Evaluation of antiviral activity of terpenophenols and some of their *N*- and *O*-derivatives*

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A comparative evaluation of the antiviral activity of a number of new and previously synthesized terpenophenols and their *N*- or *O*-containing derivatives against the A/Puerto Rico/8/34 (H1N1) virus strain was carried out. 2-Isobornylphenol, 1,2-dihydroxy-6-isobornyl-4-methylbenzene, 2-isobornyl-1,4-benzoquinone, and *N*-butyl-4-hydroxy-3,5-diisobornylbenzamide showed the highest activity.

Key words: terpenophenols, Mannich bases, hydroxymethyl derivatives, antiviral activity.

The search for antiviral agents among natural compounds, which can be isolated from available and renewable plant materials, and their derivatives is a modern innovative approach to the development of new antiviral drugs. Plant-produced bioactive secondary metabolites, which include monoterpenoids and terpenophenols, are of interest as matrices for synthetic and semi-synthetic structural modifications, synthesis of combinatorial libraries of compounds, and study of the structure-activity relationship. Almost all compounds used as anti-flu drugs, including Remantadine, Amantadine, Favipiravir, Oseltamivir (Tamiflu), Zanamivir (Relenza), and Ingavirin, are polyfunctional cyclic hydrocarbons having a small framework and branched side chains and containing NH_2, NH, and OH groups.[1]

It is known that compounds with a bornane (bicyclo-[2.2.1]heptane) structure, which include isobornylphenols, have antioxidant activity, as well as membraneprotective and cardioprotective, membrane stabilizing, hemorheological, and antithrombogenic properties.[2—10] Some representatives of isobornylphenols are used in medicine for the treatment of respiratory diseases[11], showing antimicrobial[12] and antiviral activity.[13] The introduction of various substituents into the structures of organic molecules underlies the design of new drugs. For instance, the presence of the aminomethyl substituent in a molecule of phenolic compounds can lead to the appearance of antiviral activity.[14] For the synthesis of Mannich bases, 1-adamantylamine, which is an active substance for the prevention and treatment of the influenza A virus, can serve as an amine component.[1] There are examples of the synthesis of effective antiviral agents containing terpene and adamantyl substituents in their molecules.[15]

This paper presents the results of a primary assessment of antiviral activity of a number of terpenophenols with isobornyl, bornyl, and isocamphyl substituents and their *N*- or *O*-containing derivatives and the analysis of the structure-property relationships for these compounds.

Results and Discussion

Compounds **1**—**38** were chosen as the objects of this study. Based on previously synthesized terpenophenols **1**—**6**, derivatives **7**—**12** were obtained by hydroxymethylation using paraformaldehyde and boric acid (Scheme 1).

Terpenophenols **1**—**6**, **13**—**19** and their derivatives **29**, **30** were synthesized according to known methods.[8,16—19] Hydrochlorides **21**—**28** were prepared to increase the solubility of previously prepared Mannich bases[6,7,20] in DMSO. Compounds **13**—**30** are racemates.

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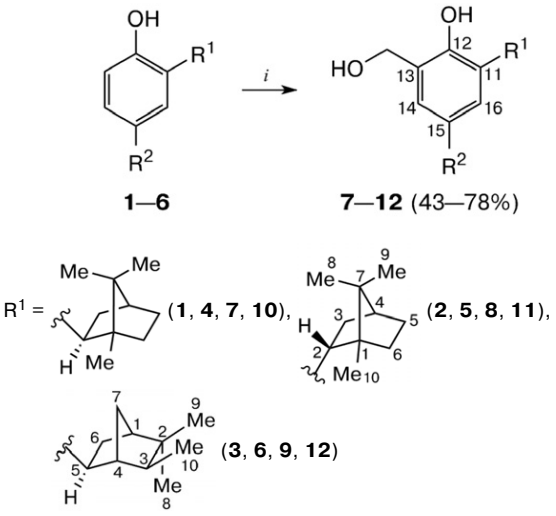
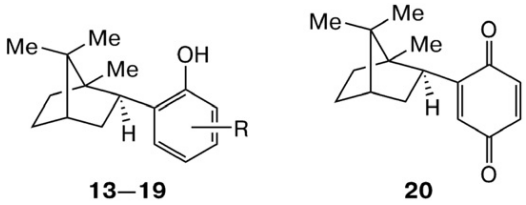
Scheme 1*



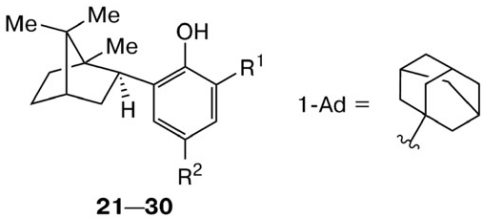
R^2 = H (**1**, **2**, **3**, **7**, **8**, **9**), Me (**4**, **5**, **6**, **10**, **11**, **12**)

Reagents and conditions; *i*. HCHO, H_3BO_3, PhMe, reflux, 10—12 h.



R = 6-Me (**13**), 5-Me (**14**), 2,4-Me_2 (**15**), 2-OH (**16**), 2-OH, 4-Me (**17**), 3-OH (**18**), 4-OH (**19**)

By condensation of substituted isobornylbenzaldehydes with 1-adamantylamine followed by reduction (*in situ*) of intermediate imines, aminomethyl



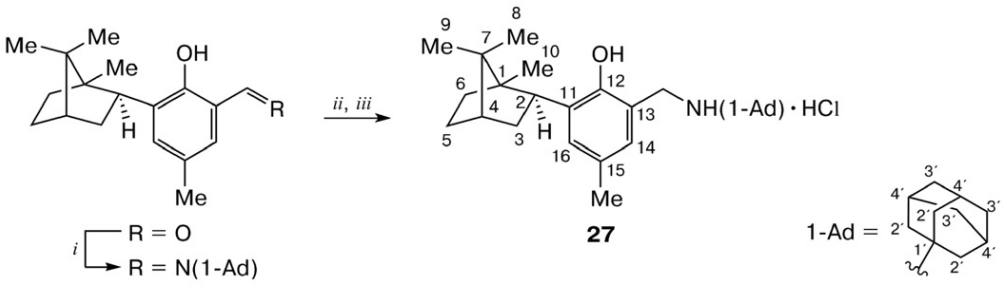
Compound	R^1	R^2
21	$CH_2NMe_2 \cdot HCl$	H
22	$CH_2NMe_2 \cdot HCl$	Me
23	Me	$CH_2NMe_2 \cdot HCl$
24	$CH_2NMe_2 \cdot HCl$	$CH_2NMe_2 \cdot HCl$
25	$CH_2N(CH_2CH_2)_2O \cdot HCl$	Me
26	Me	$CH_2N(CH_2CH_2)_2O \cdot HCl$
27	$CH_2NH(1\text{-Ad}) \cdot HCl$	Me
28	Me	$CH_2NH(1\text{-Ad}) \cdot HCl$
29	CH_2NO_2	Me
30	C≡N	Me

derivatives containing the 1-adamantyl group at the nitrogen atom were synthesized for the first time; they were also converted into the corresponding hydrochlorides **27** and **28**. The synthesis of compound **27** is shown in Scheme 2 as an example.

