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, 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 membrane-protective 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 amino-methyl 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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By condensation of substituted isobornylbenzaldehydes with 1-adamantylamine followed by reduction (in situ) of intermediate imines, aminomethyl 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 $^1$H 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 $^1$H and $^{13}$C NMR spectra of these compounds, the signals of protons and carbon atoms of the substituted terpenophenolic skeleton were observed.

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**Scheme 1***

| Compound | R<sub>1</sub> | R<sub>2</sub> |
|----------|-------------|-------------|
| 21       | CH<sub>3</sub>NMe<sub>2</sub> • HCl | H            |
| 22       | CH<sub>3</sub>NMe<sub>2</sub> • HCl | Me           |
| 23       | Me          | Me           |
| 24       | CH<sub>3</sub>NMe<sub>2</sub> • HCl | Me           |
| 25       | CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub> • HCl | Me           |
| 26       | Me          | Me           |
| 27       | CH<sub>2</sub>NH(1-Ad) • HCl | Me           |
| 28       | CH<sub>2</sub>NH(1-Ad) • HCl | Me           |
| 29       | CH<sub>3</sub>NO<sub>2</sub> | Me           |
| 30       | C=O         | Me           |

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**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<sub>4</sub>, MeOH, 5—20 °C, 40 min. *iii.* HCl (EtOH), Et<sub>2</sub>O, 20 °C, 40 min.

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* 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.
The SSCC value ($J = 16.0 \text{ Hz}$) in the $^1\text{H}$ 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 $\text{CC}_{50} > 600 \text{ mol L}^{-1}$. The lowest toxicity was exhibited by 2-(dimethylaminomethyl)-6-isobornyl-4-methylphenol 22 with $\text{CC}_{50} > 880 \text{ mol L}^{-1}$. However, all non-toxic derivatives showed no significant virus-inhibiting activity except benzamide 34 with two isobornyl substituents (selectivity index $\text{SI} = 21$). 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, 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 ($\text{CC}_{50} = 173$ and 158 $\text{ mol L}^{-1}$, respectively), at the same time, these compounds show no antiviral activity. 2-Isobornylphenol (1) and 2-isocamphylphenol (3) showed moderate antiviral activity ($\text{SI} = 10$ 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 | $\text{CC}_{50}$ | $\text{IC}_{50}$ | SI | $\text{CC}_{50}$ | $\text{IC}_{50}$ | SI |
|----------|-----------------|-----------------|----|-----------------|-----------------|----|
|          | $\mu\text{mol L}^{-1}$ |                 |    | $\mu\text{mol L}^{-1}$ |                 |    |
| 1        | 8±0.7           | 0.5±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±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. $\text{CC}_{50} (\text{M±SD})$ 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; $\text{IC}_{50} (\text{M±SD})$ is a compound concentration resulting in the 50% reduction in the cytodestructive action of the virus; selectivity index ($\text{SI}$) is the ratio of $\text{CC}_{50}$ to $\text{IC}_{50}$.\"
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. $^1$H 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 $^1$H 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 Sorbil 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$_2$O, and 0.5 mL of concentrated H$_2$SO$_4$). 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.

| Compound | HCoV-OC43 | HPIV-3 | AdV5 |
|----------|-----------|--------|------|
|          | CC$_{50}$ | IC$_{50}$ | SI | CC$_{50}$ | IC$_{50}$ | SI | CC$_{50}$ | IC$_{50}$ | SI |
|          | $\mu$mol L$^{-1}$ | $\mu$mol L$^{-1}$ |          | $\mu$mol L$^{-1}$ | $\mu$mol L$^{-1}$ |          | $\mu$mol L$^{-1}$ | $\mu$mol 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 |
To synthesize compounds 7 and 28, 2-hydroxy-3-isobornyl-5-methylbenzaldehyde and 4-hydroxy-3-isobornyl-5-methylbenzaldehyde 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 borosaliclyl ester. The product was extracted with diethyl ether (3×15 mL), washed with water (15 mL), dried over Na2SO4, the solvent was removed under reduced pressure. The residue was purified by column chromatography (using a mixture of CCl4 and acetone, 10 : 0 → 10 : 1, as an eluent).

1-Hydroxy-2-oxymethyl-6-(1,7,7-trimethylbicyclo[2.2.1]hept-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.

1-Hydroxy-2-oxymethyl-6-(1R,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)phenol (9). A colorless powder, m.p. 116 °C, Rf 0.59 (eluent: CCl4—acetone, 10 : 1). Yield 0.22 g (43%). 

