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SYNTHESIS AND EVOLUTION OF ANTIOXIDANT, ANTICOAGULATION, AND ANTIAGGREGATION ACTIVITIES OF LEVOGLUCOSENONE ADDUCTS CONTAINING METHYL-SUBSTITUTED PHENYL FRAGMENTS

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Adducts of levoglucosenone with *p*-cresol, 3,4-dimethylphenol, and 2,3,6-trimethylphenol were synthesized in one step. The antioxidant, anticoagulation, and antiaggregation activities of the obtained levoglucosenone derivatives were studied. All adducts exhibited anticoagulation and antiaggregation activities at the level of aspirin. The antioxidant activity of the synthesized compounds was assessed from the rate of their reaction with the peroxyl radical of 1,4-dioxane. As a result, all levoglucosenone derivatives examined in the present study were found to reduce the radical-chain oxidation rate. The highest inhibitory activity was found for (1*S*,2*R*,5*R*)-2-(4-hydroxy-2,3,5-trimethylphenyl)-6,8-dioxabicyclo[3.2.1]octan-4-one. The effective inhibition rate constant of this addition product of 2,3,6-trimethylphenol with levoglucosenone was double that of ionol. The obtained results opened up the prospect of synthesizing optically active phenols for further development of drugs with desired pharmacological properties.

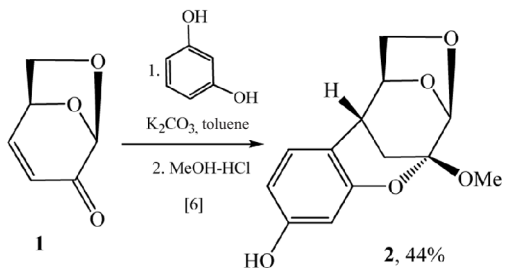
Keywords: levoglucosenone, phenol, antioxidant activity, anticoagulation activity, antiaggregation activity.

Levoglucosenone (**1**) is a pyrolysis product of cellulose and an attractive compound for synthesizing various biologically active compounds and their analogs and precursors. Synthons of prostanoids, nucleosides, and tetrodotoxin and analogs of eleuthesides and other natural compounds are prepared from it [1 – 5]. The presence of reactive centers in levoglucosenone and its solubility in various solvents make it convenient to use in organic synthesis.

Previously, adduct **2** of **1** with resorcinol (Scheme 1) was synthesized by us. Its *in vitro* anticoagulation and antiaggregation activities were studied [6].

Later, antioxidant activity was found for adduct **2** [7, 8]. In continuation of this research, the influence of methyl substituents in the phenol derivatives on the antioxidant, anticoagulation, and antiaggregation activity of the obtained levoglucosenone adducts was studied by us.

Scheme 1



EXPERIMENTAL CHEMICAL PART

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance III 500 MHz spectrometer at operating frequencies 500.13 MHz (^1H) and 125.47 MHz (^{13}C). $^1H(^1H$ COSY, $^1H(^1H$ NOESY, $^1H(^{13}C$ HMBC, and $^1H(^{13}C$ HSQC

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spectra were recorded on the same spectrometer. Mass spectra were recorded on an LCMS-2010 EV HPLC(mass-spectrometer (Shimadzu) with a single quadrupole in positive- and negative-ion modes at capillary potential 4.5 and (3.5 kV, respectively, with electrospray ionization and MeCN(H_2O eluent. Elemental analyses were performed on a Euro-2000 CHNS(O) analyzer. Optical rotation angles were determined on a PerkinElmer 341 polarimeter. Melting points were determined on a Boetius apparatus with a PHMK 05 microscope. Analytical TLC used Sorbfil PTSKh-AF-A plates (Sorbpolimer, Krasnodar). Column chromatography used silica gel (Macherey Nagel 60, particle size 0.063 – 0.2 mm).

General method for adding phenols to levoglucosenone

A solution of levoglucosenone (**1**, 1 mol) and methylphenol (1 mol) in C_6H_6 (7 mL) at 0°C was stirred and treated with $FeCl_3$ (0.2 mol). The temperature was slowly raised to ambient. Stirring was continued until the reaction was finished (from 90 to 150 h) (TLC monitoring). The reaction mixture was treated with saturated aqueous $NaHCO_3$ solution (2 mL). The reaction products were extracted with EtOAc (3 × 10 mL). The extract was dried over $MgSO_4$. The solvent was distilled off. The solid was chromatographed over a silica gel column (eluent petroleum-ether(EtOAc, 2:1).

