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FULL PAPER

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Synthesis and Antioxidant Capacity of Some Derivatives of Sesamol at the C-6 Position

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Several synthetic approaches (aminomethylation, alkylation, condensation, etc.) have been used to synthesize derivatives based on the sesamol (**1**), natural phenol. The set of methods, including the study of antioxidant activity (AOA) by the ability to inhibit the initiated oxidation of animal lipids, radical scavenging activity, Fe^{2+}-chelation ability, as well as a comparative assessment of membrane-protective activity under the conditions of H_2O_2-induced hemolysis of mice red blood cells (RBCs), was used to analyze the antioxidant potential of the synthesized compounds. The synthesized derivatives have demonstrated different activity in the listed test systems, and we have identified compounds which appear to be most promising for a detailed study of their pharmacological properties.

Keywords: Mannich bases, alkylation, antioxidant activity, oxidative hemolysis, synthesis.

Introduction

Sesamol (benzo[*d*][1,3]dioxol-5-ol, compound (**1**) is a well-known phytophenol originating from sesamin and sesamoline when sesame (*Sesamum indicum* L.) seeds are roasted.[1,2] It is believed that it is the presence of sesamol (**1**) possessing high AOA that makes sesame oil highly resistant to oxidation.[1,3,4] Compound **1** is used as an antioxidant in the food industry and is a promising pharmaceutical raw material, having, in addition to antioxidant properties and the ability to prevent atherosclerosis, anti-inflammatory, anti-aging, antimutagenic, anticarcinogenic, antihepatotoxic, antifungal, and other activities.[2,4,5] Sesamol (**1**) combines phenolic and methylenedioxy moieties in its structure, and the AOA of phenolic compounds of various origins is usually associated with the presence of OH moieties. Benzodioxole derivatives are widespread in the environment and have a wide spectrum of biological activity, including AOA.[5–7] Several studies have already tried to enhance the pharmacological properties of sesamol (**1**) and develop its bioactive analogs using simple chemical approaches, since the introduction of other functional groups may allow to change the biological effect of the synthesized products.[5,8] As such, transformations accompanied by the introduction of aminomethyl, terpene or alkyl moieties into the phenol molecule may be used. These reactions are often used in medicinal chemistry.[9–11] In addition, it has recently been demonstrated that structures containing two sesamol moieties in one molecule are significantly more active than compound **1** in their anti-glycation capacities and $ONOO^-$ scavenging ability.[12] Therefore, the preparation of such analogs is a promising avenue for further study and use (for example, as potential antioxidants for medicinal and technical purposes and in food industry).

The aim of this work was to synthesize and evaluate the antioxidant potential (*in vitro*) of sesamol derivatives at the C-6 position, as well as to identify the most

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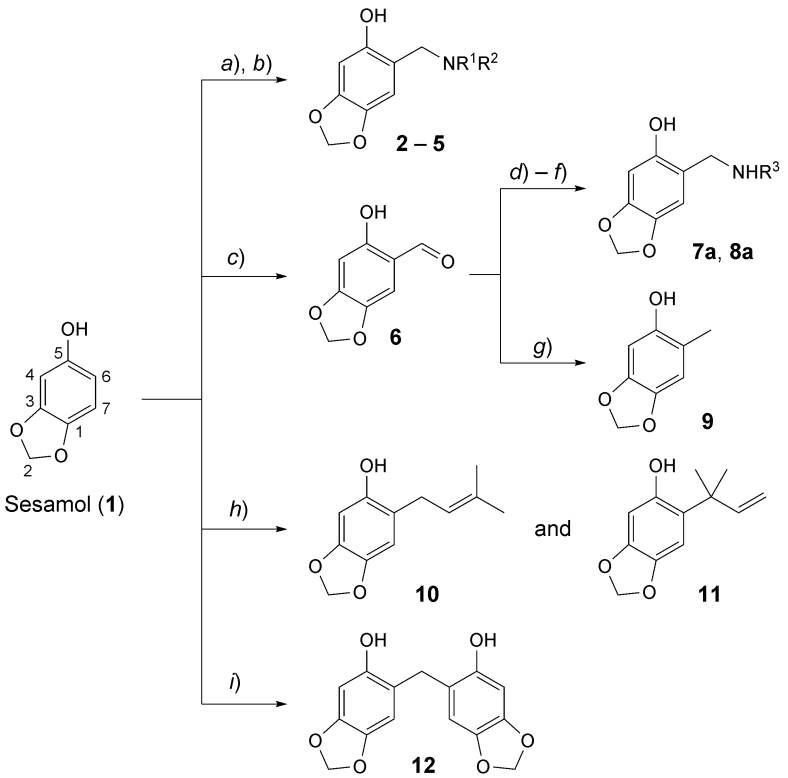
promising products for further studies among them. The presented study is a continuation of our work searching for effective antioxidants among derivatives based on natural and synthetic phenolic compounds.[13–21] In our study, a comprehensive assessment of the AOA of the derivatives was carried out using both simple and widespread methods (e.g., radical scavenging activity (RSA) in the DPPH-test) and more biologically relevant approaches (such as the ability of compounds to inhibit the oxidation of a model substrate containing animal lipids, as well as to protect mammalian RBCs from death under conditions of acute oxidative stress).

