was found for compound **7** with two isobornyl moieties.

Experimental

^1H and ^{13}C NMR spectra of the synthesized compounds were recorded with a Bruker Avance II 300 spectrometer at the working frequencies of 300.17 and 75.5 MHz, respectively. The ^1H NMR signals were attributed using the NOESY technique, the ^{13}C NMR signals were assigned with the aid of the *J*-resolved experiments and the HSQC and HMBC correlation techniques. Diffuse reflectance IR spectra were recorded with a Shimadzu IR Prestige 21 FT-IR spectrophotometer in KBr pellets. Elemental analysis was performed on a vario Micro cube analyzer operating in CHNS mode. The spectrophotometric measurements were carried out on a Thermo Spectronic Genesys 20 spectrophotometer. The reaction course was monitored by TLC on the precoated plates Sorbfil (LLC Imid). The spots of the compounds were visualized by treatment of the TLC plates with a $KMnO_4$ solution ($KMnO_4$ (15 g), H_2O (300 mL), concentrated H_2SO_4 (0.5 mL)). Melting points were measured with a Sanyo Gallenkamp MPD350 apparatus and are given uncorrected. Aldehyde **1** was synthesized by the known procedure,[24] derivatives **2**—**5** were described by us earlier.[11,15,23,25]. Sodium borohydride $NaBH_4$ (Daejung Co.), BHT, and DPPH (both Alfa

Table 3. Comparative evaluation of AOA of derivatives **6**—**10** at a concentration of 1 μmol L^{-1} assessed using H_2O_2-induced hemolysis of red blood cells

Compound	TBA-RS/nmol L^{-1}	metHb/oxyHb	ferrylHb/oxyHb	I_{fl}/arb. units
Control	2.17±0.04	2.20±0.18	1.09±0.06	9.20±0.12
BHT	1.87±0.04	1.88±0.10	1.14±0.03	7.87±0.10
6	1.93±0.05	2.73±0.19	0.54±0.01	9.14±0.18
7	1.51±0.04	0.78±0.04	0.61±0.01	6.22±0.04
8	1.67±0.05	1.20±0.14	0.93±0.03	7.57±0.21
9	2.03±0.03	2.69±0.09	0.75±0.04	8.73±0.47
10	2.02±0.05	1.96±0.05	0.75±0.02	8.24±0.17

* The forms of hemoglobin, in which the iron atom (a complexing agent) has different formal charges, are as follows: oxyhemoglobin (oxyHb, Fe^{2+}), methemoglobin (metHb, Fe^{3+}), ferrylhemoglobin (ferrylHb, Fe^{4+}). Methemoglobin and ferrylhemoglobin, in which the formal charges of heme iron are higher than in oxyhemoglobin, cannot function as oxygen carriers.

Aesar) were used as purchased. Alfa Aesar silica gel (0.06—0.2 mm) was used for the column chromatography.

Some physicochemical studies of the synthesized compounds were performed on the equipment of the Center for Collective Use "Chemistry" of the Institute of Chemistry of Komi Science Center, the Ural Branch of the Russian Academy of Sciences (RAS). Biological activity of the synthesized compounds was studied using the equipment of the Center for Collective Use "Molecular Biology" of the Institute of Biology of Komi Science Center, the Ural Branch of the RAS. For the experiments, the laboratory mice from the scientific collection of experimental animals of the Institute of Biology of the Komi Scientific Center, the Ural Branch of the RAS were used (http://www.ckp-rf.ru/usu/471933/). The animals were kept and all experiments with them were carried out in accordance with the "Regulations on the vivarium of experimental animals" of the Institute of Biology of the Komi Scientific Center, the Ural Branch of the RAS (protocol No. 1 dated 01.24.2017), taking into account the sanitary-hygienic and bioethical aspects (http://www.ckp-rf.ru/usu/471933/).

Synthesis of alcohols 6—10 (general procedure). To a solution or a suspension of aldehyde **1—5** (1.0 mmol) in anhydrous MeOH (15 mL), $NaBH_4$ (0.189 g, 5.0 mmol) was added at ~5 °C (bath temperature) and the mixture was stirred for 1.5 h. After the reaction completion, the mixture was warmed to room temperature, treated with 2 *M* NaOH (12 mL), stirred 5 min, diluted with diethyl ether (30 mL), and stirring was continued for 15 min. The organic layer was separated, washed with 2 *M* NaCl to pH ~7.0, dried with anhydrous K_2CO_3, and co-evaporated with small amount of pentane. The product was collected by filtration and washed with petroleum ether. Compound **6** was additionally purified by silica gel column chromatography (elution with $CHCl_3$).