(1*R*,9*R*,10*R*,13*S*)-4-Methyl-8,11,15-trioxatetracyclo-[7.4.1.1^{10,13}.0^{2,7}]pentadeca-2,4,6-trien-9-ol (3). The reaction time was 150 h. Yield 0.106 g (19%) from **1** (0.30 g). R_f 0.31 (petroleum ether — EtOAc, 2:1). White crystals, mp 147°C. $[\alpha]_D^{20}$ –151° (c 1.0, CH_3OH). PMR ($CDCl_3$, δ, ppm): 1.84 (ddt, 1H, $^2J_{14B\text{-}14A}$ 12.5 Hz, $^3J_{14B\text{-}1}$ 3.5 Hz, $^3J_{14B\text{-}10}$ 1.5 Hz, $^3J_{14B\text{-}13}$ 1.5 Hz, 14-CH_2^B), 2.27 (s, 3H, CH_3), 2.25 (br.s, 1H, OH), 2.50 (dd, 1H, $^2J_{14A\text{-}14B}$ 12.5 Hz, $^3J_{14}$A-1 3.5 Hz, 14-CH_2^A), 2.94 (q, 1H, $^3J_{1\text{-}13}$ 3.5 Hz, $^3J_{1\text{-}14A}$ 3.5 Hz, $^3J_{1\text{-}14B}$ 3.5 Hz, 1-CH), 3.94 (dd, 1H, $^2J_{12B\text{-}12A}$ 7.5 Hz, $^3J_{12B\text{-}13}$ 4.6 Hz, 12-CH_2^B), 4.18 (ä, 1H, $^2J_{12A\text{-}12B}$ 7.5 Hz, 12-CH_2A), 4.44 (ddä, 1H, $^3J_{13\text{-}12B}$ 4.6 Hz, $^3J_{13\text{-}1}$ 3.5 Hz, $4J_{13\text{-}14B}$ 1.5 Hz, 13-CH), 5.23 (d, 1H, $^3J_{10\text{-}14B}$ 1.5 Hz, 10-CH), 6.78 (d, 1H, $^3J_{6\text{-}5}$ 8.2 Hz, 6-CH), 6.84 (d, 1H, $4J_{3\text{-}5}$ 1.6 Hz, 3-CH), 6.97 (dd, 1H, $^3J_{5\text{-}6}$ 8.2 Hz, $^3J_{5\text{-}3}$ 1.6 Hz, 3-CH), ^{13}C NMR ($CDCl_3$, δ, ppm): 20.46 (CH_3), 29.11 (C-14), 39.12 (C-1), 68.38 (C-12), 77.58 (C-13), 96.88 (C-9), 104.29 (C-10), 115.33 (C-6), 124.24 (C-2), 127.44 (C-3), 128.90 (C-5), 129.50 (C-4), 154.02 (C-7). Mass spectrum, *m*/*z* (I_{rel}, %): 235 $[M + H]^+$ (100). Found, %: C 66.59, H 5.59. $C_{13}H_{14}O4$. Calc., %: C 66.66, H 6.02.