To assess antiviral activity and cytotoxicity, the set of compounds was supplemented with previously synthesized 2,6-diisobornylphenol derivatives **31**—**36**, **38** and new nitro derivative **37**. Compounds **31**—**38** are *meso*-stereoisomers; compounds **36** and **37** are *E*-isomers.

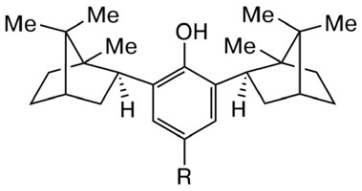
The ^1H and ^{13}C NMR spectra, IR spectra, and the elemental analysis data obtained for new products **8**, **9**, **11**, **12**, **21**—**28**, and **37** correspond to the expected structures. In the ^1H and ^{13}C NMR spectra of these compounds, the signals of protons and carbon atoms of the substituted terpenophenolic skeleton were observed.

Scheme 2



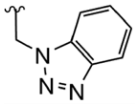
Reagents and conditions: *i*. 1-Adamantylamine hydrochloride, KOH, 4Å molecular sieves, MeOH, heating at the reflux temperature for 4.5 h. *ii*. $NaBH_4$, MeOH, 5→20 °C, 40 min. *iii*. HCl (EtOH), Et_2O, 20 °C, 40 min.

* The numbering of C atoms is used for the convenience of interpreting NMR spectra and may not correspond to the numbering recommended by IUPAC. Compounds **1**, **3**, **4**, **6**, **7**, **9**, **10**, and **12** are racemates, the structures corresponding to one of their enantiomers are given in Scheme 1.



31—38

R = CH_2OH (**31**), CH_2OMe (**32**), COOH (**33**), C(O)NHBu (**34**), CH_2NHPh (**35**), CH=CHCOOH (**36**); $CH=CHNO_2$ (**37**),



(**38**)

The SSCC value (J = 16.0 Hz) in the ^1H NMR spectrum of compound **37** makes it possible to identify this compound as having the *E*-configuration of substituents relative to the double bond of the nitrovinyl fragment.

The evaluation of antiviral activity of compounds **1**—**38** against the A/Puerto Rico/8/34 (H1N1) influenza strain *in vitro* was performed for the first time (Table 1). In general, the studied compounds are characterized by high cytotoxicity except for compounds **22**, **32**, **34**, **35**, **38**, for which CC_{50} > 600 μmol L^{-1}. The lowest toxicity was exhibited by 2-(dimethylaminomethyl)-6-isobornyl-4-methylphenol **22** with CC_{50} > 880 μmol L^{-1}. However, all non-toxic derivatives showed no significant virus-inhibiting activity except benzamide **34** with two isobornyl substituents (selectivity index SI = 21). The low toxicity of derivatives with two isobornyl substituents in aromatic ring, with the exception of carboxyl derivatives **33** and **36**, is consistent with previous results,[21] according to which the introduction of a second bulky substituent into an isobornylphenol molecule leads to a decrease in its toxicity.

Taking phenols **1**—**6** and their hydroxymethyl derivatives **7**—**12** as an example, it is shown that the structure of the terpene substituent in this chemical system does not substantially affect the virus-inhibiting activity. Hydroxymethyl derivatives with the isocamphyl substituent in the aromatic ring (compounds **9** and **12**) showed the lowest cytotoxicity (CC_{50} = 173 and 158 μmol L^{-1}, respectively), at the same time, these compounds show no antiviral activity. 2-Isobornylphenol (**1**) and 2-isocamphylphenol (**3**) showed moderate antiviral activity (SI = 10 and 8, respectively). The presence of the methyl and/or hydroxyl group in

Table 1. Evaluation of cytotoxic and antiviral activity of terpenophenols and their derivatives *in vitro*

Compound	CC_{50}	IC_{50}	SI	Compound	CC_{50}	IC_{50}	SI
	μmol L^{-1}				μmol L^{-1}		
1	8±0.7	0.8±0.2	10	**20**	12±0.8	0.5±0.1	24
2	9±1	>5	2	**21**	28±2	9±0.2	3
3	8±1	1±0.2	8	**22**	>880	>880	1
4	15±1	3±0.4	5	**23**	3±0.2	>1	3
5	9±0.5	2±0.3	4	**24**	6±0.4	1.7±0.2	4
6	22±2	12±3	2	**25**	23±2	>8	3
7	11±0.9	>4	3	**26**	3±0.1	>1	3
8	4±0.1	>4	1	**27**	9±0.5	2±0.2	5
9	173±14	>127	1	**28**	3±0.2	0.5±0.1	6
10	8±1	>4	2	**29**	40±3	>35	1
11	12±0.7	2±0.3	5	**30**	11±0.7	>4	3
12	158±12	>120	1	**31**	28±2	>28	1
13	21±0.4	>10	2	**32**	>730	>730	1
14	12±0.8	>4.5	3	**33**	4±0.2	1±0.1	4
15	13±0.8	1.4±0.2	9	**34**	>644	30±4	21
16	16±0.8	>13	1	**35**	>636	212±25	3
17	11±1	0.7±0.1	16	**36**	3±0.1	2±0.2	1
18	6±0.4	2±0.2	3	**37**	37±2	>25	1
19	8±0.4	1±0.2	8	**38**	>602	504±62	1
				Remantadine	331±29	48±6	7

Note. CC_{50} (M±SD) is the 50% cytotoxic concentration, which is a compound concentration reducing the optical density in the wells of cell culture plates by a factor of two compared to that of control wells, in which the compound was not added; IC_{50} (M±SD) is a compound concentration resulting in the 50% reduction in the cytodestructive action of the virus; selectivity index (SI) is the ratio of CC_{50} to IC_{50}.

the *ortho* or *para* position of the 2-isobornylphenol molecule contributed to the manifestation of antiviral activity of 2,4-dimethyl-6-isobornylphenol **15** (SI = 9), 1,2-dihydroxy-6-isobornyl-4-methylbenzene **17** (SI = 16), and 1,4-dihydroxy-2- isobornylbenzene **19** (SI = 8). It should be noted that the inhibitory action of the oxidized form **20** is three times higher (SI = 24) than that of non-oxidized 1,4-dihydroxy-2-isobornylbenzene **19**. As compared to 2-hydroxymethyl-6-isobornyl-4-methylphenol **10** (CC_{50} = 8 μmol L^{-1}), the introduction of the nitromethyl group in the *ortho* position (compound **29**) reduced toxicity (CC_{50} = 40 μmol L^{-1}), but simultaneously completely eliminated antiviral activity (IC_{50} > 35 μmol L^{-1}).

