Synthesis of (1*S*)-(+)-camphor-10-sulfonic acid derivatives and investigations *in vitro* and *in silico* of their antiviral activity as the inhibitors of filovirus infections*

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N-Heterocycle-containing (1*S*)-(+)-camphor-10-sulfonamide derivatives were synthesized. Their antiviral activity against the Ebola and Marburg viruses was estimated using a pseudovirus system based on the vesicular stomatitis virus. The derivatives bearing morpholine and triazole moieties demonstrated the highest inhibitory activity towards the Ebola virus glycoprotein. A moderate activity against the Marburg virus was found for a compound containing the piperidine moiety. A molecular modeling of the interaction between the synthesized derivatives and the binding site of glycoprotein of the Ebola virus was performed.

Key words: Marburg virus, Ebola virus, pseudotyped viruses, (1*S*)-(+)-camphor-10-sulfonic acid, *N*-heterocycles, molecular docking.

The Marburg and Ebola viruses belonging to the filoviruses family cause severe hemorrhagic fevers in humans and nonhuman primates, which are characterized by a high viremia and multiple organ failure with the mortality rate of up to 90%. To date, there are neither officially approved vaccines nor a standard therapy, although some experimental vaccines and treatment methods have demonstrated promising results on nonhuman primates.[1]

Our previous work[2] revealed that derivatives of camphor and borneol (bicyclic monoterpenoids of the 1,7,7-trimethylbicyclo[2.2.1]heptane family) exhibit a broad range of the antiviral activity. Camphor and borneol are used as pharmaceuticals. Camphor is a component of various ointments used to control the symptoms of a cold. An oil solution of camphor administered parenterally causes analeptic and cardiotonic effects, while its topical application has antimicrobial, irritant, analgesic, and anti-inflammatory effects. Borneol has been used in traditional Chinese and Japanese medicine in the cases of unconsciousness and convulsions.

We have already demonstrated that compounds containing a camphor moiety, imino groups and/or tertiary charged nitrogen atoms exhibit a high antiviral activity against the influenza virus. A pronounced inhibitory activity against the influenza virus was also observed[3—5] for heterocyclic derivatives of (−)-borneol.[6,7] We have found that camphor and borneol heterocyclic derivatives are promising inhibitors of vaccinia virus, which is a typical member of the family *Orthopoxvirus* that includes *Variola Virus*.[8,9] The antiviral activity of camphor and borneol derivatives was also investigated against the Marburg virus. Borneol esters containing six-membered heterocycles were found promising among the studied derivatives.[10] These compounds possess also an antiulcer activity.[11] Thus, the camphor and borneol moieties are promising for designing the inhibitors of various viral infections.

In the present work, (1*S*)-(+)-camphor-10-sulfonic acid (**1**) was selected as the starting compound containing a desired skeleton. It should be noted that some of its derivatives were previously synthesized in order to evaluate their biological activity. Potential anti-tuberculosis agents[12] and antagonists of chemokine CXCR3[13] and oxytocin[14] receptors have been found among those derivatives, but the antiviral activity of this class of agents has not been previously estimated.

Results and Discussion

The target compounds were synthesized according to Scheme 1. At the first step, (1*S*)-(+)-camphor-10-sulfonyl

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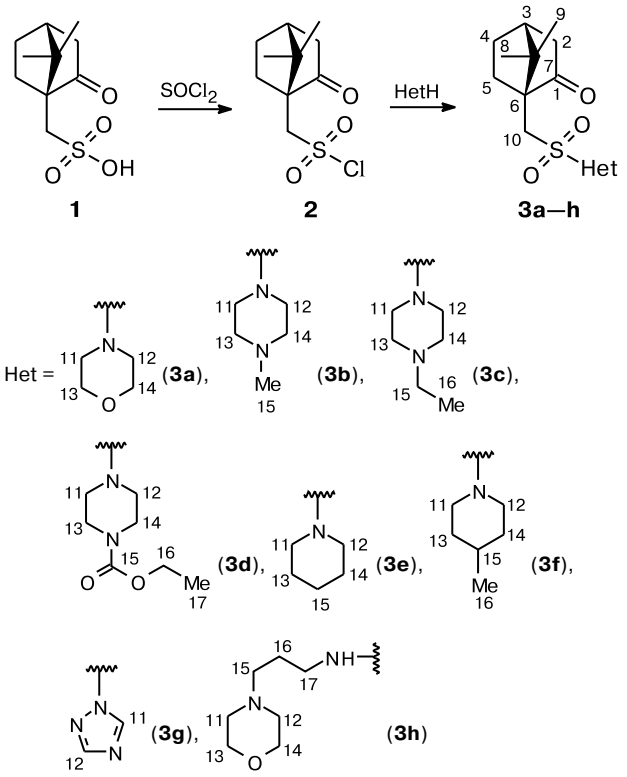
chloride (**2**) was prepared. A library of (1*S*)-(+)-camphor-10-sulfonamides bearing a heterocyclic moiety was obtained at the second step by the reaction of sulfonyl chloride **2** with various *N*-nucleophiles in the presence of Et_3N under stirring at room temperature. The structure of obtained compounds was determined by ^1H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry (HRMS).