(1*R*,9*R*,10*R*,13*S*)-4,5-Dimethyl-8,11,15-trioxatetracyclo-[7.4.1.1^{10,13}.0^{2,7}]pentadeca-2,4,6-trien-9-ol (4). The reaction time was 90 h. Yield 0.25 g (41%) from **1** (0.30 g). R_f 0.25 (petroleum ether — EtOAc, 3:1). White crystals, mp 160° C. $[\alpha]_D^{20}$ –163° (c 1.0, CH_3OH). PMR ($CDCl_3$, δ, ppm): 1.83 (ddt, 1H, $^2J_{14B\text{-}14A}$ 12.5 Hz, $^3J_{14B\text{-}10}$ 1.0 Hz, 14-CH_2B), 2.18 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.48 (dd, 1H, $^2J_{14A\text{-}14B}$ 12.5 Hz, $^3J_{14A\text{-}1}$ 3.2 Hz, 14-CH_2^A), 2.91 (dd, 1H, $^3J_{1\text{-}13}$ 4.6 Hz, $^3J_{1\text{-}14A}$ 3.2 Hz, 1-CH), 3.87 (br.s, 1H, OH), 3.93 (dd, 1H, $^2J_{12}$B-12A 7.5 Hz, $^3J_{12B\text{-}13}$ 4.6 Hz, 12-CH_2B), 4.15 (d, 1H, $^2J_{12A\text{-}12B}$ 7.5 Hz, 12-CH_2^A), 4.42 (ò, 1H, $^3J_{13\text{-}12B}$ 4.6 Hz, $^3J_{13\text{-}1}$ 4.6 Hz, 13-CH), 5.23 (d, 1H, $^3J_{10\text{-}14B}$ 1.0 Hz, 10-CH), 6.70 (s, 1H, 6-CH), 6.79 (s, 1H, 3-CH), ^{13}C NMR ($CDCl_3$, δ, ppm): 18.79 (CH_3), 19.68 (CH_3), 29.26 (C-14), 38.71 (C-1), 68.33 (C-12), 77.65 (C-13), 96.84 (C-9), 104.26 (C-10), 116.65 (C-6), 121.64 (C-2), 127.84 (C-3), 128.17 (C-4), 136.72 (C-5), 154.07 (C-7). Mass spectrum, *m*/*z* (I_{rel}, %): 249 $[M + H]^+$ (100). Found, %: C 67.75, H 6.49. $C_{14}H_{16}O_4$. Calc., %: C 67.73, H 6.50.

(1*S*,2*R*,5*R*)-2-(4-Hydroxy-2,3,5-trimethylphenyl)-6,8-dioxabicyclo[3.2.1]octan-4-one (5). The reaction time was 90 h. Yield 0.11 g (25%) from **1** (0.20 g). R_f 0.53 (petroleum ether — EtOAc, 2:1). White crystals, mp 150° C. $[\alpha]_D^{20}$ –264° (c 1.0, CH_3OH). PMR ($CDCl_3$, δ, ì. ä.): 2.19 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.53 (d, 1H, $^2J_{3B\text{-}3A}$ 16.9 Hz, 3-CH_2B), 3.06 (dd, 1H, $^2J_{3A\text{-}3B}$ 16.9 Hz, $^3J_{3A\text{-}2}$ 8.7 Hz, 3-CH_2A), 3.66 (d, 1H, $^3J_{2\text{-}3A}$ 8.7 Hz, 2-CH), 4.07 (dd, 1H, $^2J_{7B\text{-}7A}$ 7.5 Hz, $^3J_{7B\text{-}1}$ 5.2 Hz, 7-CH_2B), 4.18 (d, 1H, $^2J_{7A\text{-}7B}$ 7.5 Hz, 7-CH_2A), 4.62 (d, 1H, $^3J_{1\text{-}7B}$ 5.2 Hz, 1-CH), 4.81 (br.s, 1H, OH), 5.21 (s, 1H, 5-CH), 6.85 (s, 1H, 6′-CH), ^{13}C NMR ($CDCl_3$, δ, ppm): 12.42 (CH_3), 15.38 (CH_3), 16.07 (CH_3), 37.27 (C-3), 42.20 (C-2), 68.49 (C-7), 77.32 (C-1), 101.39 (C-5), 120.22 (C-1′), 122.66 (C-2′), 126.75 (C-6′), 131.56 (C-3′), 132.20 (C-5′), 151.08 (C-4′), 201.17 (C-4). Mass spectrum, *m*/*z* (I_{rel}, %): 263 $[M + H]^+$ (100). Found, %: C 68.62, H 6.88. $C_{15}H_{18}O_4$. Calc., %: C 68.68, H 6.92.