Results and Discussion

Aminomethyl derivatives of compound **1** containing a tertiary amine moiety **2–5** were synthesized in 69–76% yields *via* the Mannich reaction using aqueous solution of formaldehyde and the corresponding secondary amines (dimethylamine, piperidine, morpholine, and thiomorpholine); amines **2** and **3** were also intentionally (see below) converted to new hydrochlorides **2a** and **3a**, respectively (*Scheme 1*, paths *a*, *b*).

Aldehyde **6** was synthesized by formylation of sesamol (**1**) using the Duff reaction according to a convenient procedure. Variants of this synthesis for compound **6** have already been described in the literature and included refluxing the reaction mixture in TFA for 2–4 h showing 45–54% yields.[22–24] In our modification to obtain the same product we used the more accessible and cheaper AcOH instead of TFA. The synthesis time was reduced significantly (only 15 min of refluxing), and the yield of the target compound was 61% (*Scheme 1*, path *c*).

Further, aldehyde **6** was used as a starting compound to synthesize intermediate (*in situ*) Schiff bases, the reduction of the double bond of the imine moiety of which resulted in new Mannich bases with butylamine



NR^1R^2 = NMe_2 (**2**), **2**·HCl (**2a**), $N(CH_2CH_2)_2CH_2$ (**3**), **3**·HCl (**3a**), $N(CH_2CH_2)_2O$ (**4**), $N(CH_2CH_2)_2S$ (**5**)
NHR^3 = NHBu·HCl (**7a**), NHC_8H_{17}·HCl (**8a**)

Scheme 1. Synthesis of compounds **2**–**12**. Reagents and conditions: *a*) HCHO (aq. soln.), R^1R^2NH, EtOH, r.t., 3.5 h; *b*) amine **2** or **3**, HCl (EtOH soln.), Et_2O, r.t., 15 min; *c*) hexamethylenetetramine, AcOH (90% aq. soln.), reflux, 15 min; *d*) R^3NH_2, molecular sieves (4 Å), benzene, reflux, 1 h; *e*) $NaBH_4$, MeOH, 0 °C→r.t., 1 h; *f*) HCl (EtOH soln.), Et_2O, r.t., 1 h; *g*) Zn (dust), AcOH, reflux, 2 h; *h*) prenol, montmorillonite KSF, CH_2Cl_2, reflux, 2.5 h; *i*) HCHO, montmorillonite KSF, CH_2Cl_2, reflux, 3 h.

and octylamine moieties. Due to the lability of these secondary amines during storage and/or standing in solution (TLC data), we converted them to more stable hydrochlorides **7a** and **8a**, the yields of the latter being 52% and 65%, respectively (*Scheme 1*, paths *d*–*f*).

Later, we synthesized *C*-substituted derivatives of sesamol (**1**). Thus, the reduction of the formyl moiety of compound **6** using Zn/AcOH gave methylsesamol (**9**) with 73% yield (*Scheme 1*, path *g*). Prenylsesamol (**10**) and its isomer **11** in 42% and 13% yields were synthesized by the alkylation reaction of sesamol (**1**) with prenol under the conditions of heterogeneous catalysis in presence of montmorillonite KSF clay (*Scheme 1*, path *h*). Condensation of compound **1** with paraformaldehyde in presence of the same clay resulted in methylenebisphenol **12** (*Scheme 1*, path *i*), with 66% yield. Catalysis with KSF clay in phenols alkylation and condensation reactions have been previously successfully used in one of our laboratories.[13,14]

The data of ^{1}H, ^{13}C-NMR spectroscopy, IR spectroscopy and elemental analysis of products **3**–**12** was consistent with the expected structures. In the ^{1}H- and ^{13}C-NMR spectra of the obtained compounds, in addition to the signals characteristic of sesamol, we observed signals of additional moieties introduced into the C-6 position (see *Figure S1* – *S52* (*Supporting Information*) for the structures of the products, their NMR and IR spectra).

The substitution in the C-6 position is confirmed by the X-ray diffraction data for amine **4** (*Figure 1*). Compound **4** crystallizes with one molecule in asymmetric unit cell. Molecular conformation is stabilized by relatively strong intramolecular O3-H3···N1 hydrogen bond (O–H, 0.88(3) Å; O···N, 2.693(2) Å; H···N, 1.89(3) Å; ∠OHN, 150(2)°) which additionally stabilizes the observed molecular conformation.

The results obtained on the substitution in the indicated position are also consistent with the literature

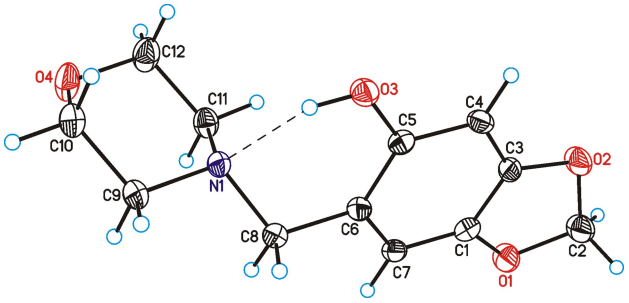


Figure 1. General view of compound **4** in representation of atoms by thermal ellipsoids at 50% probability. Intramolecular H-bond is shown by dashed lines.

on other previously obtained mono-C-6-derivatives of sesamol, such as kakuol and its analogs,[25] Mannich and Betti bases[26–32] diarylbutanes,[33] (het)arylpyrrolidines,[34] allylsesamol.[35]

To assess the antioxidant potential of the synthesized compounds **2**–**5**, **7a**–**12**, we used an already established set of methods.[13,15–21,36,37] Sesamol (**1**) and the standard antioxidant BHT (2,6-di-*tert*-butyl-4-methylphenol)[38,39] were taken as the most suitable reference compounds.

