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SYNTHESIS OF 5-(HYDROXY-, CHLORO-, BROMOMETHYL)FURAN-2-ENONES BASED ON FRUCTOSE AND THEIR ANTIOXIDANT ACTIVITY

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New enones were synthesized from 5-hydroxymethylfurfurol (5-HMF) and its derivatives using Wittig reactions of various phosphoranes. The synthesized enones were observed to affect free-radical oxidation in model systems, in particular, to suppress generation of reactive oxygen species.

Keywords: 5-hydroxymethylfurfurol, phosphorus ylides, Wittig reaction, phosphoranes, imides, enones, antioxidant activity.

Renewable and easily accessible natural resources could be exhausted in the near future at the existing rate of utilization so that alternative processes for renewable resources, in particular plant carbohydrates, must be developed [1]. The platform furan compound 5-hydroxymethylfurfurol (5-HMF) and its derivatives [2–8] have recently received heightened interest because they can be produced from various carbohydrates.

Herein, syntheses of new enones based on Wittig reactions of 5-HMF and its derivatives (obtained from fructose) with various phosphoranes are reported. The last included phenyl(triphenylphosphoranylidene)ethanone (**1**), benzyl(triphenylphosphoranylidene)succinimide (**2**), phenyl(triphenylphosphoranylidene)succinimide (**3**), *o*-fluorophenyl(triphenylphosphoranylidene)succinimide (**4**), and methyl(triphenylphosphoranylidene)acetate (**5**). The antioxidant activity of the synthesized compounds was studied.

5-HMF, which was obtained from fructose by refluxing in DMSO without isolation from the reaction mixture, underwent Wittig reactions with the ylides at room temperature to form compounds **6**–**9** (Scheme 1). The reaction products were isolated by flash chromatography over silica gel. Use of methyl 2-(triphenylphosphoranylidene)acetate (**5**) formed a mixture of the *cis*- and *trans*-isomers **10a** and **10b** in a 4:1 ratio with the *trans*-isomer dominating. The ylide obtained from maleic anhydride did not react even with thermal activation, for which resin formation was observed.

The Wittig reaction according to the given method (one-pot) turned out to be ineffective (product yields of **11**–**17** <10%) for 5-bromomethylfurfurol (5-BMF) and 5-chloromethylfurfurol (5-CMF). However, the Wittig reaction formed primarily *trans*-enones **11a**, **12**–**14**, **15a**, **16**, and **17** if pure halo-derivatives 5-BMF and 5-CMF were used [10, 11] (Scheme 2). The reaction products were isolated by flash chromatography over silica gel. *cis*-Isomers **11b** and **15b** formed if methyl 2-(triphenylphosphoranylidene)acetate (**5**) was used as the Wittig reagent. An insignificant amount of phosphonium salt **14** precipitated during preparation of 5-(bromomethyl)furan-2-enone (**13**).

The structures of the pure isolated compounds were proven using physicochemical analytical methods. PMR spectra had characteristic resonances in the range δ 6.3–6.6 ppm for the olefinic protons. The enone structures were confirmed more exactly by 2D NMR HSQC and HMBC experiments.