Synthesis of compounds 20. A solution (126 mL) of chlorine dioxide, ClO2, in CH2Cl2 was added to phenol 19 (1.38 g, 5.6 mmol) (the phenol : ClO2 molar ratio was 1 : 2). The ClO2 solution in CH2Cl2 was obtained by extraction of ClO2 from water (15 mL), dried over Na2SO4, the solvent was removed under reduced pressure. Separation of the products was carried out by column chromatography using chloroform as an eluent.

2-Hydroxy-4-methyl-6-(2,2,3-trimethylbicyclo[2.2.1]hept-2-yl)phenol (12). A pale yellow semi-crystalline powder, m.p. 0.57 (eluent: CCl4—acetone, 10 : 1). Yield 0.36 g (66%). Spectroscopic characteristics of the compound corresponds to those reported previously.

Antiviral activity of terpenophenols. Calculated (%): C, 79.03; H, 9.61. IR (KBr), cm−1: 3460, 3198 (OH); 2976, 2949, 2874, 1479, 1468 (CH3, CH2); 1611 (C=C); 1258, 1223, 1157, 1138, 1015 (C—O); 860, 785 (=C—H). 13C NMR (CDCl3), δ: 14.80, 18.76, 19.86 (C(8)), C(9), C(10); 20.84 (ArCH3); 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)); 65.10, 124.93, 125.88 (C(14), C(15), C(16)); 124.04, 134.76 (C(11), C(13)); 153.98 (C(12)). 1H NMR (CDCl3), δ: 7.07 (s, 1 H, ArOH). 13C NMR (CDCl3), δ: 14.80, 18.76, 19.86 (C(8)), C(9), C(10); 20.84 (ArCH3); 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)); 65.10, 124.93, 125.88 (C(14), C(15), C(16)); 124.04, 134.76 (C(11), C(13)); 153.98 (C(12)).
2-(1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl)cyclohexa-2,5-dien-1,4-dione (20). A dark brown powder, m.p. 105—106 °C, Rf 0.59 (eluens: CHCl3). Yield 1.3 g (95%). Found (%): C, 78.49; H, 8.21. C35H30O2. 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)). \(^1\)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\(_2\)O (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\(_2\)O and dried. To isolate dihydrochloride 24, the ether solution was separated, the oily residue was successively washed with chilled Et\(_2\)O (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-2-yl)phenol dihydrochloride (21). A colorless powder, m.p. 255—256 °C. Yield 0.31 g (92%). Found (%): C, 71.20; H, 9.43; N, 4.11. C\(_{35}\)H\(_{30}\)ClNO. Calculated (%): C, 71.09; H, 9.55; N, 4.14. IR (KBr), ν/cm\(^{-1}\): 3358 (OH); 2949, 2876, 2737, 1473 (CH\(_2\), CH\(_3\)); 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, 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 (brs, 1 H, OH); 10.53 (brs, 1 H, N\(^{+}\)HCl). \(^1\)C NMR (DMSO-d\(_6\)), δ: 12.22 (C(10)); 17.07 (ArCH\(_2\)); 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(2)); 47.56 (C(7)); 49.35 (C(11)); 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-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\(_{37}\)H\(_{33}\)Cl\(_2\)N\(_2\)O. Calculated (%): C, 63.30; H, 9.18; N, 6.71. IR (KBr), ν/cm\(^{-1}\): 3381, 3238, 3221 (OH); 2951, 2878, 2691, 1472 (CH\(_2\), CH\(_3\)); 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 2 H each, 2 ArCH\(_2\)); 7.44, 7.61 (both s, 1 H each, 1 H(14), 1 H(16)); 9.40 (brs, 1 H, OH); 10.59, 10.97 (both brs, 1 H each, 2 N\(^{+}\)HCl). \(^1\)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-2-yl)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), v/cm\(^{-1}\): 3316, 3221 (OH); 2951, 2928, 2874, 2668, 2583, 2542, 2467, 1468 (CH\(_2\)CH\(_2\)); 1612 (C=C); 1194, 1124, 1084, 1053 (C—O); 874, 777 (C—H). H NMR (DMSO-d\(_6\)), \(\delta\): 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\(_2\)); 2.86—3.52 (m, 5 H, 1 H, 2 H(1), N(CH\(_2\)CH\(_2\))\(_2\)O, partly overlapped with the HOD signal); 3.59—4.06 (m, 4 H, N(CH\(_2\)CH\(_2\))\(_2\)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–). 13C NMR (DMSO-d\(_6\)), δ: 12.22 (C(1)); 49.38 (C(1)); 49.46, 50.55 (N(CH\(_2\)CH\(_2\))\(_2\)O); 59.11 (ArCH\(_2\)); 63.08 (N(CH\(_2\)CH\(_2\))\(_2\)O); 117.00, 128.92, 131.09 (C(14), C(16)); 155.16 (C(12)).