The results of the study on non-cellular model systems are shown in *Table 1*. It was shown that not all compounds actively inhibited Fe^{2+}/ascorbate-initiated oxidation of animal lipids in a heterogeneous medium (oil-water emulsion). Thus, at a concentration of 10 μM, derivatives **8a**–**12** showed high AOA in this system, which follows from a significant decrease in the concentration of TBARS in their presence as compared to the control ($p = 0.021$). In this respect these compounds significantly surpassed sesamol (**1**) ($p = 0.021$) and were comparable in activity to BHT. Previously, it was shown that trolox, an analog of vitamin E, at the same concentration had an extremely weak inhibitory effect on brain lipid peroxidation (LPO) despite the high RSA in the DPPH-test.[19,20,37] In order to identify the most effective compound, we studied this group of derivatives at a concentration of 1 μM: the highest activity was observed in prenylsesamol (**10**) and methylenebisphenol **12**, which, along with compound **11**, were significantly more active than BHT ($p = 0.021$). Derivatives **1**–**5**, **7a** were additionally tested at a concentration of 100 μM. In this group, hydrochloride **7a** was more active than sesamol (**1**) ($p = 0.021$). Thus, the assessment of AOA in the concentration range of 1–100 μM made it possible to arrange the compounds in the following order according to their efficacy: **10**–**12** > BHT > **8a** > **7a** > **1** > **2**–**5**. It should be noted that sesamol (**1**) was also inferior in its activity to BHT in the system of Fe^{2+}-ascorbate initiated mitochondrial LPO.[6]

In order to detail the mechanisms behind such significant differences in AOA between sesamol (**1**) and its derivatives, their Fe^{2+}-chelation ability (Fe^{2+}-CA) and RSA in the DPPH-test (*Table 1*) were studied. The highest Fe^{2+}-CA was found in Mannich bases **2** and **3**, it was slightly lower in amines with morpholine and thiomorpholine moieties **4** and **5**. Notably, the compounds **7a** and **8a** with secondary amine moieties differed only in the trace Fe^{2+}-CA. Apparently, the low activity of these derivatives is due to the protonation of nitrogen atoms in course of synthesis of the corresponding hydrochlorides. This hypothesis was confirmed experimentally

Table 1. Comparative evaluation of AOA (test on the substrate from brain),[a] Fe^{2+}-chelation ability (test with FerroZine™ Iron Reagent), and RSA (test with DPPH) of the derivatives at different concentrations.[b]

Sample	TBARS [nmol/mL]			Fe^{2+}-Chelation ability [%]	RSA [%]	
	10 μM	1 μM	100 μM	10 μM	100 μM	10 μM
Control[c]	60.2 ± 1.0	60.9 ± 0.3	60.9 ± 0.3	–	–	–
Intact[d]	28.1 ± 0.2	40.4 ± 0.6	40.4 ± 0.6	–	–	–
BHT	4.4 ± 0.1	47.9 ± 0.5	–	10.2 ± 0.4	38.1 ± 0.7	3.9 ± 0.1
1	50.4 ± 0.5	–	7.9 ± 0.3	2.2 ± 1.1	82.7 ± 0.1	41.8 ± 1.1
2	54.7 ± 0.3	–	20.4 ± 0.1	85.6 ± 0.9	88.6 ± 0.2	39.0 ± 0.5
3	55.2 ± 1.2	–	10.0 ± 0.4	78.5 ± 1.1	84.7 ± 0.1	34.8 ± 0.7
4	59.2 ± 1.0	–	36.7 ± 0.3	27.6 ± 1.6	93.2 ± 0.0	60.9 ± 0.3
5	53.8 ± 0.6	–	10.6 ± 0.1	31.7 ± 1.9	92.3 ± 0.1	57.7 ± 1.4
7a	47.2 ± 0.6	–	2.8 ± 0.1	0.0 ± 0.0	92.3 ± 0.2	63.8 ± 1.4
8a	5.1 ± 0.1	47.1 ± 0.6	–	4.3 ± 2.2	91.5 ± 0.3	47.2 ± 0.4
9	7.1 ± 0.2	53.0 ± 0.8	–	2.6 ± 1.2	93.3 ± 0.1	33.0 ± 0.7
10	4.2 ± 0.1	10.7 ± 0.3	–	4.2 ± 1.7	93.3 ± 0.6	38.7 ± 0.7
11	4.4 ± 0.0	24.1 ± 0.2	–	2.9 ± 1.6	89.5 ± 0.3	16.9 ± 0.5
12	4.1 ± 0.2	8.5 ± 0.1	–	0.2 ± 0.2	94.6 ± 0.1	39.2 ± 1.4
2a	–	–	–	4.5 ± 2.3	–	–
3a	–	–	–	16.0 ± 0.7	–	–

[a] The ability to inhibit the accumulation of secondary LPO products reacting with 2-thiobarbituric acid (thiobarbituric acid reactive substances, TBARS) in an organic substrate 1 h after initiating LPO with Fe^{2+}/ascorbate was assessed. [b] The values are presented as mean ± SEM ($n = 4$). [c] Control – sample without the compounds in which LPO was initiated. [d] Intact – sample without the compounds in which LPO was not initiated.