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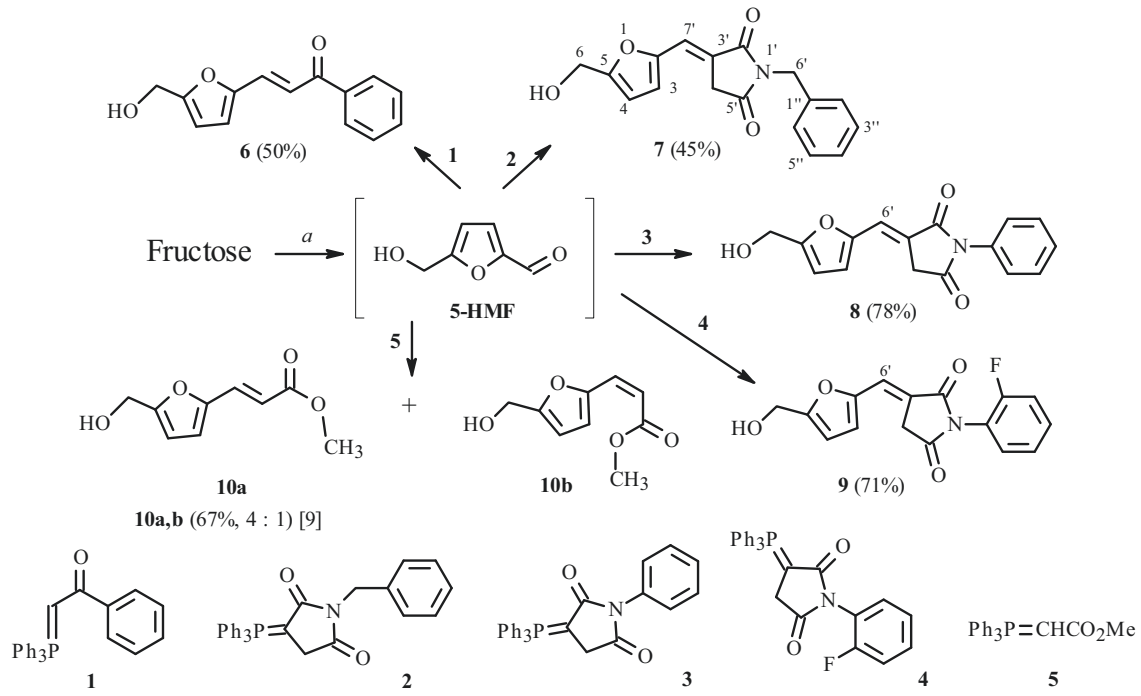
TABLE 1. Chemiluminescence Parameters of Model System Generating Reactive Oxygen Species (ROS) in the Presence of New HMF Derivatives (0.1 mL of Added Sample), %

Compound	Light sum	Spontaneous emittance	Flash	Maximum emittance	Slope
Control	100	100	100	100	100
5-Hydroxy-6-methyluracil	69*	25*	68*	30*	15*
5-HMF	59*	138	98*	82*	100
6	32*	85*	41*	35*	6*
7	32*	11*	62*	33*	9*
8	36*	131	50*	39*	9*
9	91*	100	132	87*	151
10a	37*	28*	46*	40*	23*
10b	40*	85*	41*	37*	6*
11a	14*	104	67*	18*	28*
12	71*	70*	72*	66*	100
13	63*	55*	73*	52*	90*
14	96*	94*	78*	114*	90*
15	44*	13*	68*	72*	90*
16	67*	80*	91*	78*	100
17	36*	58*	66*	45*	100

*Statistically significant differences vs. the control.