The data obtained indicate that within the studied set of derivatives, a substantial modification of the skeleton of 2-isobornylphenol, including the introduction of nitrogen-containing substituents of different complexity, does not result in an increase in the effect against the A/Puerto Rico/8/34 strain. The highest antiviral activity in this set of derivatives was found for compounds **27** and **28** containing the 1-adamantylamino group (SI = 5 and 6, respectively), which, however, exhibit rather high toxicity (9 and 3 μmol L^{-1}). When evaluating pairs of *ortho*/*para* isomers **22** and **23**, **25** and **26**, **27** and **28**, it was found that the presence of the aminomethyl group in the *para* position led to an increase in the cytotoxicity of the compounds.

The antiviral potential of the most active compounds (**20** and **34**) and phenol **1**, which is the least substituted compound, was additionally assessed against other human respiratory viruses: coronavirus OC43, human parainfluenza virus type 3, and human adenovirus type 5 (Table 2). As can be seen, the virus-inhibiting activity of these compounds against human respiratory viruses was lower than against human influenza viruses. At the same time, enveloped viruses (coronavirus and parainfluenza virus) turned out to be more sensitive to the action of isobornylphenol derivatives than non-enveloped adenovirus, however, none of the studied compounds blocked their reproduction to a level of SI > 10.

Despite the fact that the studied compounds showed rather moderate antiviral activity, we were able to identify the leading compounds among them. Note that the cytotoxicity of phenolic compounds represents a substantial barrier to the development of new candidates for drug. The data obtained contribute to the basis for the design of new compounds with improved cytotoxicity and preserved antiviral properties.

Experimental

The analysis of the synthesized compounds was partly performed using the equipment of the Center of Collective Usage "Chemistry" of the Institute of Chemistry, Komi Scientific Center, Ural Branch of the Russian Academy of Sciences. ^1H and ^{13}C NMR spectra of the prepared compounds were recorded on a Bruker Avance II 300 spectrometer (300.17 and 75.5 MHz) in DMSO-d_6 and $CDCl_3$. The assignment of ^1H signals was carried out using NOESY, that of ^{13}C signals was performed on the basis of ^{13}C NMR spectra recorded in the *J*-modulation mode, as well as on the basis of HSQC and HMBC experiments. Diffuse reflectance IR spectra were recorded on a Shimadzu IR Prestige 21 FTIR spectrometer in KBr pellets (solid compounds) or in thin layers (liquid compounds). Elemental analysis was carried out on a vario Micro cube analyzer. Melting points were determined using a Sanyo Gallenkamp MPD350 device, no corrections were applied. An Optical Activity polAAr 3001 polarimeter was used to measure the specific rotations. The progress of the reactions was monitored by TLC on Sorbfil plates (JSC IMID, RF). The chromatographic zones of the reaction products were detected by treating the plates with a solution of $KMnO_4$ (15 g of $KMnO_4$, 300 mL of H_2O, and 0.5 mL of concentrated H_2SO_4). Preparative chromatographic separation was carried out on columns filled with silica gel (0.06—0.2 mm, Alfa Aesar).

1-Adamantylamine (Alfa Aesar), sodium borohydride (Daejung Co.), paraformaldehyde (technical grade), and boric acid (*puriss.*) were used without an additional purification. Solvents were dried and purified according to standard procedures. Molecular sieves (4Å) were calcined at 140 °C for 3 h. Compounds **1**—**6**, **31**—**36**, and **38** were synthesized according to known methods.[16,17,22—29] Reported earlier Mannich bases were used in the syntheses of hydrochlorides

Table 2. Antiviral activity of isobornylphenoles against human respiratory viruses

Compound	HCoV-OC43			HPIV-3			AdV5		
	CC_{50}	IC_{50}	SI	CC_{50}	IC_{50}	SI	CC_{50}	IC_{50}	SI
	μmol L^{-1}			μmol L^{-1}			μmol L^{-1}		
1	364±26	61±13	6	195±13	22±4	9	386±30	>140	<3
20	25±2	4±0.4	6	8±0.8	0.8±0.1	10	22±2	>16	<2
34	>640	127±19	5	>640	62±9	10	>640	356±45	2
Ribavirin	>400	64±9	6	>400	25±3	16	>400	>400	1

21—**26**.[6,7,20] To synthesize compounds **27** and **28**, 2-hydroxy-3-isobornyl-5-methylbenzaldehyde[17] and 4-hydroxy-3-isobornyl-5- methylbenzaldehyde[18] of >98% purity (GC) were used.

Synthesis of compounds 7—12 (general procedure). A mixture of phenol **1**—**6** (2.0 mmol), paraformaldehyde (0.09 g, 3 mmol), and boric acid (0.19 g, 3 mmol) in toluene (20 mL) were heated at the reflux temperature for 10—12 h in a bulb equipped with a Dean—Stark trap. Every 4 h, paraformaldehyde (0.02 g, 0.75 mmol) and toluene (5 mL) were added to the mixture. When reaction was completed, the solvent was removed under reduced pressure, water (10 mL) was added to the residue, and the resulting mixture was left for ~12—15 h to hydrolyze the intermediate borosalicylic ester. The product was extracted with diethyl ether (3×15 mL), washed with water (15 mL), dried over Na_2SO_4, the solvent was removed under reduced pressure. The residue was purified by column chromatography (using a mixture of CCl_4 and acetone, 10 : 0 → 10 : 1, as an eluent).

2-Hydroxymethyl-6-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol (7). A colorless powder, m.p. 82 °C. Yield 0.33 g (63%). Spectroscopic characteristics of the compound corresponds to those reported previously.[30]

2-Hydroxymethyl-6-{(1*R*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl}phenol (8). A colorless powder, m.p. 116 °C, R_f 0.59 (eluent: CCl_4—acetone, 10 : 1). Yield 0.22 g (43%). $[\alpha]_D^{25}$ +80.4 (*c* 0.28, $CHCl_3$). Found (%): C, 78.67; H, 9.12. $C_{17}H_{24}O_2$. Calculated (%): C, 78.42; H, 9.29. IR (KBr), ν/cm^{-1}: 3574, 3395, 3221 (OH); 2978, 2955, 2924, 2880, 2723, 2687, 1479, 1456 (CH_3, CH_2); 1591 (C=C); 1229, 1207, 1078, 1001 (C—O); 826, 793, 756 (=C—H). ^{1}H NMR ($CDCl_3$), δ: 0.78, 0.94, 1.10 (all s, 3 H each, C(8)H_3, C(9)H_3, C(10)H_3); 1.08—1.30, 1.31—1.69, 1.71—1.94, 1.98—2.29 (all m, 1 H, 3 H, 2 H, 2 H, 2 H(3), 1 H(4), 2 H(5), 2 H(6), $CH_2O\underline{H}$); 3.66—3.84 (m, 1 H, H(2)); 4.80, 4.87 (both AB-system, 1 H each, $C\underline{H}_2OH$, *J* = 12.6 Hz, *J* = 12.6 Hz); 6.78—6.99, 7.20—7.31 (both m, 2 H, 1 H, 1 H(14), 1 H(15), 1 H(16)); 7.31 (s, 1 H, ArOH). ^{13}C NMR ($CDCl_3$), δ: 14.80, 18.77, 19.85 (C(8), C(9), C(10)); 28.43, 28.95, 34.89 (C(3), C(5), C(6)); 40.66 (C(2)); 45.69 (C(4)); 50.31, 50.58 (C(1), C(7)); 65.10 (CH_2OH); 119.04, 125.34, 129.91 (C(14), C(15), C(16)); 124.19, 130.28 (C(11), C(13)); 155.11 (C(12)).