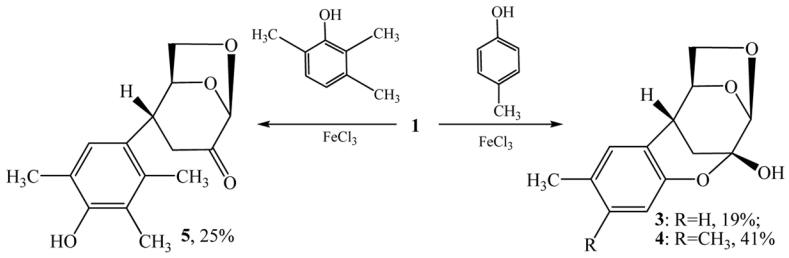
EXPERIMENTAL BIOLOGICAL PART

The experiments were conducted in compliance with requirements of Good Laboratory Practice Rules of the Eurasian Economic Union for Drug Circulation (Decision of the EEC Council of Nov. 3, 2016, No. 81 “On approval of Good Laboratory Practice Rules of the Eurasian Economic Union for Drug Circulation”) [9].

Antiaggregation and anticoagulation activity. Antiaggregation and anticoagulation activity was assessed *in vitro* using 16 healthy donor-male rabbits 18 – 24 years old. The study was approved by the Ethics Committee of Bashkir State Medical University, Ministry of Health of Russia (No. 1 of Feb. 20, 2019). Informed consent was obtained from all study participants for blood collection.

The influence of the compounds on platelet aggregation was studied using the Born method [10] on an AT-02 aggregometer (NPF Medtekh, Russia). Adenosyl diphosphate (ADP) at a concentration of 20 μg/mL and collagen at a concentration of 5 mg/mL (Tekhnologiya-Standart, Russia) were used as aggregation inductors. The influence of the compounds on the maximum aggregation (MA) amplitude, rate of aggregation, and time to reach MA for ADP-induced

Scheme 2

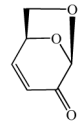
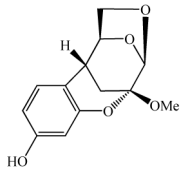
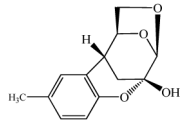
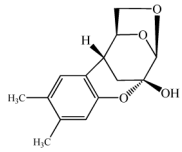
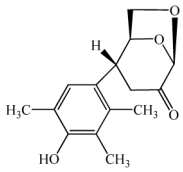


platelet aggregation was studied. The latent period of aggregation, which corresponded to platelet release, was evaluated in the collagen-induced platelet aggregation test. Acetylsalicylic acid (ASA, powder substance, Shandong Xinhua Pharmaceutical Co., Ltd., China) was used as a reference.

The anticoagulation activity was determined by standard clotting tests [11] on a Solar CGL 2110 turbidimetric hemocoagulometer (ZAO SOLAR, Belarus). The activated partial thromboplastin time (APTT), prothrombin time (PT), and fibrinogen concentration were studied by the Clauss method. The reference drug was heparin sodium (heparin sodium, 5000 IU/mL solution for injection, 1-mL ampuls, OAO Sintez, Russia).

According to the literature [9], the influence of the new compounds on the hemostasis system should be evaluated considering the effect of the reference drug. The effects of ASA and heparin sodium were studied long ago, including under laboratory conditions at Bashkir State Medical Univer-

TABLE 1. Effects of Compounds **1 – 5** and Reference Drugs on Platelet Aggregation and APTT in Humans, Me (0.25 – 0.75)

No.	Compound	Latent period, % of control	Maximum amplitude, % of control	Aggregation rate, % of control	Lengthening of APTT, % of control
1		+13.7 (10.6 – 15.9)$^{*,\#}$	–18.9 (17.4 – 21.1)$^{*,\#}$	–21.6 (18.3 – 23.1)$^{*,\#}$	+1.7 (1.5 – 3.7)
2		+7.2 (5.4 – 8.6)$^{*,\#}$	–10.2 (7.6 – 12.3)$^{*,\#}$	–14.9 (12.4 – 17.3)$^{*,\#}$	+2.5 (1.4 – 4.2)
3		+14.5 (13.8 – 17.2)$^{*,\#}$	–19.5 (17.1 – 21.6)$^{*,\#}$	–12.9 (12.1 – 15.7)*	+11.3 (9.4 – 12.1)*
4		+5.1 (4.2 – 7.9)$^{\#}$	–20.5 (18.1 – 24.3)$^{*,\#}$	–28.4 (24.5 – 31.5)$^{*,\#}$	+8.3 (7.4 – 10.2)*
5		+21.4 (19.9 – 24.7)$^{*,\#}$	–17.9 (17.1 – 22.4)$^{*,\#}$	–20.4 (18.1 – 22.3)$^{*,\#}$	+9.8 (8.9 – 11.4)*
	Acetylsalicylic acid	–2.1 (1.1 – 2.6)	–13.7 (10.8 – 16.4)*	–10.5 (7.6 – 12.3)*	+10.5 (8.7 – 13.4)*
	Heparin sodium	–	–	–	+20.3 (19.7 – 21.4)*