Scheme 1



Currently, the majority of researches on the discovery of antiviral compounds are aimed at inhibitors of the specific enzyme of RNA-containing viruses, RNA-dependent RNA polymerase. The replication carried out by this enzyme is the most important step in the life cycle of a virus, but its occurrence means that the virus has already been introduced into the cell. In order to minimize the virus effect on the body, it is necessary to block it during its entering into the cell.

Filoviruses and, in particular, the Ebola and Marburg viruses, contain on their surface only the one glycoprotein (GP) that ensures the pathogen penetration into the cell. This protein is a suitable target since it is absent in mammalian cells same as the RNA-dependent RNA polymerase. The compounds synthesized in the present work were evaluated as inhibitors of the uptake of filovirus pathogens into the host cell. The evaluation of inhibitory activity was performed using pseudotyped viruses of the one cycle. Operations with Marburg and Ebola viruses can only be performed in laboratories equipped at the highest biosafety level (BSL-4), which makes the large-scale screening of various low-molecular compounds difficult. The usage of pseudovirus systems allows one to screen the inhibitors of highly pathogenic infections in laboratories of BSL-2 level. This technology is safe and highly efficient. According to this procedure, pseudovirus particles that mimic the molecular features of the surface of a natural virus are prepared. Since pseudoviruses are not capable of replication, a high degree of safety in the working environment is maintained.

The values of half maximal inhibition concentrations (IC_{50}) and half maximal cytotoxic concentrations (CC_{50}) were determined for all the investigated compounds. According to the acquired experimental data, camphor-10-sulfonamide derivatives **3a—h** inhibit the glycoprotein of the Ebola virus (GP EBOV) more efficiently than the glycoprotein of the Marburg virus (GP MARV). This fact was revealed by a comparison of the IC_{50} values for the Ebola pseudovirus, which varied from 0.9 to 540 μmol L^{-1}, while these values for the Marburg virus were in the range of 231—450 μmol L^{-1}. The most efficient GP EBOV inhibitors were derivatives **3a** and **3g** bearing moieties of morpholine and triazole, respectively (IC_{50} = 0.9±0.5 (**3a**) and 1.0±0.4 μmol L^{-1} (**3g**)). Moreover, these compounds exhibited a low toxicity, which led to high values of the selectivity index (SI_{EBOV}) of compounds **3a** and **3g** (921 and 1764, respectively). Derivative **3h** containing an aliphatic linker between the sulfamide group and morpholine moiety has also demonstrated the high inhibitory activity, its SI_{EBOV} value was 232. A high SI_{EBOV} value (134) was also found for piperazine derivative **3d** bearing a *N*-ethoxycarbonyl substituent at the piperazine ring. Compounds **3b,c** containing the piperazine ring with an alkyl substituent at the position 4 caused a significantly lower effect on the ability of Ebola virus to enter into the host cell (IC_{50} = 91±4 (**3b**) and 540±20 μmol L^{-1} (**3c**)). Piperidine derivatives **3e—f** exhibited a moderate ability to inhibit the GP EBOV. A well-known antidepressant, sertraline, was chosen as the reference drug since there are reported data[15] confirming the efficient binding of this drug to GP EBOV.

To simulate a possible mechanism of GP EBOV blocking by the synthesized compounds, we performed the molecular docking of these compounds into the active binding site of known inhibitors using an XP (*extra precision*) docking algorithm implemented in the Glide program (Schrödinger Suite[16] 2016-1). Models (PDB IDs: 6F6S, 6F6N, 6F6I, and 6F5U)[17] representing the envelope glycoprotein (GP1) of the Ebola virus (Zaire ebolavirus, strain Mayinga-76) were selected in combination with pharmacologically significant inhibitors (resolution of 2.07 Å). Table 1 shows values of the minimum binding energy obtained from the calculated docking function. The dock-

Table 1. Inhibitory activity of the synthesized derivatives against Marburg and Ebola pseudoviruses

Compound	IC_{50}[a]/μmol L^{-1}		CC_{50}[b] /μmol L^{-1}	SI_{EBOV}[c]	$-E_{bind}$[d] /kcal mol^{-1}
	GP MARV	GP EBOV			
3a	331±11	0.9±0.5	829±24	921	5.118
3b	—	540±20	795±25	1.5	4.074
3c	365±9	91±4	761±32	8	3.601
3d	268±14	5±1	671±18	134	4.073
3e	231±9	60±8	835±40	14	5.436
3f	450±20	49±7	797±19	16	5.398
3g	—	1±0.4	1764±59	1764	4.007
3h	359±12	3±1	697±21	232	3.758
Benztropine	—	—	—	—	7.835
Bepridil	—	—	—	—	5.200
Ibuprofen	—	—	—	—	6.245
Paroxetine	—	—	—	—	8.387
Toremifene	—	—	—	—	6.966
Sertraline	—[e]	0.7±0.3	408±26	543	8.240