2-Hydroxymethyl-6-(2,2,3-trimethylbicyclo[2.2.1]hept-*exo*-5-yl)phenol (9). A colorless oil, R_f 0.57 (eluent: CCl_4—acetone, 10 : 1). Yield 0.31 g (60%). Found (%): C, 78.19; H, 9.36. $C_{17}H_{24}O_2$. Calculated (%): C, 78.42; H, 9.29. IR (thin layer), ν/cm^{-1}: 3381 (OH); 2961, 2876, 2722, 1454 (CH_3, CH_2); 1593 (C=C); 1258, 1211, 1138, 1103, 1080, 997 (C—O); 825, 783, 750 (=C—H). ^{1}H NMR ($CDCl_3$), δ: 0.90, 0.92, 1.07 (all s, 3 H each, C(8)H_3, C(9)H_3, C(10)H_3); 1.30—1.52, 1.68—1.88, 1.91—2.00, 2.14—2.38 (all m, 2 H, 2 H, 1 H, 2 H, 1 H(1), 1 H(3), 1 H(4), 2 H(6), 2 H(7)); 1.66 (br.s, 1 H, $CH_2O\underline{H}$); 3.02 (t, 1 H, 1 H(5), *J* = 7.5 Hz); 4.83, 4.85 (both s, 1 H each, $C\underline{H}_2OH$); 6.74—6.94, 7.10—7.22 (both m, 2 H, 1 H, 1 H(14), 1 H(15), 1 H(16)); 7.37 (s, 1 H, ArOH). ^{13}C NMR ($CDCl_3$), δ: 16.28, 24.82, 27.65 (C(8), C(9), C(10)); 32.76, 33.55 (C(6), C(7)); 39.60 (C(2)); 40.43 (C(5)); 48.87, 49.84, 51.13 (C(1), C(3), C(4)); 64.95 (CH_2OH); 119.35, 124.93, 125.88 (C(14), C(15), C(16)); 124.04, 134.76 (C(11), C(13)); 153.98 (C(12)).

2-Hydroxymethyl-4-methyl-6-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol (10). A light yellow powder, m.p. 69 °C. Yield 0.43 g (78%). Spectroscopic characteristics of the compound corresponds to those reported previously.[31]

2-Hydroxymethyl-4-methyl-6-{(1*R*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl}phenol (11). A beige powder, m.p. 124 °C, R_f 0.58 (eluent: CCl_4—acetone, 10 : 1). Yield 0.25 g (46%). $[\alpha]_D^{27}$ +57.7 (*c* 0.35, $CHCl_3$). Found (%): C, 78.62; H, 9.53. $C_{18}H_{26}O_2$. Calculated (%): C, 78.79; H, 9.55. IR (KBr), ν/cm^{-1}: 3460, 3198 (OH); 2976, 2949, 2874, 1479, 1468 (CH_3, CH_2); 1618 (C=C); 1263, 1244, 1217, 1153, 1026 (C—O); 874, 781, 733 (=C—H). ^{1}H NMR ($CDCl_3$), δ: 0.77, 0.94, 1.10 (all s, 3 H each, C(8)H_3, C(9)H_3, C(10)H_3); 1.04—1.31, 1.31—1.46, 1.46—1.67, 1.72—1.96, 2.06—2.25 (all m, 1 H, 2 H, 1 H, 2 H, 2 H, 2 H(3), 1 H(4), 2 H(5), 2 H(6), $CH_2O\underline{H}$); 2.30 ($ArCH_3$); 3.63—3.80 (m, 1 H, 1 H(2)); 4.69—4.90 (m, 2 H, $C\underline{H}_2OH$); 6.71, 7.04 (both s, 1 H, 1 H, 1 H(14), 1 H(16)); 7.07 (s, 1 H, ArOH). ^{13}C NMR ($CDCl_3$), δ: 14.80, 18.76, 19.86 (C(8), C(9), C(10)); 20.84 ($ArCH_3$); 28.47, 28.94, 34.81 (C(3), C(5), C(6)); 40.66 (C(2)); 45.67 (C(4)); 50.30, 50.49 (C(1), C(7)); 65.06 (CH_2OH); 124.07, 127.96, 129.94 (C(11), C(13), C(15)); 125.96, 130.32 (C(14), C(16)); 152.74 (C(12)).

2-Hydroxymethyl-4-methyl-6-(2,2,3-trimethylbicyclo[2.2.1]hept-*exo*-5-yl)phenol (12). A pale yellow semi-crystalline product, R_f 0.57 (eluent: CCl_4—acetone, 10 : 1). Yield 0.36 g (66%). Found (%): C, 79.03; H, 9.34. $C_{18}H_{26}O_2$. Calculated (%): C, 78.79; H, 9.55. IR (thin layer), ν/cm^{-1}: 3381 (OH); 2957, 2889, 2870, 1477 (CH_3, CH_2); 1611 (C=C); 1258, 1223, 1157, 1138, 1015 (C—O); 860, 785 (=C—H). ^{1}H NMR ($CDCl_3$), δ: 0.90, 0.92, 1.07 (all s, 3 H each, C(8)H_3, C(9)H_3, C(10)H_3); 1.28—1.49, 1.69—1.86, 1.94—2.00, 2.13—2.35 (all m, 2 H, 2 H, 1 H, 2 H, 1 H(1), 1 H(3), 1 H(4), 2 H(6), 2 H(7)); 1.64 (br.s, 1 H, $CH_2O\underline{H}$); 2.99 (t, 1 H, 1 H(5), *J* = 7.5 Hz); 4.78, 4.80 (both s, 1 H each, $C\underline{H}_2OH$); 6.68, 6.95 (both s, 1 H each, 1 H(14), 1 H(16)); 7.13 (s, 1 H, ArOH). ^{13}C NMR ($CDCl_3$), δ: 16.29, 24.82, 27.65 (C(8), C(9), C(10)); 20.74 ($ArCH_3$); 32.79, 33.59 (C(6), C(7)); 39.60 (C(2)); 40.40 (C(5)); 48.89, 49.84, 51.14 (C(1), C(3), C(4)); 64.89 (CH_2OH); 123.93, 128.38, 134.51 (C(11), C(13), C(15)); 125.39, 126.45 (C(14), C(16)); 151.58 (C(12)).