Note: $^{*}p \le 0.05$ vs. the control; $^{\#}p \le 0.05$ vs. ASA; compounds vs. heparin sodium for $p \le 0.05$. Mean and 25 and 75 percentiles are given, $n = 6$.

sity, Ministry of Health of Russia [11]. The screening concentrations were the calculated IC_{20} values of the reference drugs, which were 2×10^{-3} M for ASA and 5×10^{-4} g/mL for heparin sodium.

Antioxidant activity was studied by a volumetric method using radical-chain oxidation of 1,4-dioxane as a model. 1,4-Dioxane was the oxidation substrate; chlorobenzene, the solvent for the initiator (azobisisobutyronitrile, AIBN), which was prepared for the tests as before [12]. 1,4-Dioxane was oxidized by atmospheric oxygen at 60°C. Absorption of oxygen was monitored using a universal differential manometer. The effective inhibition rate constant fk_7, which characterized the antioxidant activity of the test compound, was found from the dependence of the oxidation rate of 1,4-dioxane on the concentration of the tested compound, which was transformed into the coordinates of Eq. 1 (Fig. 1).

$$F = w_0 \cdot w^{-1} - w \cdot (w_0)^{-1} = fk_7 \, [\mathrm{InH}] \, (2k_6 \, w_i)^{-0.5}, \qquad (1)$$

where [InH] is the initial concentration of the tested compound (M); w_0 and w, the initial oxygen absorption rate without and with InH, respectively (mol·L^{-1}·s^{-1}); $2k_6$ and fk_7, rate constants for chain breaking oxidation by recombination of peroxyl radicals of 1,4-dioxane.

Statistical analysis used the Statistica 10.0 program suite (StatSoft Inc., USA). The distributions were checked for normalcy using the Shapiro(Wilk criterion. The mean and 25 and 75 percentiles and the minimum and maximum values were calculated to describe variational series. One-factor dispersion analysis (if the dataset obeyed normal distribution laws and the dispersions of all sets were equal; F-criterion) or the Kruskal–Wallis test (if the dataset did not obey normal distribution laws; H-criterion) was performed. The critical level of significance p for statistical criteria was set at 0.05.

RESULTS AND DISCUSSION

Crystalline adducts **3**, **4**, and **5** were synthesized by reacting levoglucosenone (**1**) with *p*-cresol, 3,4-dimethylphenol, and 2,3,6-trimethylphenol in equimolar amounts in C_6H_6 in the presence of $FeCl_3$ (Scheme 2). The reaction times and yields depended on the number of substituents and were 150 h and 18.9%, 90 h and 41%, and 90 h and 25%, respectively. The low yield and long reaction time in the first instance were most probably related to the lower reactivity of *p*-cresol in the electrophilic substitution reaction as compared to 3,4-dimethylphenol with two electron-donating substituents. The drop in yield in the last instance was presumably explained by steric hindrance and the lack of a ketalization step that drove the transformation toward more complete product formation.

The structures of **3 – 5** were proved using PMR and ^{13}C NMR spectra and 2D standard correlation methods. The lack of resonances for the carbonyl atom of the carbohydrate moiety in the ^{13}C NMR spectra of **3** and **4** together with a resonance for quaternary C atoms at 96.88 and 96.84 ppm, respectively, were indicative of the formation of the ketal. However, the ketone of adduct **5** resonated at 201.17 ppm in the ^{13}C NMR spectrum.