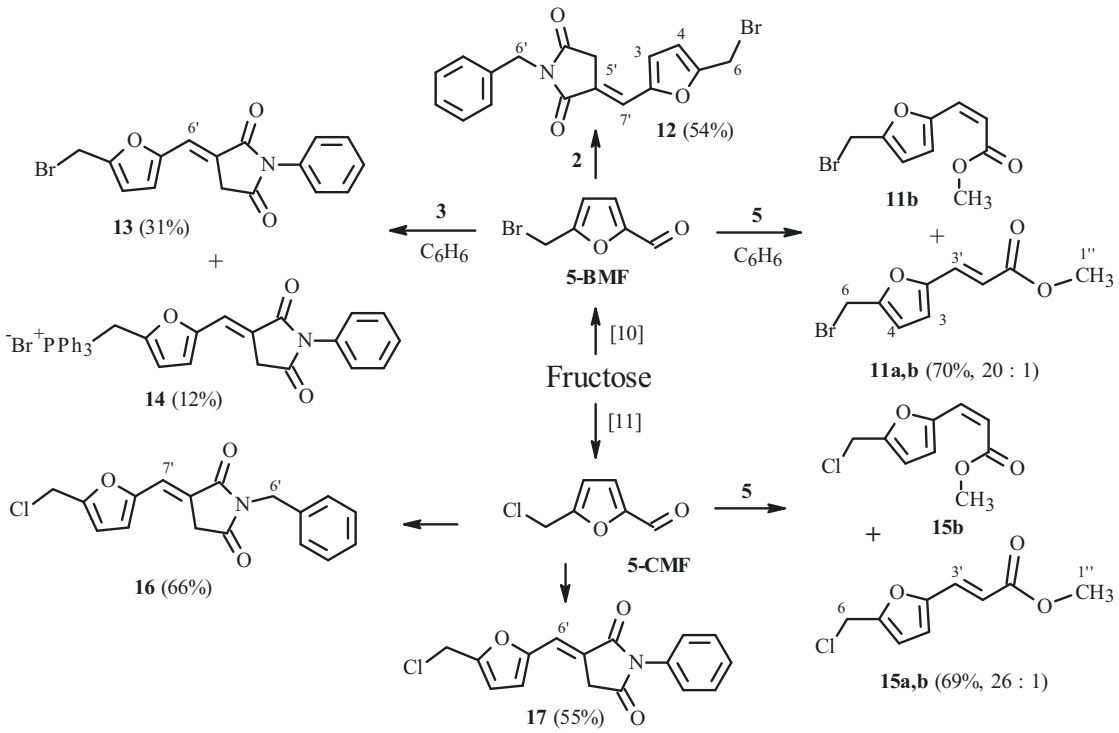


a. Δ, 150°C, 2.5 h, DMSO

Scheme 1

The antioxidant activity of the compounds was studied in chemiluminescence model systems using luminol, sodium citrate, and iron. Table 1 presents the experimental results.

Table 1 shows that all synthesized compounds possessed antioxidant activity of various strengths. Compounds **6** and **7** decreased to the greatest extent the light sum and maximum emission amplitude in model reactive oxygen species (ROS) systems. This was indicative of their ability to suppress the formation of oxygen radicals better than 5-hydroxy-6-methyluracil (by 2 times) and to quench chemiluminescence in the model systems related to generation of ROS.



Scheme 2

Thus, the synthesized compounds could suppress formation of ROS, which was of practical significance with respect to the discovery of new biologically active compounds based on 5-HMF derivatives.

EXPERIMENTAL

Equipment at the Khimiya Center for Collective Use, UfIC, UFRC, RAS, was used in the work. NMR spectra were recorded in $CDCl_3$ with TMS internal standard on a Bruker Avance III 500 high-resolution spectrometer (operating frequency 500 MHz for ^1H and 125.76 MHz for ^{13}C). Elemental analyses were performed on a Euro EA-3000 C,H,N,S-analyzer. The course of reactions and purity of products were monitored by TLC on Sorbfil PTSKh-AF-A plates using petroleum ether–EtOAc (4:1).

General Method for Preparing 6–9. Crystalline fructose (Sladis, 2.8 mmol, 0.5 g; natural fructose sugar, Arkom LLC) was dissolved in DMSO (2.5 mL) and heated to 150°C for 2 h with constant stirring (67% yield of 5-HMF). The reaction mixture was cooled to room temperature, treated with the appropriate phosphorane (2 mmol), held at room temperature for 1 h, poured into distilled H_2O (5 mL), treated with NaCl (1 g), and extracted (3 ×) with EtOAc. The extract was dried over $MgSO_4$ and evaporated. The products were separated by column chromatography over silica gel.

(2′*E*)-3′-[5-(Hydroxymethyl)furan-2-yl]-1′-phenylprop-2′-en-1′-one (6). Yield 45%, dark-yellow powder, mp 86–89°C. IR (m.o., ν, cm^{-1}): 702, 778, 1016, 1214, 1462, 1600, 1663, 1672. ^1H NMR ($CDCl_3$, δ, ppm, J/Hz): 3.24 (1H, br.s, OH), 4.62 (2H, s, H-6), 6.31 (1H, d, J = 3.2, H-4), 6.62 (1H, d, J = 3.2, H-3), 7.31–7.58 (5H, m, H-2′, 3′, 2″, 4″, 6″), 7.95 (2H, m, H-3″, 5″). ^{13}C NMR ($CDCl_3$, δ, ppm): 57.25 (CH_2, C-6), 110.19 (CH, C-4), 117.58 (CH, C-3), 118.88 (CH, C-3′), 128.46 (CH × 2, C-2″, 6″), 128.63 (CH × 2, C-3″, 5″), 130.77 (CH, C-2′), 132.91 (CH, C-4″), 137.97 (C, C-1″), 151.37 (C, C-2), 157.30 (C, C-5), 190.10 (O=C, C-1′). Found, %: C, 73.59; H, 5.32. $C_{14}H_{12}O_3$. Calcd, %: C, 73.67; H, 5.30; O, 21.03.