Study of biological activity of compounds 1—38. The following materials and reagents were used: influenza virus, antiviral activity of terpenophenols.
strain A/Puerto Rico/8/34 (H1N1); human parainfluenza virus type 3 (HPV-3); human coronavirus OC43 (HCoV-OC43); human adenovirus type 5 (AdV5); complete α-MEM medium containing 1-glutamine (2 mM), gentamycin (250 μg mL−1), Biologit, Saint-Petersburg, cat. No. 1.3.17.1), 10% fetal bovine serum (Biologit, Saint-Petersburg, cat. No 1.3.9.1); physiologic saline (a 0.9% solution of NaCl in distilled water, sterile, Biologit, Saint-Petersburg, cat. No 1.2.1.3); a trispin solution (0.1 mg mL−1, Sigma, USA, T1426); 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT, ICN Biochemicals Inc., Aurora, Ohio).

Cell lines MDCK (ATCC, USA, cat. No. CRL-2378.1) were used in this study. Influenza virus (ATCC, USA, cat. No. CCL-81), and MA-104 (ATCC, USA, cat. No. CRL-2378.1); 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-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% CO2 for 1 h. After that, 0.1 mL of the virus in α-MEM medium containing L-glutamine (2 mM) was introduced into the wells at a multiplicity of infection of 0.01 TCID50 per cell, and the cell culture plates with cells were incubated in an atmosphere of 5% CO2 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 (IC50) resulting in a 50% reduction in viral cell destruction was calculated for each compound. Calculations of 50% cytotoxic (CC50) and 50% inhibitory (IC50) 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 CC50 to IC50, was calculated.