when comparing Fe^{2+}-CA of compound pairs **2** and **2a**, **3** and **3a** – in both cases, we observed a sharp decrease in activity when passing from free bases to salts. Derivatives **1**–**5**, **7a**–**12** demonstrated high RSA and significantly surpassed BHT in this parameter at concentrations of 10 and 100 μM ($p = 0.021$ and 0.021). The ability to reduce the stable DPPH radical significantly depended on the structure of the substituent at the C-6 position, which follows from the analysis of data for a concentration of 10 μM. In this way, the introduction of a 2-methylbut-3-en-2-yl substituent led to a significant decrease in the RSA of the corresponding derivative **11** compared to sesamol (**1**) ($p = 0.021$), which is probably due to the steric hindrances of its interaction with the DPPH radical. A high RSA in the DPPH-test for some aminomethyl derivatives based on 6-allylsesamol containing the morpholine moiety was also demonstrated by *Guo et al.*[8] A statistically significant increase in RSA was noted for derivatives **4**, **5**, **7a**, **8a** with morpholinomethyl, thiomorpholinomethyl, butylaminomethyl, and octylaminomethyl moieties, respectively. A similar enhancement of RSA due to the introduction of aminomethyl moieties into the molecule in the *ortho*-position with respect to the phenolic hydroxy group was also recorded in our previous work.[16]

Our results on the parameters of RSA and Fe^{2+}-CA do not explain the ability of derivatives **7a**, **10**–**12** to effectively protect unsaturated fatty acids of brain lipid from Fe^{2+}/ascorbate-initiated oxidation. According to the regression analysis, Spearman's rank correlation coefficient between the indicators characterizing AOA (10 μM) and RSA (10 μM) was −0.41 ($p = 0.12$, $n = 19$), AOA (10 μM) and Fe^{2+}-CA (100 μM) was −0.56 ($p = 0.06$, $n = 12$). It should be noted that often we were unable to identify significant relationships between RSA (DPPH-test) and the parameters obtained using the above test systems. This fact indicates that the ability to interact with radicals is an important, but not the sole mechanism responsible for the AOA compounds in relation to biomolecules and living cells.[18,21] It is known that, in addition to the role of radical occludents and/or metal chelators, antioxidant molecules, including sesamol (**1**), can exhibit surface-active properties, which allow them to reduce the interfacial tension and create more stable reverse micelles in emulsions.[3,40] It can be assumed that significant differences in the AOA of the derivatives considered in this work in the lipid emulsion are the cause of differences in the lipophilicity of the structurally heterogeneous set of the presented compounds. Earlier, we have shown a low AOA of individual Mannich bases in the model of Fe^{2+}/ascorbate-initiated oxidation of an emulsion containing brain lipids, which

may be due to the high polarity of these compounds and the phenomenon of the polar paradox.[16,17] The high AOA of derivative **12** in this particular model can be associated with the presence of two methylenedioxy moieties in the molecule. It is known that this moiety can be actively metabolized both *in vivo* and *in vitro*, and the main metabolic pathway is its recyclization and demethylation to the catechol moiety[7,41] which confer antioxidant properties to the molecule. A high AOA in the same model was previously demonstrated for natural and synthetic allylpolyalkoxybenzenes containing a methylenedioxy moiety in the structure of the molecule, the DPPH-test also showed their low RSA.[36]

Before proceeding to a comparative assessment of MPA derivatives on the model of oxidative hemolysis of mice RBCs, a study of their hemolytic activity (cytotoxicity) was carried out. The mammalian RBCs be used extensively as a simple model system for investigating the potential mechanisms of cell injury and be applied to study the *in vitro* toxicity of different agents.[42] The hemolysis test is a standard procedure for assessing the degree of toxicity and biocompatibility.[43,44] It was shown that compounds **1**–**5**, **7a**–**12** at a concentration of 10 μM do not reduce the viability of RBCs during the entire incubation period. In both control and experimental samples, it is at least 95% (see *Table S1* (*Supporting Information*)), which made it possible to carry out further studies on living cells in a fairly wide range of concentrations.

The results of the study of MPA on the model of H_2O_2-induced hemolysis are shown in *Figure 2* and in *Tables S2–S4* (*Supporting Information*). As follows from the data obtained, the biological activity of the derivatives substantially depended on the concentration of the compounds. Thus, at 10 μM, compounds **4**, **8a**, **10**, and **11** turned out to be the most active. MPA of these derivatives (after 5 h incubation) statistically significantly surpassed ($p = 0.005$, 0.005, 0.003, and 0.011, respectively) the activity of sesamol (**1**) and was comparable to the BHT activity. The effectiveness of trolox at the same concentration under conditions of H_2O_2-induced oxidative stress (decreased hemolysis) was lower than BHT and amounted to about 20%.[37] Interestingly, methylenebisphenol **12**, which showed the highest AOA on the substrate obtained from brain of lab animals (*Table 1*), in this experiment showed a high prooxidant activity, which follows from a sharp increase in the level of hemolysis compared to the control during the entire period of cell incubation (*Table S2* (*Supporting Information*)). Weak prooxidant activity was also noted for Mannich bases **2** and **3**.