(3′*Z*)-1′-Benzyl-3′-{[5-(hydroxymethyl)furan-2-yl]methylidene}pyrrolidine-2′,5′-dione (7). Yield 75%, dark-yellow powder, mp 165–168°C. ^1H NMR ($CDCl_3$, δ, ppm, J/Hz): 3.67 (2H, s, H-4′), 3.75 (1H, br.s, OH), 4.49 (2H, s, H-6), 4.68 (2H, s, H-6′), 6.51 (1H, d, J = 3.4, C-4), 6.92 (1H, d, J = 3.4, H-3), 7.24 (1H, s, H-7′), 7.21–7.44 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$, δ, ppm): 34.03 (CH_2, C-4′), 41.45 (CH_2, C-7′), 55.83 (CH_2, C-6), 109.85 (CH, C-4), 117.90 (CH, C-3), 121.14 (C, C-7′), 127.89 (2CH, C-2″, 6″), 127.27 (CH, C-4″), 128.37 (2CH, C-3″, 5″), 135.79 (C, C-3′), 136.23 (C, C-1″), 149.73 (C, C-2), 159.15 (C, C-5), 170.09 (O=C, C-2′), 174.23 (O=C, C-5′). Found, %: C, 68.88; H, 5.12; N, 4.79. $C_{17}H_{15}NO_4$. Calcd, %: C, 68.68; H, 5.09; N, 4.71; O, 21.53.

(3′*E*)-3′-{[5-(Hydroxymethyl)furan-2-yl]methylidene}-1′-phenylpyrrolidine-2′,5′-dione (8). Yield 78%, dark-yellow powder, mp 183–186°C. IR (m.o., ν, cm^{-1}): 669, 694, 759, 1164, 1217, 1388, 1456, 1651, 1687, 1768. ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 3.71 (2H, s, H-4′), 4.13 (1H, br.s, OH), 4.49 (2H, s, H-6), 6.44 (1H, d, J = 3.2, H-4), 6.83 (1H, d, J = 3.2, H-3), 7.34 (1H, s, H-6′), 7.27–7.49 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$, δ, ppm): 34.53 (CH_2, C-4′), 56.21 (CH_2, C-6), 110.13 (CH, C-4), 118.14 (CH, C-3), 120.02 (CH, C-6′), 121.67 (C, C-3′), 127.32 (2CH, C-2″, 6″), 128.43 (CH, C-4″), 129.01 (2CH, C-3″, 5″), 132.99 (C, C-1″), 150.40 (C, C-2), 159.52 (C, C-5), 169.93 (O=C, C-2′), 174.18 (O=C, C-5′). Found, %: C, 67.85; H, 4.63; N, 4.95. $C_{16}H_{13}NO_4$. Calcd, %: C, 67.84; H, 4.63; N, 4.94; O, 22.59.

(3′*E*)-1′-(6″-Fluorophenyl)-3′-{[5-(hydroxymethyl)furan-2-yl]methylidene}pyrrolidine-2′,5′-dione (9). Yield 71%, brown powder, mp 195–198°C. IR (m.o., ν, cm^{-1}): 669, 721, 765, 813, 904, 1015, 1160, 1378, 1462, 1505, 1648, 1700, 1769. ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 3.78 (2H, s, H-4′), 4.02 (1H, br.s, OH), 4.42 (2H, s, H-6), 6.43 (1H, d, J = 3.1, H-4), 6.90 (1H, d, J = 3.1, H-3), 7.34 (1H, s, H-6′), 7.23–7.52 (4H, m, C_6H_4). ^{13}C NMR ($CDCl_3$, δ, ppm): 34.72 (CH_2, C-4′), 56.23 (CH_2, C-6), 110.28 (C, C-3′), 110.55 (CH, C-4), 116.70 (CH, J = 18.9, C-2″), 119.02 (CH, C-3), 120.31 (C, J = 12.6, C-6″), 120.92 (CH, C-6′), 125.32 (CH, C-4″), 130.44 (CH, C-3″), 131.64 (CH, C-5″), 150.12 (C, C-2), 157.45 (C-F, J = 250.1, C-1″), 159.70 (C, C-5), 169.45 (O=C, C-2′), 173.54 (O=C, C-5′). Found, %: C, 63.72; H, 3.98, N, 4.62. $C_{16}H_{12}NO_4F$. Calcd, %: C, 63.79; H, 4.01; F, 6.31; N, 4.65; O, 21.24.