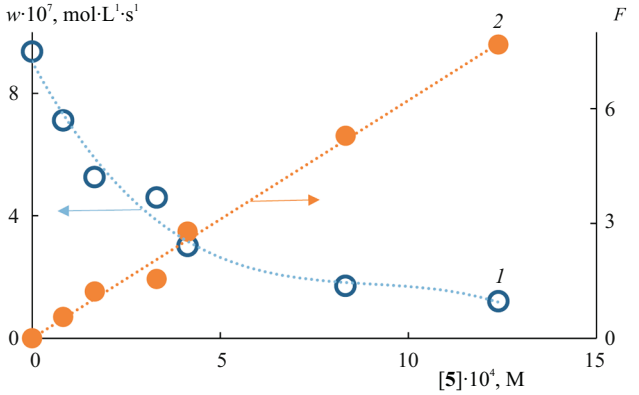


Fig. 1. Dependence of radical-chain oxidation rate of 1,4-dioxane on concentration of compound **5** (*1*); transformation of dependence in coordinates of Eq. 1 (*2*). Along the abscissa, concentration of **5** (M); along the ordinate, oxidation rate (mol·L$^{(1}$·s$^{(1}$) (left) and effectiveness of inhibition by **5** (right). Reaction conditions: [1,4-dioxane] = 9.8 M; [AIBN] = 1.04·10$^{(2}$ M; 60°C.

As expected, the addition of the aromatic phenols to **1** occurred with strict control by the 1,6-anhydro bridge. The transformations of *p*-cresol and 3,4-dimethylphenol finished with ketalization of the ketone because of steric factors [6].

Anticoagulation and antiaggregation activity *in vitro* of compounds 1 – 5

Previous research results [6] established that **1** and ketal **2** exhibited antiaggregation activity exceeding that of the reference drug ASA according to the MA values (Table 1). Levoglucosenone (**1**) and ketal **2** were more effective than ASA at lengthening the latent period of aggregation, which characterized the extent of platelet release. The platelet aggregation rate, like for ASA, decreased for all these derivatives. Compounds **3**, **4**, and **5** exhibited antiaggregation activities exceeding the values of ASA and ketal **2** for lowering the MA of platelet aggregation. It is noteworthy that all compounds caused hypocoagulation, increasing the APTT by

TABLE 2. Effective Reaction Rate Constant of 1,4-Dioxane Peroxyl Radical with Compounds **2 – 5**

Compound	Interval of tested compound concentration change, M	fk_7, L·mol^{-1}·s^{-1} (60°C)
3	$(0.40 – 8.33) \cdot 10^{-3}$	$(3.56 \pm 0.41) \cdot 10^3$
2	$(1.33 – 8.67) \cdot 10^{-3}$	$(5.01 \pm 0.36) \cdot 10_3$
4	$(0.58 – 5.00) \cdot 10^{-3}$	$(6.96 \pm 0.36) \cdot 10^3$
5	$(0.08 – 12.40) \cdot 10^{-3}$	$(62.79 \pm 2.46) \cdot 10^3$
Ionol [12, 13]	-	$28 \cdot 10^3$

1.7 – 11.3% as compared to the control and did not affect the fibrinogen concentration and prothrombin time. Compounds **2**, **3**, and **4** had the greatest anticoagulant potential. However, these compounds were inferior to heparin sodium, which lengthened the APTT by an average of 20.3%.

The antioxidant activity of **1 – 5** was evaluated from the rate of their reaction with peroxyl radicals formed in water via initiated oxidation of 1,4-dioxane. It was found that **1** did not suppress the radical oxidation rate of 1,4-dioxane. Therefore, it did not react with peroxyl radicals. Compounds **2 – 5** exhibited antioxidant properties. Figure 1 used the adduct of **1** with 2,3,6-trimethylphenol (**5**) as an example to show that the oxidation rate decreased if its concentration was increased. The transformation of this dependence into coordinates of Eq. 1 allowed the effective rate constant of the reaction of **5** with peroxyl radicals of 1,4-dioxane to be calculated. Data obtained for **2 – 4** were analogously processed. Table 2 presents the results and shows that all derivatives of **1** exhibited antioxidant activity. Compound **5** gave the best results. The effective rate constant of the reaction for it was $fk_7 = 6.3 \cdot 10^4$ L·mol^{-1}·s^{-1}, which was more than double that found for the classical inhibitor ionol under these same conditions, $fk_7 = 2.8 \cdot 10^4$ L·mol^{-1}·s^{-1} [12, 13].