4-Hydroxymethyl-2,6-di-*tert*-butylphenol (6). Colorless powder, m.p. 141—143 °C (*cf.* Ref. 26: 140—145 °C (MeOH)). Yield 0.106 g (45%). Found (%): C, 76.49; H, 10.44. $C_{15}H_{24}O_2$. Calculated (%): C, 76.23; H, 10.24. IR (KBr), ν/cm^{-1}: 3568, 3522 (OH); 2945, 2953, 2914, 2872, 1481, 1435 (CH_3, CH_2); 1584 (C=C); 1204, 1113, 1013 (C—O); 881 (=C—H). ^{1}H NMR spectral data are in agreement with those described previously.[26] ^{13}C NMR ($CDCl_3$), δ: 30.26 (2 C($\underline{C}H_3)_3$); 34.34 (2 $\underline{C}(CH_3)_3$); 66.10 (CH_2OH); 124.44 (C(3), C(5)); 131.62, 136.13 (C(2), C(4), C(6)); 153.52 (C(1)).

4-Hydroxymethyl-2-{(1*S*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl}-6-{(1*R*,2*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl}phenol (7). Colorless powder. Yield 0.317 g (80%). The spectral properties are in agreement with those described earlier.[11]

4-Hydroxymethyl-2-*tert*-butyl-6-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol (8). Beige powder, m.p. 125—127 °C. Yield 0.263 g (83%). Found (%): C, 79.86; H, 10.01. $C_{21}H_{32}O_2$. Calculated (%): C, 79.70; H, 10.19. IR (KBr), ν/cm^{-1}: 3638, 3597, 3416 (OH); 2953, 2874, 2729, 1458, 1437 (CH_3, CH_2); 1593 (C=C); 1204, 1169, 1130 (C—O); 877 (=C—H). ^{1}H NMR ($CDCl_3$), δ: 0.79, 0.85, 0.87 (all s, 3 H each, C(8′)H_3, C(9′)H_3, C(10′)H_3); 1.32—1.47 (m, 11 H, 1 H(5′), 1 H(6′), C($CH_3)_3$)); 1.56—1.79 (m, 2 H, 1 H(3′), 1 H(6′)); 1.84—2.02 (m, 2 H, 1 H(4′), 1 H(5′)); 2.24—2.38 (m, 1 H, 1 H(3′)); 2.89 (t, 1 H, 1 H(2′), *J* = 8.5 Hz); 4.60 (s, 2 H, C$\underline{H}_2$OH); 4.80 (s, 1 H, ArOH); 7.15, 7.19 (both s, 1 H each, 1 H(3), 1 H(5)). ^{13}C NMR ($CDCl_3$), δ: 12.22 (C(10′)); 20.22 (C(9′)); 21.38 (C(8′)); 27.59 (C(5′)); 29.79 (C($\underline{C}H_3)_3$); 34.29 (C(3′)); 34.50 ($\underline{C}(CH_3)_3$); 40.33 (C(6′)); 45.39 (C(4′)); 46.31 (C(2′)); 48.39 (C(7′)); 49.53 (C(1′)); 66.13 (CH_2OH); 123.89, 124.96 (C(3), C(5)); 128.83, 131.38, 135.73 (C(2), C(4), C(6)); 153.18 (C(1)).

4-Hydroxymethyl-2-methyl-6-(1,7,7-trimethylbicyclo[2.2.1]-hept-*exo*-2-yl)phenol (9). Beige powder. Yield 0.207 g (75%). The spectral properties are in agreement with those described earlier.[12]