The prooxidant activity of sesamol (**1**) was previously identified in studies by *Toorani et al.* on lipid systems different in physical structure and degree of unsaturation. The authors explain this by the relative contribution of antioxidant molecules and their radicals to side

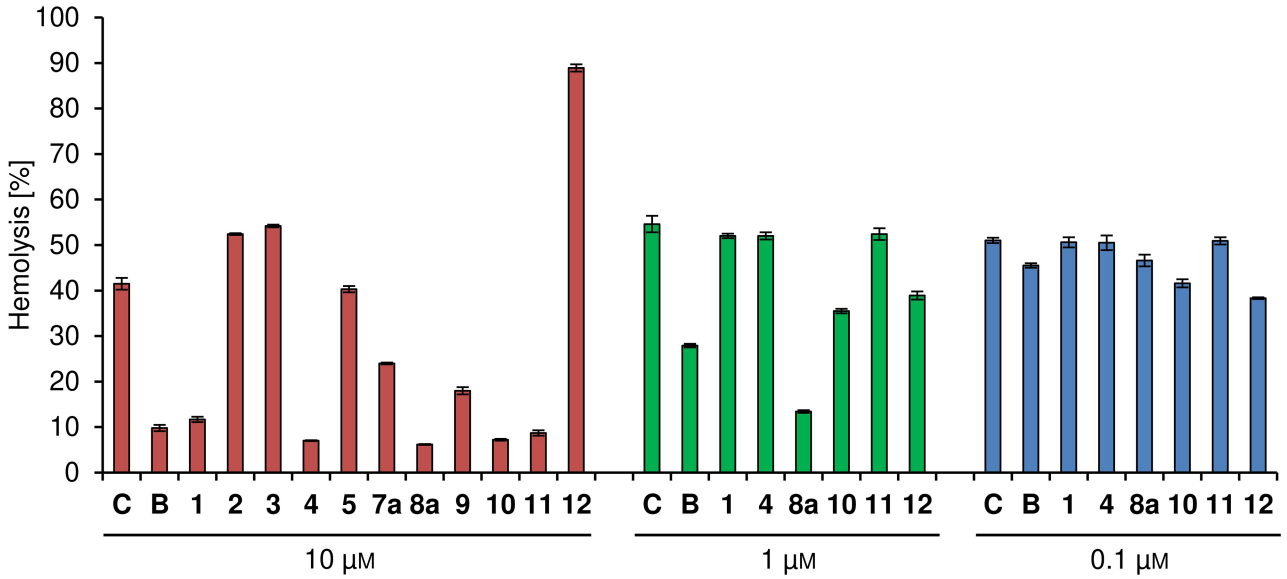


Figure 2. Comparative evaluation of membrane-protective activity of the derivatives at concentrations of 10, 1, and 0.1 μM (model of RBCs oxidative hemolysis; 5 h after injection of H_2O_2). The values are presented as mean ± SEM ($n = 4–10$). C – control sample, B – BHT. See *Tables S2–S4* (*Supporting Information*) for the exact values of parameters.

reactions of chain initiation and propagation, and at the same time the participation of sesamol molecules (**1**) in the main reaction of chain termination. Thus, the activity of sesamol (**1**) is due to the balance between antioxidant and prooxidant potential,[3] which may depend on the ratio of antioxidant and substrate concentrations.

In order to identify the most effective compound, as well as to clarify the biological activity of methylenebisphenol **12**, a similar experiment was carried out for concentrations of 1 and 0.1 μM (*Figure 2* and *Tables S2 – S4* (*Supporting Information*)). Hydrochloride **8a** showed the highest MPA at a concentration of 1 μM, as in the previous experiment, with activity significantly exceeding that of sesamol (**1**) and BHT ($p = 0.014$). Prooxidant activity for methylenebisphenol **12** changed to the antioxidant, in its presence RBCs destruction under the influence of H_2O_2 was significantly lower than in the control ($p = 0.009$). However, this compound was somewhat inferior to BHT ($p = 0.009$). Sesamol (**1**) exhibited extremely low MPA at the indicated concentration, while derivatives **8a**, **10**, and **12** were significantly more active ($p = 0.014$, 0.014, and 0.009, respectively). At a concentration of 0.1 μM prenylsesamol (**10**) and methylenebisphenol **12** were the most effective compounds, they also showed the highest inhibitory efficacy in Fe^{2+}/ascorbate-initiated oxidation of animal lipids in a heterogeneous medium (*Table 1*). It should be noted that sesamol (**1**) and BHT at this concentration only slightly increased cell survival under conditions of acute oxidative stress.

Analysis of the presented data (*Figure 2*) allows us to conclude that MPA of compounds **1**, **4**, **8a**, **10**, **11**, and BHT decreases with decreasing concentration, while methylenebisphenol **12**, on the contrary, exhibits high protective activity only at low concentrations. Thus, at a concentration of 10 μM, Mannich bases **4** and **8a** are the most effective membrane protectors, while at a concentration of 0.1 μM, derivative **12** is the most effective membrane protector.

Although the results of the assessment of RSA in the DPPH-test and Fe^{2+}-CA presented in this work did not allow to predict the biological activity of individual sesamol derivatives upon contact with living cells, the assessment of the considered parameters allows us to assume the mechanisms of action of the compounds. The presence of a high RSA or Fe^{2+}-CA did not yet guarantee a high AOA in a biological model system, and the most biologically relevant model was a heterogeneous medium containing easily oxidized animal lipids. The use of this model made it possible to assume that the most active membrane protectors in the low concentration range can be found among derivatives **8a**–**12** (*Table 1*), which was generally confirmed by the MPA assessment (*Figure 2*).