Thus, adducts of levoglucosenone with *p*-cresol, 3,4-dimethylphenol, and 2,3,6-trimethylphenol were synthesized in one step. Their antioxidant, anticoagulation, and antiaggregation activities were studied. All adducts were observed to exhibit anticoagulation and antiaggregation activity at the level of ASA. The antioxidant activity of (1*S*,2*R*,5*R*)-2-(4-hydroxy-2,3,5-trimethylphenyl)-6,8-dioxabicyclo[3.2.1]octan-4-one was double that of ionol. The results were of special interest for developing drugs based on levoglucosenone adducts with given pharmacological properties.

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Conflict of interest

We declare no conflict of interest.

Contributions of authors

FAV formulated the idea and research goals and problems, developed the synthesis methodology, and analyzed and summarized literature data; LKhF analyzed and summarized the research results, wrote the article text, edited and wrote the article, and described the spectral characteristics of the synthesized compounds; LShK performed the experiments of the chemical part of the article; LRYa analyzed and summarized the research results and wrote the article on the antioxidant activity of the synthesized compounds; ARM performed the experiments on the antioxidant activity of the synthesized compounds; RLS theoretically justified the antioxidant activity of the synthesized compounds; ZAV performed the experiments on the anticoagulation and antiaggregation activities of the synthesized compounds; AVS analyzed and summarized the research results and wrote the article on the anticoagulation and antiaggregation activity of the synthesized compounds.

REFERENCES

1. Z. J. Witczak (ed.), *Levoglucosenone and Levoglucosans: Chemistry and Applications*, ATL Press, Mount Prospect (1994).
2. M. S. Miftakhov, F. A. Valeev, and I. N. Gaisina, *Russ. Chem. Rev.*, **63**, 869 – 882 (1994); doi: 10.1070 / RC1994v063n10ABEH000123.
3. Z. J. Witczak and K. Tatsuta (eds.), *Carbohydrate Synthons in Natural Products Chemistry: Synthesis Functionalization, and Applications*, American Chemical Society, Washington (2003).
4. A. M. Sarotti, M. M. Zanardi, and R. A. Spanevello, *Curr. Org. Synth.*, **9**, 439 – 459 (2012); doi: 10.2174 / 157017912802651401.
5. M. B. Comba, Y.-H. Tsai, A. M. Sarotti, et al., *Eur. J. Org. Chem.*, **2018**(5), 590 – 604 (2018); doi: 11.10.1002 / EJOC.201701227.
6. L. Kh. Faizullina, Yu. A. Khalilova, F. A. Valeev, et al., *Khim. Geterotsikl. Soedin.*, **57**, 966 – 969 (2021); doi: 10.1007 / s10593-021-03007-0.
7. L. Kh. Faizullina, Yu. A. Khalilova, Yu. S. Galimova, et al., *Butlerov. Soobshch.*, **65**(11), 108 – 113 (2021).
8. A. R. Migranov, Yu. A. Khalilova, L. R. Yakupova, et al., *Vestn. Bashk. Univ.*, **29**(4), 881 – 885 (2022); doi: 10.33184 / bulletin-bsu-2022.4.11.
9. A. N. Mironov (ed.), *Handbook for Preclinical Drug Studies* [in Russian], Vol. 1, Grif i K, Moscow (2012).
10. K. G. Gurevich, A. L. Urakov, P. P. Purygin, et al., *Khim.-farm. Zh.*, **56**(11), 21 – 27 (2022); doi: 10.30906 / 0023-1134-2022-56-11-21-27.
11. K. G. Gurevich, A. L. Urakov, A. V. Basantsev, et al., *Khim.-farm. Zh.*, **55**(2), 8 – 12 (2021); doi: 10.30906 / 0023-1134-2021-55-8-15-20.
12. L. R. Yakupova, V. R. Khairullina, A. Ya. Gerchikov, R. L. Safiullin, et al., *Kinet. Katal.*, **49**(3), 387 – 391 (2008); doi: 10.1134 / S0023158408030075.
13. L. Valgimigli, *Biomolecules*, **13**(9), 1291 – 1324 (2023); doi: 10.3390 / biom13091291.