Synthesis of compound 20. A solution (126 mL) of chlorine dioxide, ClO_2, in CH_2Cl_2 was added to phenol **19** (1.38 g, 5.6 mmol) (the phenol : ClO_2 molar ratio was 1 : 2). The ClO_2 solution in CH_2Cl_2 was obtained by extraction of ClO_2 from an aqueous solution with a concentration of 6 g L^{-1}, the organic layer was separated and dried over Na_2SO_4. The reaction mixture was kept at room temperature under continuous stirring for 1.5 h. The process of the reaction was monitored by TLC (eluent: chloroform). After the completion of the reaction, the reaction mixture was washed with water until the neutral reaction and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. Separation of the products was carried out by column chromatography using chloroform as an eluent.

2-(1,7,7-Trimethylbicyclo[2.2.1]hept-*exo*-2-yl)cyclohexa-2,5-dien-1,4-dione (20). A dark brown powder, m.p. 105—106 °C, R_f 0.59 (eluent: $CHCl_3$). Yield 1.3 g (95%). Found (%): C, 78.49; H, 8.21. $C_{16}H_{20}O_2$. Calculated (%): C, 78.65; H, 8.25. IR (KBr), ν/cm^{-1}: 2949, 2875, 1460 (CH_3, CH_2); 1656 (C=O). ^{1}H NMR ($CDCl_3$), δ: 0.74 (s, 3 H, C(10)Me); 0.83 (s, 3 H, C(9)Me); 0.85 (s, 3 H, C(8)Me); 1.33—1.36 (m, 2 H, H(5), H(6)); 1.55—1.58 (s, 2 H, H(3), H(6)); 1.65—1.88 (s, 2 H, H(4), H(5)); 1.92—1.97 (s, 1 H, H(3)); 3.08 (t, 1 H, H(2), J = 8.4 Hz); 6.66—6.83 (m, 3 H, H(13), H(14), H(16)). ^{13}C NMR ($CDCl_3$), δ: 13.97 (C(10)); 19.94 (C(9)); 21.12 (C(8)); 27.28 (C(5)); 33.09 (C(3)); 39.52 (C(6)); 44.90 (C(4)); 45.31 (C(2)); 48.84 (C(1)); 50.90 (C(7)); 132.59 (C(16)); 135.69 (C(14)): 137.32 (C(13)); 152.60 (C(11)); 187.82 (C=O); 188.07 (C=O).

Synthesis of compounds 21—26 (general procedure). To a solution of the corresponding amine (1.0 mmol) in Et_2O (5—20 mL), a 2 *M* HCl solution in EtOH was added dropwise until pH <6, and the mixture was vigorously stirred at room temperature for 30—60 min. The precipitated hydrochloride was filtered off (with the exception of compound **24**), washed with a little amount of chilled Et_2O and dried. To isolate dihydrochloride **24**, the ether solution was separated, the oily residue was successively washed with chilled Et_2O (6 mL) and pentane (2×6 mL); the solvents were removed under reduced pressure; the residue was dried.

2-[(Dimethylamino)methyl]-6-(1,7,7-trimethylbicyclo-[2.2.1]hept-*exo*-2-yl)phenol hydrochloride (21). A colorless powder, m.p. 255—256 °C. Yield 0.30 g (93%). Found (%): C, 70.59; H, 9.44; N, 4.28. $C_{19}H_{30}ClNO$. Calculated (%): C, 70.46; H, 9.34; N, 4.32. IR (KBr), ν/cm^{-1}: 3078 (OH); 2953, 2876, 2695, 2720, 1454 (CH_3, CH_2); 1593 (C=C); 1209 (C—O); 773, 754 (=C—H). ^{1}H NMR (DMSO-d_6), δ: 0.68, 0.79, 0.83 (all s, 3 H each, C(8)H_3, C(9)H_3, C(10)H_3); 1.17—1.45 (m, 1 H, 1 H(5)); 1.45—1.68 (m, 3 H, 1 H(3), 2 H(6)); 1.75—1.92 (m, 2 H, 1 H(4), 1 H(5)); 2.03—2.28 (m, 1 H, 1 H(3)); 2.69 (s, 6 H, N(CH_3)$_2$); 3.34 (t, 1 H, 1 H(2), J ≈ 9.3 Hz, partly overlapped with the HOD signal); 4.31, 4.39 (both AB-system, 1 H each, ArCH_2, J = 12.9 Hz, J = 12.9 Hz); 6.80—7.00 (m, 1 H, 1 H(15)); 7.16—7.46 (m, 2 H, 1 H(14), H(16)); 8.94 (br.s, 1 H, OH); 10.32 (br.s, 1 H, N$^+$HCl$^-$). ^{13}C NMR (DMSO-d_6), δ: 12.16 (C(10)); 20.03 (C(9)); 21.28 (C(8)); 27.06 (C(5)); 33.47 (C(3)); 38.88 (C(6), partly overlapped with the solvent signal); 41.06, 41.68 (N(CH_3)$_2$); 44.44 (C(2)); 44.98 (C(4)); 47.62 (C(7)); 49.45 (C(1)); 55.19 (ArCH_2); 118.25, 132.81 (C(11), C(13)); 119.71 (C(15)); 129.32, 130.22 (C(14), C(16)); 155.29 (C(12)).

2-[(Dimethylamino)methyl]-4-methyl-6-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol hydrochloride (22). A colorless powder, m.p. 263—264 °C. Yield 0.31 g (93%). Found (%): C, 70.93; H, 9.71; N, 4.02. $C_{20}H_{32}ClNO$. Calculated (%): C, 71.09; H, 9.55; N, 4.14. IR (KBr), ν/cm^{-1}: 3098 (OH); 2945, 2874, 2691, 1474 (CH_3, CH_2); 1610 (C=C); 1221 (C—O); 877, 883, 787 (=C—H). ^{1}H NMR (DMSO-d_6), δ: 0.68, 0.79, 0.83 (all s, 3 H each, C(8)H_3, C(9)H_3, C(10)H_3); 1.17—1.40 (m, 1 H, 1 H(5)); 1.40—1.63 (m, 3 H, 1 H(3), 2 H(6)); 1.66—1.94 (m, 2 H, 1 H(4), 1 H(5)); 2.01—2.34 (m, 1 H, 1 H(3)); 2.22 (s, 3 H, ArCH_3); 2.68 (s, 6 H, N(CH_3)$_2$); 3.30 (t, 1 H, 1 H(2), J ≈ 8.5 Hz, partly overlapped with the HOD signal); 4.25, 4.33 (both AB-system, 1 H each, ArCH_2, J = 12.5 Hz, J = 12.5 Hz); 7.05, 7.15 (both s, 1 H each, 1 H(14), 1 H(16)); 8.66 (br.s, 1 H, OH); 10.24 (br.s, 1 H, N$^+$HCl$^-$). ^{13}C NMR (DMSO-d_6), δ: 12.15 (C(10)); 20.04 (C(9)); 20.47 (ArCH_3); 21.30 (C(8)); 27.06 (C(5)); 33.40 (C(3)); 38.88 (C(6), partly overlapped with the solvent signal); 41.08, 41.74 (N(CH_3)$_2$); 44.45 (C(2)); 44.98 (C(4)); 47.62 (C(7)); 49.45 (C(1)); 55.31 (ArCH_2); 118.16, 128.16, 132.74 (C(11), C(13), C(15)); 130.03, 130.34 (C(14), C(16)); 152.96 (C(12)).