4-Hydroxymethyl-2-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol (10). Beige powder, m.p. 109—111 °C. Yield 0.200 g (77%). Found (%): C, 78.54; H, 9.33. $C_{17}H_{24}O_2$. Calculated (%): C, 78.42; H, 9.29. IR (KBr), ν/cm^{-1}: 3345, 3130, 3096, 3021 (OH); 2949, 2976, 2747, 1440 (CH_3, CH_2); 1610 (C=C); 1252, 1117 (C—O); 822 (=C—H). ^{1}H NMR ($CDCl_3$), δ: 0.79, 0.84, 0.89 (all s, 3 H each, C(8′)H_3, C(9′)H_3, C(10′)H_3); 1.28—1.53 (m, 2 H, 1 H(5′), 1 H(6′)); 1.55—1.74 (m, 2 H, 1 H(3′), 1 H(6′)); 1.78—1.95 (m, 2 H, 1 H(4′), 1 H(5′)); 2.17—2.32 (m, 1 H, 1 H(3′)); 3.13 (t, 1 H, 1 H(2′), *J* = 8.8 Hz); 4.60 (s, 2 H, C$\underline{H}_2$OH); 5.07 (s, 1 H, ArOH); 6.73, 7.04 (both d, 1 H each, 1 H(5), 1 H(6)), *J* = 8.0 Hz, *J* = 8.0 Hz); 7.31 (s, 1 H, 1 H(3)). ^{13}C NMR ($CDCl_3$), δ: 12.31 (C(10′)); 20.31 (C(9′)); 21.39 (C(8′)); 27.49 (C(5′)); 33.84 (C(3′)); 39.88 (C(6′)); 45.42, 45.55 (C(4′), C(2′)); 48.08 (C(7′)); 49.85 (C(1′)); 65.63 (CH_2OH); 115.04, 125.70 (C(5), C(6)); 127.66 (C(3)); 129.92, 132.27 (C(2), C(4)); 154.55 (C(1)).

Radical scavenging activity of compounds **6—10** was estimated using the DPPH assay as earlier described.[27] The test compounds at a concentration of 10 μmol L^{-1} were added to a solution of DPPH in MeOH, stirred for 30 min and then the optical density of the solution was measured at λ = 517 nm.

Antioxidant activity of the compounds was estimated by their ability to inhibit the LPO in the mouse brain and testicular homogenates.[28—30] Removed mouse brain and testicles were homogenized in 10% saline (pH 7.4), centrifuged for 10 min to obtain supernatant (S1). The test compounds were added to the supernatant as the solutions in acetone at the final concentrations of 1 and 10 μmol L^{-1}. After 30 min, the LPO was initiated by adding either freshly prepared $FeCl_2$ and ascorbic acids[31,32] (mouse brain homogenate) or H_2O_2 (testicular homogenate). The test samples were incubated at 37 °C for 1—3 h under gentle agitation using a Biosan ES-20 orbital shaker-incubator. The optical density of the samples was measured at λ = 532 nm; the TBA-RS content was calculated using its extinction coefficient of $1.56 \cdot 10^5$ L mol^{-1} cm^{-1}.[30,33]

Hemolytic activity (cytotoxicity), membrane-protective and antioxidant properties were evaluated using mouse red blood cell suspension in phosphate buffered saline (pH 7.4).

Cytotoxicity of compounds **6—10** was measured *in vitro* by their ability to induce erythrocyte hemolysis. The solutions of the compounds in acetone were added to the erythrocyte suspension to a final concentration of 10 μmol L^{-1} and the samples were incubated at 37 °C for 5 h using a Biosan ES-20 orbital shaker-incubator.

Membrane-protective and antioxidant activities of compounds **6—10** were assessed by the degree of inhibition of the induced hemolysis, inhibition of the accumulation of the secondary LPO products, and oxidation of oxyHb in erythrocytes. For this, the test compounds were added to the erythrocyte suspension, to a final concentration of 1 μmol L^{-1}, after 30 min the

hemolysis was initiated by adding a H_2O_2 solution (0.006%). The reaction mixtures were incubated at 37 °C for 5 h under gentle agitation on an orbital shaker-incubator. Every 60 min, an aliquot was taken, centrifuged for 5 min (1600 *g*), and the amount of hemoglobin released was determined by reading optical density of the supernatant at $\lambda = 524$ nm.[34] The degree of hemolysis was calculated as the ratio of the hemoglobin content in supernatant over the hemoglobin content in the completely hemolyzed sample. The TBA-RS content was determined spectrophotometrically as described above. To estimate the accumulation of the products of the hemoglobin oxidation, the absorption spectra were analyzed at $\lambda = 540$—640 nm range. The content of oxyHb, metHb, and ferrylHb was calculated using the corresponding extinction coefficients.[35] The concentration of the heme degradation products formed upon oxidation of the membrane-bound hemoglobin with the reactive oxygen species was determined from the I_{fl} value at a maximum of $\lambda = 464$—468 nm (a Fluorat-2-Panorama spectrofluorometer, excitation at $\lambda = 321$ nm, emission at $\lambda = 400$—600 nm, 2-nm steps).[36—38] Each experiment was performed four-six times. The experimental results in Tables 1—3 are expressed as an arithmetic mean and a standard error (M ± SE). The results were processed statistically using Microsoft Office Excel 2007 and 2010 software.

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