Method for Preparing 11–17. Pure 5-BMF and 5-CMF were prepared by the known methods [10, 11] and reacted with various phosphoranes in equimolar amounts in C_6H_6 at room temperature. The course of the reactions was monitored by TLC until the starting compounds disappeared. Compounds were isolated pure by column chromatography over silica gel.

Methyl (2′*E*)-3′-[5-(Bromomethyl)furan-2-yl]prop-2′-enoate (11a). Yield 67%, white powder, mp 102–104°C. IR (m.o., ν, cm^{-1}): 644, 709, 817, 964, 999, 1168, 1196, 1209, 1272, 1311, 1516, 1635, 1643, 1700. ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 3.77 (3H, s, H-1″), 4.43 (2H, s, H-6), 6.34 (1H, d, J = 15.7, H-2′), 6.42 (1H, d, J = 3.3, H-3), 6.51 (1H, d, J = 3.3, H-4), 7.34 (1H, d, J = 15.7, H-3′). ^{13}C NMR ($CDCl_3$, δ, ppm): 22.81 (CH_2, C-6), 51.67 (CH_3, C-5′), 112.21 (CH, C-4), 115.78 (CH, C-2′), 116.44 (CH, C-3), 130.56 (CH, C-3′), 151.47 (C, C-2), 152.47 (C, C-5), 167.19 (O=C, C-1′). Found, %: C, 44.19; H, 3.69; Br, 32.49. $C_9H_9BrO_3$. Calcd, %: C, 44.11; H, 3.70; Br, 32.60; O, 19.59.

Methyl (2′*Z*)-3′-[5-(Bromomethyl)furan-2-yl]prop-2′-enoate (11b). Yield 3%, transparent oil. ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 3.77 (3H, s, H-1″), 4.49 and 5.18 (1H each, s, H-6), 5.79 (1H, d, J = 12.9, H-2′), 6.48 (1H, d, J = 3.4, H-3), 6.72 (1H, d, J = 12,9, H-3′), 7.64 (1H, d, J = 3.4, H-4). ^{13}C NMR ($CDCl_3$, δ, ppm): 23.05 (CH_2, C-6), 51.42 (CH_3, C-1″), 112.72 (CH, C-4), 115.16 (CH, C-2′), 117.98 (CH, C-3), 130.15 (CH, C-3′), 151.29 (C, C-2), 151.44 (C, C-5), 166.28 (O=C, C-1′). Found, %: C, 44.12; H, 3.7; Br, 32.54. $C_9H_9BrO_3$. Calcd, %: C, 44.11; H, 3.70; Br, 32.60; O, 19.59.

1′-Benzyl-3′-{[5-(bromomethyl)furan-2-yl]methylidene}pyrrolidine-2′,5′-dione (12). Yield 54%, yellow powder, mp 183°C. IR (m.o., ν, cm^{-1}): 642, 743, 799, 978, 1018, 1076, 1156, 1219, 1346, 1391, 1456, 1649, 1695, 1758. ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 3.64 (2H, s, H-4′), 4.49 (2H, s, H-6), 4.79 (2H, s, H-6′), 6.48 (1H, d, J = 3.4, H-4), 6.53 (1H, d, J = 3.4, H-3), 7.39 (1H, s, H-7′), 7.23–7.44 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$, δ, ppm): 22.87 (CH_2, C-6), 34.48 (CH_2, C-4′), 42.47 (CH_2, C-6′), 112.38 (CH, C-4), 117.90 (CH, C-3), 120.04 (CH, C-7′), 122.10 (C, C-3′), 127.97 (CH, C-4″), 128.69 (2CH, C-2″, 6″), 128.86 (2CH, C-3″, 5″), 135.90 (C, C-1″), 151.51 (C, C-2), 153.48 (C, C-5), 170.22 (O=C, C-2′), 174.09 (O=C, C-5′). Found, %: C, 56.68; H, 3.91; Br, 22.16; N, 3.86. $C_{17}H_{14}BrNO_3$. Calcd, %: C, 56.69; H, 3.92; Br, 22.18; N, 3.89; O, 13.33.