4-[(Dimethylamino)methyl]-2-methyl-6-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol hydrochloride (23). A colorless powder, m.p. 253—254 °C. Yield 0.31 g (92%). Found (%): C, 71.20; H, 9.43; N, 4.11. $C_{20}H_{32}ClNO$. Calculated (%): C, 71.09; H, 9.55; N, 4.14. IR (KBr), ν/cm^{-1}: 3358 (OH); 2949, 2920, 2876, 2733, 1477 (CH_3, CH_2); 1595 (C=C); 1188, 1169 (C—O); 885, 818, 793 (=C—H). ^{1}H NMR (DMSO-d_6), δ: 0.69, 0.79, 0.84 (all s, 3 H each, C(8)H_3, C(9)H_3, C(10)H_3); 1.20—1.40 (m, 1 H, 1 H(5)); 1.40—1.62 (m, 3 H, 1 H(3), 2 H(6)); 1.69—1.90 (m, 2 H, 1 H(4), 1 H(5)); 2.10—2.29 (m, 1 H, 1 H(3)); 2.19 (s, 3 H, ArCH_3); 2.59 (s, 6 H, N(CH_3)$_2$); 3.27 (t, 1 H, 1 H(2), J = 8.8 Hz, partly overlapped with the HOD signal); 4.02, 4.14 (both AB-system, 1 H each, ArCH_2, J = 12.7 Hz, J = 12.7 Hz); 7.07, 7.28 (both s, 1 H each, 1 H(14), 1 H(16)); 8.46 (br.s, 1 H, OH); 10.53 (br.s, 1 H, N$^+$HCl$^-$). ^{13}C NMR (DMSO-d_6), δ: 12.22 (C(10)); 17.07 (ArCH_3); 20.16 (C(9)); 21.34 (C(8)); 27.13 (C(5)); 31.51 (C(3)); 39.15 (C(6), partly overlapped with the solvent signal); 40.95 (N(CH_3)$_2$); 44.64 (C(2)); 45.02 (C(4)); 47.56 (C(7)); 49.35 (C(1)); 59.57 (ArCH_2); 120.06, 123.94, 130.77 (C(11), C(13), C(15)); 128.53, 130.74 (C(14), C(16)); 155.07 (C(12)).

2,4-Bis[(dimethylamino)methyl]-6-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol dihydrochloride (24). A light beige caramel-like product. Yield 0.40 g (95%). Found (%): C, 63.51; H, 9.11; N, 6.59. $C_{22}H_{38}Cl_2N_2O$. Calculated (%): C, 63.30; H, 9.18; N, 6.71. IR (KBr), ν/cm^{-1}: 3381, 3238, 3221 (OH); 2951, 2878, 2691, 1472 (CH_3, CH_2); 1616 (C=C); 1188, 1180 (C—O); 822, 795 (=C—H). ^{1}H NMR (DMSO-d_6), δ: 0.69, 0.79, 0.84 (all s, 3 H each, C(8)H_3, C(9)H_3, C(10)H_3); 1.20—1.42 (m, 1 H, 1 H(5)); 1.42—1.67 (m, 3 H, 1 H(3), 2 H(6)); 1.68—1.95 (m, 2 H, 1 H(4), 1 H(5)); 2.11—2.36 (m, 1 H, 1 H(3)); 2.19 (s, 3 H, ArCH_3); 2.45—2.88 (m, 12 H, 2 N(CH_3)$_2$, partly overlapped with the solvent signal); 3.34 (t, 1 H, H(2), J ≈ 8.8 Hz, partly overlapped with the HOD signal); 3.99—4.29, 4.29—4.53 (both m, 2 H each, 2 ArCH_2); 7.44, 7.61 (both s, 1 H each, 1 H(14), 1 H(16)); 9.40 (br.s, 1 H, OH); 10.59, 10.97 (both br.s, 1 H each, 2 N$^+$HCl$^-$). ^{13}C NMR (DMSO-d_6), δ: 12.18 (C(10)); 20.14 (C(9)); 21.32 (C(8)); 27.07 (C(5)); 33.46 (C(3)); 38.88 (C(6), partly overlapped with the solvent signal); 40.49, 41.20, 41.43, 41.66 (2 N(CH_3)$_2$); 44.58 (C(2)); 44.95 (C(4)); 47.72 (C(7)); 49.60 (C(1)); 54.95, 59.06 (2 ArCH_2); 117.93, 120.89, 133.34 (C(11), C(13), C(15)); 132.62, 133.66 (C(14), C(16)); 156.40 (C(12)).

4-Methyl-2-(morpholinomethyl)-6-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-el)phenol hydrochloride (25). A colorless powder, m.p. 252—253 °C. Yield 0.34 g (90%). Found

(%): C, 69.31; H, 8.96; N, 3.74. $C_{22}H_{34}ClNO_2$. Calculated (%): C, 69.54; H, 9.02; N, 3.69. IR (KBr), ν/cm^{-1}: 3316, 3221 (OH); 2951, 2928, 2874, 2668, 2583, 2542, 2467, 1468 (CH_3, CH_2); 1612 (C=C); 1194, 1124, 1084, 1053 (C—O); 874, 777 (=C—H). ^{1}H NMR (DMSO-d_6), δ: 0.68, 0.79, 0.83 (all s, 3 H each, C(8)H_3, C(9)H_3, C(10)H_3); 1.19—1.40 (m, 1 H, 1 H(5)); 1.40—1.65 (m, 3 H, 1 H(3), 2 H(6)); 1.66—1.91 (m, 2 H, 1 H(4), 1 H(5)); 2.02—2.29 (m, 1 H, 1 H(3)); 2.22 (s, 3 H, ArCH_3); 2.86—3.52 (m, 5 H, 1 H(2), N(C$\underline{H}_2$CH_2)$_2$O, partly overlapped with the HOD signal); 3.59—4.06 (m, 4 H, N(CH_2C$\underline{H}_2$)$_2$O); 4.34 (s, 2 H, ArCH_2); 7.10, 7.16 (both s, 1 H each, 1 H(14), 1 H(16)); 8.62 (br.s, 1 H, OH); 10.82 (br.s, 1 H, N$^+$HCl$^-$). ^{13}C NMR (DMSO-d_6), δ: 12.24 (C(10)); 20.08 (C(9)); 20.50 (ArCH_3); 21.31 (C(8)); 27.08 (C(5)); 33.48 (C(3)); 38.98 (C(6), partly overlapped with the solvent signal); 44.57 (C(2)); 44.99 (C(4)); 47.64 (C(7)); 49.45 (C(1)); 50.13, 50.81 (N(C$\underline{H}_2$CH_2)$_2$O); 54.73 (ArCH_2); 63.08 (N(CH_2C$\underline{H}_2$)$_2$O); 117.00, 128.20, 133.08 (C(11), C(13), C(15)); 130.24, 130.90 (C(14), C(16)); 153.17 (C(12)).