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References

1. M. D. Mashkovsky, Lekarstvennye sredstva [Medicines], 16 ed., Izd-vo Novaya Volna, Moscow, 2012, 166 pp. (in Russian).
2. I. Yu. Chukicheva, E. V. Buravlev, I. A. Dvornikova, I. V. Fedorova, G. A. Chernysheva, O. I. Aliev, V. I. Smol’ya- kova, A. M. Anishchenko, A. V. Sidekhmenova, M. B. Plotnikov, A. V. Kutchin, Russ. Chem. Bull., 2019, 68, 993; DOI: 10.1007/s11172-019-2590-0.
3. T. M. Plotnikova, G. A. Chernysheva, V. A. Smol’ya- kova, P. P. Shchetinin, A. V. Kutchin, I. Yu. Chukicheva, M. B. Plotnikov, Bull. Exp. Biol. Med. (Engl. Transl.), 2018, 165, 657; DOI: 10.1007/s10517-018-4235-2.
4. T. M. Plotnikova, G. A. Chernysheva, V. I. Smol’ya- kova, P. P. Shchetinin, A. V. Kutchin, I. Yu. Chukicheva, M. B. Plotnikov, Bull. Exp. Biol. Med. (Engl. Transl.), 2014, 157, 211; DOI: 10.1007/s10517-014-2527-8.
5. M. B. Plotnikov, V. I. Smolyakova, I. S. Ivanov, A. V. Kuchin, I. J. Chukicheva, E. A. Krasnov, Bull. Exp. Biol. Med. (Engl. Transl.), 2008, 145, 328; DOI: 10.1007/s10517-008-0082-x.
6. E. V. Buravlev, I. V. Fedorova, O. G. Shevchenko, A. V. Kutchin, Russ. Chem. Bull., 2019, 68, 1558; DOI: 10.1007/ s11172-019-2592-2.
7. E. V. Buravlev, O. G. Shevchenko, Russ. Chem. Bull., 2020, 69, 1971; DOI: 10.1007/s11172-020-2987-0.
8. E. V. Buravlev, O. G. Shevchenko, Russ. Chem. Bull., 2019, 68, 79; DOI: 10.1007/s11172-019-2419-1.
9. I. A. Dvornikova, E. V. Buravlev, O. G. Shevchenko, I. Yu. Chukicheva, A. V. Kutchin, Russ. Chem. Bull., 2021, 70, 2185; DOI: 10.1007/s11172-021-3330-0.
10. O. G. Shevchenko, S. N. Pylusnina, I. Yu. Chukicheva, I. V. Fedorova, A. V. Kutchin, Biochem. Moscow
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11. M. Cirri, P. Mura, P. Corvi Mora, Int. J. Pharm., 2007, 340, 84; DOI: 10.1016/j.ijpharm.2007.03.021.
12. F. Celandroni, D. Mazzantini, M. Calvigioni, S. Ceccanti, S. Vecchiani, S. Battaglia, C. Bigini, E. Ghelardi, Adv. Exp. Med. Biol., 2022, 1369, 101; DOI: 10.1007/5584_2021_664.
13. M. Verani, I. Federigi, G. Lauretani, S. Muzio, A. Carducci, Adv. Exp. Med. Biol., 2022, 1; DOI: 10.1007/5584_2022_722.
14. G. Roman, Eur. J. Med. Chem., 2015, 89, 743; DOI: 10.1016/j.ejmech.2014.10.076.
15. E. V. Suslov, E. S. Mozhaytsev, D. V. Korchagina, N. I. Bormotov, O. I. Yarovaya, K. P. Volcho, O. A. Serova, A. P. Agafonov, R. A. Maksyutov, L. N. Shishkina, N. F. Salakhutdinov, RSC Med. Chem., 2020, 11, 1185; DOI: 10.1039/d0md00108b.
16. I. Yu. Chukicheva, L. V. Spirikhin, A. V. Kuchin, Russ. J. Org. Chem., 2008, 44, 62; DOI: 10.1134/S1070428008010077.
17. A. Berkessel, M. R. Vennemann, J. Lex, Eur. J. Org. Chem., 2002, 2800; DOI: 10.1002/1099-0690(200208)2002:16<2800::AID-EJOC2800>3.0.CO;2-4.
18. E. V. Buravlev, I. Yu. Chukicheva, A. V. Churakov, A. V. Kutchin, Russ. J. Org. Chem., 2012, 48, 64; DOI: 10.1134/S1070428012010095.
19. L. N. Shishkina, L. I. Mazaletskaya, K. M. Marakulina, Yu. K. Lukanina, I. G. Pashchina, N. I. Sheludchenko, E. V. Buravlev, I. V. Fedorova, I. Yu. Chukicheva, A. V. Kutchin, Russ. Chem. Bull., 2014, 63, 2007; DOI: 10.1007/s11172-014-0692-6.
20. E. V. Buravlev, I. Yu. Chukicheva, K. Yu. Suponitskii, A. V. Kuchin, Russ. J. Gen. Chem., 2008, 78, 1411; DOI: 10.1134/S1070363208070220.
21. O. G. Shevchenko, S. N. Plyusnina, E. V. Buravlev, I. Yu. Chukicheva, I. V. Fedorova, O. V. Shchukina, A. V. Kutchin, Russ. Chem. Bull., 2017, 66, 1881; DOI: 10.1007/s11172-017-1962-x.
22. E. V. Buravlev, I. Yu. Chukicheva, O. A. Shumova, K. Yu. Suponitskii, A. V. Kutchin, Russ. J. Org. Chem., 2013, 49, 1300; DOI: 10.1346/S1070428013090108.
23. I. Yu. Chukicheva, I. V. Fedorova, A. V. Kutchin, Khimiya rastit. syryya [Chem. Plant Raw Mater.], 2009, No. 3, 63 (in Russian).
24. E. V. Buravlev, I. V. Fedorova, O. G. Shevchenko, A. V. Kutchin, Russ. Chem. Bull., 2020, 69, 1573; DOI: 10.1007/s11172-020-2937-x.
25. E. V. Buravlev, I. Yu. Chukicheva, O. G. Shevchenko, K. Yu. Suponitskii, A. V. Kutchin, Russ. Chem. Bull., 2016, 65, 1232; DOI: 10.1007/s11172-016-1440-x.
26. E. V. Buravlev, I. Yu. Chukicheva, O. V. Sukrusesha, O. G. Shevchenko, A. V. Kutchin, Russ. Chem. Bull., 2015, 64, 1406; DOI: 10.1007/s11172-015-1024-1.
27. E. V. Buravlev, I. Yu. Chukicheva, O. G. Shevchenko, A. V. Kutchin, Russ. Chem. Bull., 2017, 66, 297; 10.1007/s11172-017-1731-x.
28. E. V. Buravlev, I. A. Dvornikova, O. G. Schevchenko, A. V. Kutchin, Chem. Biodiversity, 2019, 16, e1900362; DOI: 10.1002/cbdv.201900362.
29. E. V. Buravlev, O. G. Shevchenko, A. V. Kutchin, Russ. Chem. Bull., 2021, 70, 183; DOI: 10.1007/s11172-021-3075-9.
30. I. Yu. Chukicheva, E. V. Buravlev, L. V. Spirikhin, A. V. Churakov, A. V. Kutchin, Russ. Chem. Bull., 2006, 55, 1819; DOI: 10.1007/s11172-006-0492-8.
31. E. V. Buravlev, I. Yu. Chukicheva, M. A. Elfimova, K. Yu. Suponitskii, A. V. Kutchin, Russ. J. Org. Chem., 2015, 51, 623; DOI: 10.1134/S1070428015050061.

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