Conclusions

We have obtained aminomethylated and *C*-substituted sesamol derivatives and carried out a comparative assessment of their antioxidant activity in models (*in vitro*) of various degrees of complexity. The most active antioxidant in biologically relevant test systems (emulsion of easily oxidized animal lipids and RBCs of mammalian blood) is methylenebisphenol **12**, while the highest radical scavenging activity in the DPPH-test was noted for derivatives **4**, **5**, **7a**, and **8a** with morpholinomethyl, thiomorpholinomethyl, butylaminomethyl, and octylaminomethyl moieties, respectively. The obtained data justifies further investigation of the pharmacological activity of the described compounds.

Experimental Section

General

Some physicochemical studies of the synthesized compounds were performed using the equipment of the Center of Collective Usage 'Chemistry', Institute of Chemistry, Komi Scientific Center, 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 $CHCl_3$ ($\delta_H = 7.26$ ppm, $\delta_C = 77.00$ ppm), and DMSO ($\delta_H = 2.50$ ppm, $\delta_C = 39.52$ ppm). The signals of carbon atoms were assigned using ^{13}C-NMR ^{13}C spectra in *J*-modulation mode; some assignments were made using HSQC and NOESY 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 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) or vanillin solution (3.0 g of

vanillin, 130 mL of EtOH, 0.65 mL of concentrated H_2SO_4). Silica gel 60 ('Alfa Aesar', 0.06–0.2 mm) was used for column chromatography.

Commercially available sesamol (**1**), piperidine, thiomorpholine, octylamine, montmorillonite KSF ('Alfa Aesar'), dimethylamine (40% aq. solution, 'Sigma-Aldrich'), morpholine, butylamine, prenol ('Acros Organics'), sodium borohydride ('Daejung Co.'), hexamethylenetetramine (chemically pure grade quality), formaldehyde (37% aq. solution, reagent-grade quality), and paraformaldehyde (paraform, reagent-grade quality) were used without additional purification. Molecular sieves (4 Å) were used after heating at 140 °C for 3 h. Zinc dust was pre-activated.[45] Petroleum ether (PE) with b.p. 65–70 °C was used freshly distilled. Benzene, MeOH, and CH_2Cl_2 were dried according to standard procedures.

The assays were done using the equipment of the Center of Collective Usage 'Molecular Biology', Institute of Biology, Komi Scientific Center, Ural Branch of the RAS. When studying the AOA of the compounds, no animals experiments were performed; the analyzes were carried out exclusively *in vitro*.

Incubation of mice RBCs was carried out in thermostated 'Biosan ES-20' shaker. Absorption was measured using a 'Thermo Spectronic Genesys 20' instrument. Each experiment was repeated 4–10 times. Statistical analysis was assessed by applying Microsoft Office Excel 2010, 2017, and Statistica 6.0 software packages. Experimental data are presented as arithmetic mean values with indication of standard error of mean (SEM). The statistical significance of the differences was assessed using the Mann-Whitney U-test. Regression analyses were performed, and Spearman's rank correlation coefficient was calculated in order to evaluate the interrelation between certain parameters.

Commercially available FerroZine™ Iron Reagent, phosphate buffered saline (PBS, pH 7.4) ('Sigma-Aldrich'), BHT, DPPH, 2-thiobarbituric acid (TBA), trichloroacetic acid ('Alfa Aesar'), $FeSO_4$ (reagent grade), and H_2O_2 (pure grade) solution were used as purchased.

Synthesis of Compounds **2–5**

Formaldehyde (37% aq. solution, 0.123 mL, 1.8 mmol) and amine (1.8 mmol) were added to the solution of sesamol (**1**) (0.207 g, 1.5 mmol) in EtOH (2.5 mL). The reaction mixture was stirred at r.t. for 3.5 h and the solvent was removed under reduced pressure. Amines **2**, **4**, and **5** were isolated by precipitation from PE, PE/EtOH (10:1) or EtOH, respectively, washed with small amount of cold solvent, and dried under reduced pressure. Amine **3** was isolated *via* intermediate hydrochloride: for this purpose, the residue obtained after removal of the solvent was redissolved in Et_2O (6 mL), and 2 N aq. HCl solution (2.5 mL) was added. The mixture was stirred at r.t. for 1 h, the precipitate of hydrochloride was filtered off. After drying under reduced pressure, the hydrochloride was suspended in Et_2O (10 mL), 2 N aq. NaOH solution (5 mL) was added, the mixture was vigorously stirred for 20 min, the solution was diluted with Et_2O (10 mL), and the aqueous layer was separated. The organic layer containing the free base was washed with 2 N aq. NaCl solution until pH ~ 7.0, dried over anhydrous K_2CO_3, and the solvent was removed under reduced pressure.

Hydrochlorides **2a**, **3a** were obtained from amines **2** and **3**. The free base (0.5 mmol) was suspended or dissolved in Et_2O (6 mL), 2 N ethanolic HCl solution was added dropwise to pH < 6.0, the mixture was stirred at r.t. for 15 min (in the case of the compound **2a**, a small amount of EtOH was added to dissolve the oil drops), the precipitate of final hydrochloride was filtered off, washed with small amount of cold Et_2O, and dried at reduced pressure.