2-Methyl-4-(morpholinomethyl)-6-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol hydrochloride (26). A colorless foamy product. Yield 0.28 g (74%). Found (%): C, 69.44; H, 9.11; N, 3.58. $C_{22}H_{34}ClNO_2$. Calculated (%): C, 69.54; H, 9.02; N, 3.69. IR (KBr), ν/cm^{-1}: 3337 (OH); 2949, 2874, 2675, 2637, 2592, 2550, 2465, 1477, 1452 (CH_3, CH_2); 1599 (C=C); 1194, 1126, 1082, 1055 (C—O); 866, 791 (=C—H). ^{1}H NMR (DMSO-d_6), δ: 0.69, 0.79, 0.85 (all s, 3 H each, C(8)H_3, C(9)H_3, C(10)H_3); 1.17—1.39 (m, 1 H, 1 H(5)); 1.40—1.65 (m, 3 H, 1 H(3), 2 H(6)); 1.68—1.94 (m, 2 H, 1 H(4), 1 H(5)); 2.05—2.34 (m, 1 H, 1 H(3)); 2.18 (s, 3 H, ArCH_3); 2.80—3.49 (m, 5 H, 1 H(2), N(C$\underline{H}_2$CH_2)$_2$O, partly overlapped with the HOD signal); 3.60—3.98 (m, 4 H, N(CH_2C$\underline{H}_2$)$_2$O); 4.00—4.30 (m, 2 H, ArCH_2); 7.13, 7.34 (both s, 1 H each, 1 H(14), 1 H(16)); 8.46 (br.s, 1 H, OH); 11.14 (br.s, 1 H, N$^+$HCl$^-$). ^{13}C NMR (DMSO-d_6), δ: 12.22 (C(10)); 17.08 (ArCH_3); 20.11 (C(9)); 21.35 (C(8)); 27.14 (C(5)); 33.55 (C(3)); 39.12 (C(6), partly overlapped with the solvent signal); 44.63 (C(2)); 45.02 (C(4)); 47.58 (C(7)); 49.38 (C(1)); 49.46, 50.55 (N(C$\underline{H}_2$CH_2)$_2$O); 59.11 (ArCH_2); 63.02 (N(CH_2C$\underline{H}_2$)$_2$O); 118.81, 123.91, 130.72 (C(11), C(13), C(15)); 128.92, 131.09 (C(14), C(16)); 155.16 (C(12)).

Synthesis of compounds 27 and 28. On gentle heating, 2-hydroxy-3-isobornyl-5-methylbenzaldehyde (0.27 g, 1.0 mmol) was dissolved in dry MeOH (25 mL) or 4-hydroxy-3-isobornyl-5-methylbenzaldehyde (0.27 g, 1.0 mmol) was dissolved in dry EtOH (10 mL). To the obtained solution, KOH (0.06 g, 1.0 mmol), 1-adamantylamine hydrochloride (0.19 g, 1.0 mmol), and 1.1 g of molecular sieves were added. The reaction mixture was refluxed in an argon atmosphere for 4.5 h, the clay was separated by filtration, the residue was washed successively with Et_2O and $CHCl_3$, the solvents were removed under reduced pressure. Acetone was added to the residue, the solution was filtered (from KCl), and the solvent was evaporated. The *in situ* obtained imine was dissolved in dry MeOH (10—25 mL), the mixture was cooled to ~5 °C (the bath temperature), $NaBH_4$ (0.19 g, 5.0 mmol) was added to it in portions, the mixture was stirred for 40 (in the case of compound **27**) or 90 min (in the case of compound **28**) while warming to room temperature. After the completion of the reaction, 15 mL of a 2 *M* solution of NaOH was added, the mixture was stirred for 5 min, then, 50 mL of CH_2Cl_2 (the synthesis of compound **27**) or 30 mL of Et_2O (the synthesis of compound **28**) was added, and the mixture was stirred for another 15 min. In the case of the synthesis of compound **27**, an additional extraction with CH_2Cl_2 (2×50 mL) was carried out. The organic layer was washed with a 2 *M* aqueous solution of NaCl until pH ≈ 7 and dried over anhydrous K_2CO_3. Thus obtained amine (without isolation) was converted into the hydrochloride (see the procedure for synthesis of compounds **21**—**26**).

2-[(Adamantan-1-ylamino)methyl]-4-methyl-6-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol hydrochloride (27). A colorless powder, m.p. 276—277 °C. Yield 0.27 g (61%). Found (%): C, 75.91; H, 9.66; N, 3.11. $C_{28}H_{42}ClNO$. Calculated (%): C, 75.73; H, 9.53; N, 3.15. IR (KBr), ν/cm^{-1}: 3375, 3356, 3152, 3144 (OH); 2918, 2876, 2859, 2760, 2702, 2637, 1468, 1456 (CH_3, CH_2); 1609, 1576 (C=C); 1211, 1076 (C—O); 864, 785 (=C—H). ^{1}H NMR (DMSO-d_6), δ: 0.71, 0.80, 0.85 (all s, 3 H each, C(8)H_3, C(9)H_3, C(10)H_3); 1.20—1.42 (m, 1 H, 1 H(5)); 1.42—1.89 (m, 11 H, 1 H(3), 1 H(4), 1 H(5), 2 H(6), 6 H(3′)); 1.90—2.31 (m, 10 H, 1 H(3), 6 H(2′), 3 H(4′)); 2.23 (s, 3 H, ArCH_3); 1.66—1.91 (m, 2 H, 1 H(4), 1 H(5)); 2.02—2.29 (m, 1 H, 1 H(3)); 3.29 (t, 1 H, H(2), J = 8.9 Hz, partly overlapped with the HOD signal); 3.74—4.22 (m, 2 H, ArCH_2); 7.01, 7.12 (both s, 1 H each, 1 H(14), 1 H(16)); 8.47 (br.s, 1 H, OH); 8.86 (br.s, 1 H, N$^+$HCl$^-$).^{13}C NMR (DMSO-d_6), δ: 12.46 (C(10)); 20.21 (C(9)); 20.56 (ArCH_3); 21.30 (C(8)); 27.08 (C(5)); 28.49 (C(4′)); 33.76 (C(3)); 35.26 (C(3′)); 37.38 (C(2′)); 39.69, 39.24 (C(6), ArCH_2, partly overlapped with the solvent signal); 44.70 (C(2)); 45.04 (C(4)); 47.58 (C(7)); 49.35 (C(1)); 56.94 (C(1′)); 120.95, 128.29, 133.52 (C(11), C(13), C(15)); 139.35, 129.60 (C(14), C(16)); 152.27 (C(12)).