3′-{[5-(Bromomethyl)furan-2-yl]methylidene}-1′-phenylpyrrolidine-2′,5′-dione (13). Yield 31%, yellow powder, mp 145°C. IR (m.o., ν, cm^{-1}): 641, 692, 723, 805, 977, 1022, 1116, 1158, 1200, 1366, 1465, 1699, 1765. ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 3.71 (2H, s, H-4′), 4.48 (2H, s, H-6), 5.51 (1H, d, J = 3.4, H-4), 6.98 (1H, d, J = 3.4, H-3), 7.09 (1H, s, H-6′), 7.33–7.54 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$, δ, ppm): 31.16 (CH_2, C-6), 36.34 (CH_2, C-4′), 110.35 (CH, C-3), 118.42 (CH, C-4), 120.03 (CH, C-6′), 121.93 (C, C-3′), 127.49 (2CH, C-2″, 3″), 128.61 (CH, C-4″), 129.29 (2CH, C-3″, 5″), 133.11 (C, C-1″), 150.32 (C, C-2), 159.80 (C, C-5), 169.97 (O=C, C-2′), 173.95 (O=C, C-5′). Found, %: C, 55.13; H, 3.37; Br, 22.86; N, 4.00. $C_{16}H_{12}BrNO_3$. Calcd, %: C, 55.51; H, 3.49; Br, 23.08; N, 4.05; O, 13.87.

3′-{[(5-Ethenylfuran-2-yl)methyl](triphenyl)phosphonium Bromide}-1′-phenylpyrrolidine-2′,5′-dione (14). Yield 12%, brown powder, mp176–181°C. Found, %: C, 66.96; H, 4.41; Br, 13.26; N, 2.36. $C_{34}H_{27}BrNO_3P$. Calcd, %: C, 67.11; H, 4.47; Br, 13.13; N, 2.30; O, 7.89; P, 5.09.

Methyl (2′*E*)-3′-[5-(Chloromethyl)furan-2-yl]prop-2′-enoate (15a). Yield 66.5%, white powder, mp 59°C. IR (m.o., ν, cm^{-1}): 518, 664, 701, 819, 967, 998, 1023, 1168, 1198, 1239, 1312, 1377, 1462, 1519, 1579, 1636, 1697. ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 3.79 (3H, s, CH_3-1″), 4.58 (2H, s, H-6), 6.33 (1H, d, J = 15.8, H-2′), 6.44 (1H, d, J = 3.4, H-3), 6.53 (1H, d, J = 3.4, H-4), 7.39 (1H, d, J = 15.8, H-3′). ^{13}C NMR ($CDCl_3$, δ, ppm): 37.08 (CH_2, C-6), 51.67 (CH_3, C-1″), 112.05 (CH, C-4), 115.53 (CH, C-2′), 116.37 (CH, C-3), 130.63 (CH, C-3′), 151.44 (C, C-2), 152.29 (C, C-5), 167.20 (O=C, C-1′). Found, %: C, 53.89; H, 4.52; Cl, 17.59. $C_9H_9ClO_3$. Calcd, %: C, 53.88; H, 4.52; Cl, 17.67; O, 23.93.

Methyl (2′*Z*)-3′-[5-(Chloromethyl)furan-2-yl]prop-2′-enoate (15b). Yield 2.5%, light-yellow oil. ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 3.77 (3H, s, CH_3-1″), 4.54 (2H, s, H-6), 5.80 (1H, d, J = 12.9, H-2), 6.49 (1H, d, J = 3.5, H-3), 6.76 (1H, d, J = 12.9, H-2′), 7.62 (1H, d, J = 3.5, H-4). ^{13}C NMR ($CDCl_3$, δ, ppm): 37.24 (CH_2, C-6), 51.42 (CH_3, C-1″), 112.53 (CH-4), 115.10 (CH, C-2′), 117.99 (CH, C-4), 130.21 (CH, C-3′), 151.28 (C, C-2), 151.33 (C, C-5), 166.29 (O=C, C-1′). Found, %: C, 53.79; H, 4.50; Cl, 17.56. $C_9H_9ClO_3$. Calcd, %: C, 53.88; H, 4.52; Cl, 17.67; O, 23.93.