6-((Dimethylamino)methyl)benzo[*d*][1,3]dioxol-5-ol (**2**). Light peach powder. $R_f = 0.24$ ($CHCl_3$/MeOH 50:1). M.p. 86–87 °C (M.p. 87–89 °C).[28] Yield: 0.202 g (69%). The spectral characteristics of the compound are consistent with those presented in literature.[28]

6-((Dimethylamino)methyl)benzo[*d*][1,3]dioxol-5-ol hydrochloride (**2a**). Colorless powder. M.p. 174–176 °C. Yield: 0.091 g (78%). The spectroscopic data (IR, NMR, elemental analysis) and spectra are provided in *Supporting Information*.

6-(Piperidin-1-ylmethyl)benzo[*d*][1,3]dioxol-5-ol (**3**). Colorless powder. M.p. 49–51 °C. Yield: 0.247 g (70%). $R_f = 0.35$ ($CHCl_3$/MeOH 50:1). The spectroscopic data (IR, NMR, elemental analysis) and spectra are provided in *Supporting Information*.

6-(Piperidin-1-ylmethyl)benzo[*d*][1,3]dioxol-5-ol hydrochloride (**3a**). Colorless powder. M.p. 145–147 °C. Yield: 0.083 g (87%). The spectroscopic data (IR, NMR, elemental analysis) and spectra are provided in *Supporting Information*.

6-(Morpholinomethyl)benzo[*d*][1,3]dioxol-5-ol (**4**). Beige powder. M.p. 81–82 °C. Yield: 0.270 g (76 %). R_f = 0.66 ($CHCl_3$/MeOH 50:1). The spectroscopic data (IR, NMR, elemental analysis) and spectra are provided in *Supporting Information*.

6-(Thiomorpholinomethyl)benzo[*d*][1,3]dioxol-5-ol (**5**). Colorless powder. M.p. 113–115 °C. Yield: 0.266 g (70 %). R_f = 0.83 ($CHCl_3$/MeOH 50:1). The spectroscopic data (IR, NMR, elemental analysis) and spectra are provided in *Supporting Information*.

Synthesis of Compound **6**

Hexamethylenetetramine (1.40 g, 10 mmol) and sesamol (**1**) (0.69 g, 5.0 mmol) were added to the 90 % aq. AcOH solution (7 mL). The reaction mixture was refluxed for 15 min, cooled to r.t., poured to water (10 mL), extracted with $CHCl_3$ (70 mL), and the organic layer was dried over anhydrous Na_2SO_4. The excess of solvent was removed under reduced pressure, and the product was isolated by column chromatography ($CHCl_3$ as eluent).

6-Hydroxybenzo[*d*][1,3]dioxole-5-carbaldehyde (**6**). Light yellow powder. M.p. 125–127 °C (M.p. 125–127 °C).[22] Yield: 0.506 g (61 %). R_f = 0.46 ($CHCl_3$). The spectral characteristics of the compound are consistent with those presented in literature.[22–24]

Synthesis of Compounds **7a** *and* **8a**

Molecular sieves 4 Å (0.66 g) and amine (1.05 mmol) were added to the solution of aldehyde **6** (0.166 g, 1.0 mmol) in anhydrous benzene (7.5 mL). The mixture was refluxed under an argon atmosphere for 1 h. At the end of the reaction, the molecular sieves were filtered off, washed with $CHCl_3$ and Et_2O, the solvents were removed under reduced pressure. Next, the resulting (*in situ*) Schiff base was dissolved in anhydrous MeOH (15 mL), cooled to 5 °C (bath temperature), and sodium borohydride (0.189 g, 5.0 mmol) was added. The mixture was stirred with warming to r.t. for 1 h. At the end of the reaction, 15 mL of 2 N aq. NaOH solution were added, stirred for 5 min, CH_2Cl_2 (50 mL) was added, and stirring was continued for 20 min. The organic layer was separated; aqueous layer was extracted with CH_2Cl_2 (2× 50 mL). The combined organic solution washed with 2 N aq. NaCl solution to pH ~ 7.0, and the solvent was removed under reduced pressure. At last, the resulting Mannich bases were converted into hydrochlorides (see the synthesis of compounds **2a** and **3a**).

6-((Butylamino)methyl)benzo[*d*][1,3]dioxol-5-ol hydrochloride (**7a**). Colorless powder. M.p. 132–134 °C. Yield: 0.135 g (52 %). The spectroscopic data (IR, NMR, elemental analysis) and spectra are provided in *Supporting Information*.

6-((Octylamino)methyl)benzo[*d*][1,3]dioxol-5-ol hydrochloride (**8a**). Colorless cotton-like powder. M.p. 129–131 °C. Yield: 0.205 g (65 %). The spectroscopic data (IR, NMR, elemental analysis) and spectra are provided in *Supporting Information*.

Synthesis of Compound **9**

Zinc dust (0.392 g, 6.0 mmol) was added to the solution of aldehyde **6** (0.166 g, 1.0 mmol) in glacial AcOH (6 mL), and the mixture was refluxed under stirring for 2 h. At the end of the reaction, the zinc was filtered off, washed with $CHCl_3$ (25 mL), the organic layer was separated and washed with water (35 mL). The solvents were removed under reduced pressure, and the product was isolated by column chromatography (CH_2Cl_2 as an eluent).