4-[(Adamantan-1-ylamino)methyl]-2-methyl-6-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol hydrochloride (28). A colorless powder, m.p. 238—239 °C. Yield 0.28 g (63%). Found (%): C, 75.97; H, 9.61; N, 3.21. $C_{28}H_{42}ClNO$. Calculated (%): C, 75.73; H, 9.53; N, 3.15. IR (KBr), ν/cm^{-1}: 3603, 3337 (OH); 2918, 2874, 2859, 2822, 2762, 2702, 2633, 1477, 1452 (CH_3, CH_2); 1578 (C=C); 1192, 1076 (C—O); 872, 787 (=C—H). ^{1}H NMR (DMSO-d_6), δ: 0.71, 0.80, 0.86 (all s, 3 H each, C(8)H_3, C(9)H_3, C(10)H_3); 1.23—1.41 (m, 1 H, 1 H(5)); 1.42—2.02 (m, 17 H, 1 H(3), 1 H(4), 1 H(5), 2 H(6), 6 H(2′), 6 H(3′)); 2.03—2.32 (m, 4 H, 1 H(3), 3 H(4′)); 2.20 (s, 3 H, ArCH_3); 3.27 (t, 1 H, H(2), J = 8.8 Hz, partly overlapped with the HOD signal); 3.94 (s, 2 H, ArCH_2); 7.08, 7.27 (both s, 1 H each, 1 H(14), 1 H(16)); 8.32 (br.s, 1 H, OH); 8.65 (br.s, 1 H, N$^+$HCl$^-$).^{13}C NMR (DMSO-d_6), δ: 12.21 (C(10)); 17.01 (ArCH_3); 20.34 (C(9)); 21.34 (C(8)); 27.16 (C(5)); 28.51 (C(4′)); 33.55 (C(3)); 35.24 (C(3′)); 37.49 (C(2′)); 39.24 (C(6), partly overlapped with the solvent signal); 42.92 (ArCH_2); 44.76 (C(2)); 45.06 (C(4)); 47.57 (C(7)); 49.43 (C(1)); 56.80 (C(1′)); 122.49, 123.96, 130.78 (C(11), C(13), C(15)); 127.42, 129.70 (C(14), C(16)); 154.64 (C(12)).

Study of biological activity of compounds 1—38. The following materials and reagents were used: influenza virus,

strain A/Puerto Rico/8/34 (H1N1); human parainfluenza virus type 3 (HPIV-3); human coronavirus OC43 (HCoV-OC43); human adenovirus type 5 (AdV5); complete α-MEM medium containing L-glutamine (2 m*M*), gentamycin (250 mg L^{-1}, Biolot, Saint-Petersburg, cat. No. 1.3.17.1), 10% fetal bovine serum (Biolot, Saint-Petersburg, cat. No 1.3.9.1); physiologic saline (a 0.9% solution of NaCl in distilled water, sterile, Biolot, Saint-Petersburg, cat. No 1.2.1.3); a tripsin solution (0.1 mg mL^{-1}, Sigma, USA, T1426); 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT, ICN Biochemicals Inc., Aurora, Ohio).

Cell lines MDCK (ATCC, USA, cat. No. CCL-34), Vero (ATCC, USA, cat. No. CCL-81), and MA-104 (ATCC, USA, cat. No. CRL-2378.1) were used in this study. Influenza virus was cultivated in MDCK cells, AdV5 and HCoV-OC43 viruses were cultivated in Vero cells, HPIV-3 virus was cultivated in MA-104 cells.

Cells were seeded into 96-well cell culture plates (Biologix, China, cat. No. 07-6096) in an amount of 10^4 cells per well and cultivated until the formation of a confluent monolayer. The resulting cultures were subsequently used to assess the antiviral and cytotoxic activity of the compounds.

Appropriate weighted portions of the test compounds were dissolved in DMSO to a concentration of 60 mg mL^{-1}, and a series of threefold dilutions from 600 to 8 μg mL^{-1}, which were subsequently used in experiments, were prepared from the obtained mother solutions.

Evaluation of the cytotoxic effect of the test comounds in cell culture (the MTT assay). The study of the toxicity of the compounds was carried out on the basis of the assessment of the viability of the cells of the corresponding lines using the reduction reaction of the tetrazolium dye MTT by cells in culture, the intensity of which reflects the degree of cell viability as a result of the reduction of the dye by mitochondrial and partially cytoplasmic dehydrogenases.

The test compounds at concentrations of 3.7—300 μg mL^{-1} dissolved in the cell cultivation medium were introduced into wells of a cell culture plate in the amount of 200 μL, and the plates were incubated for 72 h at 36 °C in an atmosphere of 5% CO_2. Then the cells were washed with the MEM medium, and 100 μL of a solution (0.5 mg mL^{-1}) of the tetrazolium dye MTT in the cell culture medium was added into each well. The cells were incubated at 36 °C in an atmosphere of 5% CO_2 for 2 h and, then, washed with physiologic saline for 5 min. The residue in each well was dissolved in 100 μL of DMSO, and optical density was measured using a Thermo Scientific Multiscan FC microplate photometer at λ = 540 nm. Based on the data obtained, the 50% cytotoxic concentration (CC_{50}) was calculated, which is the compound concentration reducing the optical density in the well by a factor of two as compared to the control wells, into which the compound was not added.

Study of antiviral activity of compounds. The test samples (100 μL) were added to the wells of cell culture plates containing monolayers of cells of the respective line. The cell culture plates with cells were incubated in an atmosphere of 5% CO_2 at 37 °C for 1 h. After that, 0.1 mL of the virus in α-MEM medium was introduced into the wells at a multiplicity of infection of 0.01 $TCID_{50}$ per cell, and the cell culture plates with cells were incubated in an atmosphere of 5% CO_2 at 36 °C for 72 h. The infected cells were then washed with MEM medium and cell viability assay was performed as described above. Based on the data obtained, the 50% inhibitory concentration (IC_{50}) resulting in a 50% reduction in viral cell destruction was calculated for each compound.

Calculations of 50% cytotoxic (CC_{50}) and 50% inhibitory (IC_{50}) concentrations were performed using the GraphPad Prism 6.01 software package. A 4-parameter equation of the logistic curve was taken as a working model for analysis (menu options "Nonlinear regression"—"inhibitor logarithm—response"). Based on the data obtained, for each compound and each virus, the selectivity index (SI), which is the ratio of CC_{50} to IC_{50}, was calculated.

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The authors declare no competing interests.

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