1′-Benzyl-3′-{[5-(chloromethyl)furan-2-yl]methylidene}pyrrolidine-2′,5′-dione (16). Yield 66%, yellow powder, mp 149–151°C. IR (m.o., ν, cm^{-1}): 602, 631, 656, 702, 800, 923, 979, 1018, 1056, 1157, 1209, 1270, 1314, 1346, 1392, 1456, 1463, 1651, 1697, 1757. ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 3.62 (2H, s, H-4′), 4.58 (2H, s, H-6), 4.77 (2H, s, H-6′), 6.47 (1H, d, J = 3.4, H-4), 6.62 (1H, d, J = 3.4, H-3), 7.34 (1H, s, H-7′), 7.23–7.43 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$, δ, ppm): 34.38 (CH_2, C-4′), 37.09 (CH_2, C-6), 42.42 (CH_2, C-6′), 112.23 (CH, C-3), 117.57 (CH, C-7′), 120.05 (CH, C-4), 121.97 (C, C-3′), 127.92 (CH, C-4″), 128.64 (2CH, C-2″, 3″), 128.81 (2CH, C-3″, 5″), 135.84 (C, C-1″), 151.46 (C, C-2), 153.25 (C, C-5), 170.18 (O=C, C-5′), 174.01 (O=C, C-2′). Found, %: C, 64.68; H, 4.46; Cl, 11.22; N, 4.46. $C_{17}H_{14}ClNO_3$. Calcd, %: C, 64.67; H, 4.47; Cl, 11.23; N, 4.44; O, 15.20.

3′-{[5-(Chloromethyl)furan-2-yl]methylidene}-1′-phenylpyrrolidine-2′,5′-dione (17). Yield 55%, yellow powder, 158–160°C. IR (m.o., ν, cm^{-1}): 595, 603, 656, 689, 761, 804, 878, 932, 986, 1021, 1073, 1117, 1164, 1209, 1251, 1379, 1454, 1503, 1651, 1698, 1763. ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 3.81 (2H, s, H-4′), 4.62 (2H, s, H-6), 5.49 (1H, d, J = 3.3, H-4), 6.68 (1H, d, J = 3.3, H-3), 7.48 (1H, s, H-6′), 7.35–7.49 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$, δ, ppm): 34.50 (CH_2, C-4′), 37.08 (CH_2, C-6), 112.30 (CH, C-3), 117.87 (CH, C-4), 120.75 (CH, C-6′), 121.61 (C, C-3′), 126.39 (2CH, C-2″, 6″), 128.49 (CH, C-4″), 129.08 (2CH, C-3″, 5″), 132.01 (C, C-1″), 151.49 (C, C-2), 153.48 (C, C-5), 169.47 (O=C, C-5′), 173.36 (O=C, C-2′). Found, %: C, 63.61; H, 4.07; Cl, 11.77; N, 4.66. $C_{16}H_{12}ClNO_3$. Calcd, %: C, 63.69; H, 4.01; Cl, 11.75; N, 4.64; O, 15.91.

Assessment of Antioxidant Activity. The antioxidant properties of the synthesized compounds were determined *in vitro* using a chemiluminescent model system for auto-oxidation of luminol that generated ROS and consisted of luminol, sodium citrate, and iron [12, 13]. Chemiluminescence was recorded on a KhLM-003 instrument (Russia). Chemiluminescence (CL) of the model system (MS) was characterized by spontaneous emission of a fast flash followed by a slowly developing flash. The main high-information-value parameters of the CL were the emission light sum (*S*), which was determined from the emission intensity, and the flash maximum intensity (I_{max}). The well-known inhibitor of free-radical oxidation in biological systems, 5-hydroxy-6-methyluracil, was used for comparison. The auto-oxidant was missing in control measurements.

The tested new 5-HMF derivatives in DMSO solutions (10%) were added to the MS (20 mL) for the studies. The MS in which ROS were generated consisted of phosphate buffer (20 mL, 20 mM KH_2PO_4, 105 mM KCl) with added luminol solution (10^{-5} M) and sodium citrate (50 mM). The pH of the resulting mixture was increased to 7.45 by titration with saturated KOH solution. Processes associated with ROS generation were activated by adding a solution of Fe^{2+} salts (1 mL, 50 mM). Emission was recorded for 5 min with constant stirring.

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