6-Methylbenzo[*d*][1,3]dioxol-5-ol (**9**). Light-orange powder. M.p. 58–60 °C (M.p. 58–59 °C).[46] Yield: 0.111 g (73 %). R_f = 0.32 (CH_2Cl_2). The spectroscopic data (IR, NMR, elemental analysis) and spectra are provided in *Supporting Information*.

Synthesis of Compounds **10** *and* **11**

Prenol (0.51 mL, 5 mmol) and montmorillonite KSF (0.345 g) were added to the solution of sesamol (**1**) (0.345 g, 2.5 mmol) in anhydrous CH_2Cl_2 (5 mL), and the mixture was refluxed with stirring for 2.5 h. At the end of the reaction, the clay was separated by filtration, washed with $CHCl_3$ and Et_2O, the filtrate was collected, solvents were removed under reduced pressure, and the products were isolated by column chromatography (eluent – PE/Et_2O 100:1→35:1).

6-(Methylbut-2-en-1-yl)benzo[*d*][1,3]dioxol-5-ol (**10**). Yellow brown oil. Yield: 0.217 g (42 %). R_f = 0.31 (PE/Et_2O 5:1). The spectroscopic data (IR, NMR, elemental analysis) and spectra are provided in *Supporting Information*.

6-((2-Methylbut-3-en-2-yl)benzo[*d*][1,3]dioxol-5-ol (**11**). Yellow brown oil. Yield: 0.067 g (13 %). R_f = 0.58 (PE/Et_2O 5:1). The spectroscopic data (IR, NMR,

elemental analysis) and spectra are provided in *Supporting Information*.

Synthesis of Compound **12**

Paraformaldehyde (0.075 g, 2.5 mmol) and montmorillonite KSF (0.18 g) were added to the solution of sesamol (**1**) (0.138 g, 1.0 mmol) in dry CH_2Cl_2 (5 mL), and the mixture was refluxed with stirring for 3 h. At the end of the reaction, the solids were separated by filtration, washed with $CHCl_3$ (75 mL). The filtrate was collected, and solvents were removed under reduced pressure. The product was isolated by solid-liquid extraction with PE/Et_2O mixture (10:1 v/v, 500 mL), and the solvents were removed under reduced pressure.

6,6′-Methylenebis(benzo[*d*][1,3]dioxol-5-ol) (**12**). Light-beige powder. M.p. 186–188 °C (dec.) (M.p. 183–184 °C (dec.)).[47] Yield: 0.095 g (66%). $R_f = 0.19$ ($CHCl_3$/MeOH 100:1). The spectroscopic data (IR, NMR, elemental analysis) and spectra are provided in *Supporting Information*.

X-ray diffraction Study of Compound **4**

The X-ray experiment was carried out using 'SMART APEX2 CCD' diffractometer ($\lambda(MoK_\alpha) = 0.71073$ Å, graphite monochromator, ω-scans) at 120 K. Collected data were processed by the SAINT and SADABS in APEX2 software package.[48] The structure was solved by the direct methods and refined using the full-matrix least-squares procedure against F^2 in anisotropic approximation. The refinement was carried out with the SHELXTL program.[49] Crystals of compound **4** are orthorhombic, space group $P2_12_12_1$: $a = 8.5043(2)$ Å, $b = 10.6846(2)$ Å, $c = 12.4901(3)$ Å, $V = 1134.91(4)$ Å^3, $Z = 4$, $C_{12}H_{15}O_4N$, $M = 237.25$, $d_{cryst} = 1.389$ g cm^{-3}. $wR^2 = 0.0777$ calculated on F^2_{hkl} for all 2477 independent reflections with $2\theta < 54.0°$, ($GOF = 1.090$, $R = 0.0312$ calculated on F_{hkl} for 2397 reflections with $I > 2\sigma(I)$).

CCDC No. 2050553 contain the supplementary crystallographic data for this work. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

Antioxidant Activity, DPPH Radical Scavenging Activity, and Fe^{2+}-Chelating Ability

AOA was assessed by their ability to inhibit LPO processes in substrates obtained from the brain of lab mice.[50–53] RSA was assessed according to their ability to interact with DPPH according to the established procedure.[54] Fe^{2+}-CA of compounds was determined *via* a test using FerroZine™ Iron Reagent.[55,56]

Toxicity, and Membrane-Protective Activity

We used the RBCs mass and brain tissue (see above) of intact laboratory mice obtained from the scientific collection of experimental animals at the Institute of Biology, Komi Scientific Center, Ural Branch of the RAS and registered as a unique scientific installation of the scientific and technological infrastructure of the Russian Federation (http://www.ckp-rf.ru/usu/471933/). The animals were handled in accordance with the 'Regulations on the vivarium of experimental animals' (protocol No. 1 dated 01.24.2017) taking into account sanitary-hygienic and bioethical aspects. The permission of the Ethical Committee is not necessary.

For the study, a suspension of RBCs from the blood of lab mice in PBS was used. The toxicity of the compounds was assessed *in vitro* by their ability to induce hemolysis of RBCs. MPA was determined by the degree of inhibition of H_2O_2-induced hemolysis, inhibition of the LPO secondary products accumulation. A detailed description of the experiments was presented in our previous works.[13,15–18,36]

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Author Contribution Statement

Evgeny V. Buravlev: design, synthesis, and structure elucidation. Oksana G. Shevchenko: *in vitro* activity assays. Kyrill Yu. Suponitsky: X-ray diffraction study. All

authors prepared, discussed, and approved the manuscript.

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