[a] IC_{50} is the concentration that causes death of 50% of cells infected with pseudovirus particles, which display GP belonging to the Marburg (MARV) or Ebola (EBOV) virus on their surface.
[b] CC_{50} is the concentration that causes death of 50% of uninfected cells.
[c] SI_{EBOV} is the therapeutic index, the ratio of CC_{50} to IC_{50}(EBOV).
[d] It is not the true binding energy and should be considered as an estimated value.
[e] Not determined.

ing was performed in comparison with pharmacologically significant inhibitors of the Ebola virus glycoprotein: Benztropine, Bepridil, Paroxetine, Sertraline, Ibuprofen, and Toremifene. There was a correlation of antiviral activity observed *in vitro* and *in silico* for derivative **3a** among the synthesized compounds. Thus, for compound **3a**, the lowest IC_{50} was obtained, and the modeling of blocking of GP EBOV revealed one of the lowest binding energies comparable to that of Bepridil. Figure 1 shows the non-covalent interactions of derivative **3a** and the reference drug (Sertraline) with the amino acid residues at the GP EBOV binding site. The Sertraline configuration is characterized by the penetration of one of the aromatic cycles into the deep pocket B of the binding site, while the most of its molecule occupies the central hydrophobic part of that binding site and the larger pocket A. According to the docking data, Sertraline does not form any hydrogen bonds with amino acid residues of the binding site, while in the

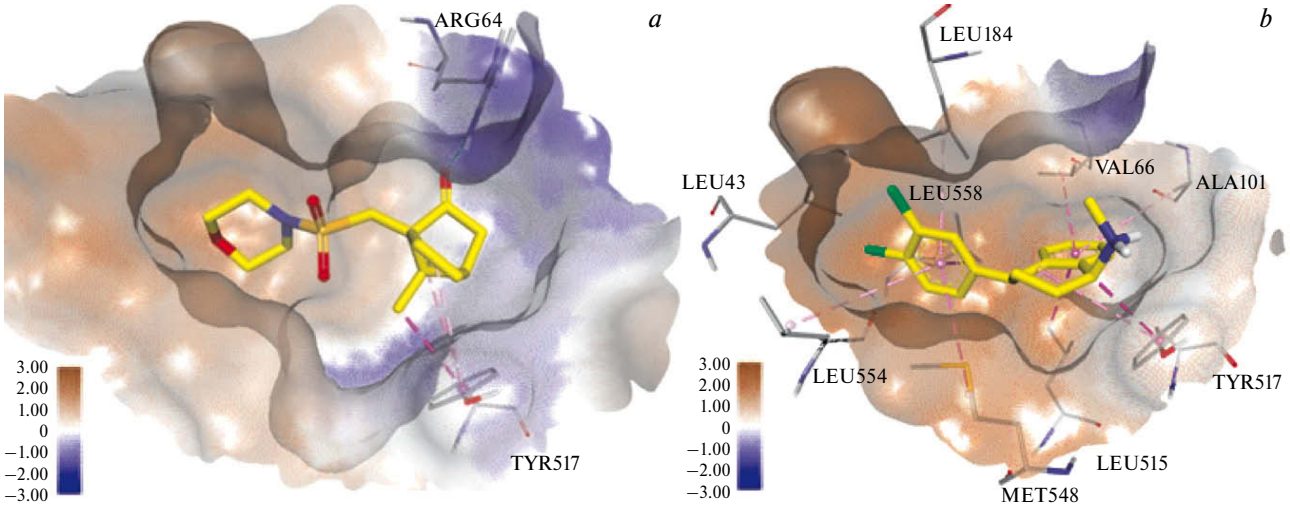


Fig. 1. Non-covalent interactions of derivative **3a** (*a*) and the reference drug Sertraline (*b*), with amino acid residues of the binding site of the glycoprotein of Ebola virus. The interactions are indicated by dashed lines: green lines correspond to the hydrogen bonds and pink lines represent the hydrophobic interactions.
Note. Figure 1 is available in full color on the web page of the journal (http://link.springer.com/journal/11172).

case of derivative **3a**, a hydrogen bond between its carbonyl group and the Arg64 residue of GP EBOV was observed. The hydrophobic moiety of camphor is located in the central part of the binding site.

The analysis of inhibitory activity towards GP MARV for compounds **3a**—**h** revealed that the minimum value of IC_{50} is characteristic of derivative **3e** bearing the piperidine moiety. These data are consistent with the results reported previously,[10] whereby a borneol derivative containing both heterocyclic moiety and ester group linked to a piperidine ring has proved to be a good inhibitor of Marburg virus penetration into the cell. The other derivatives either demonstrated a low inhibitory activity or did not affect the virus ability to enter into the cell.

Therefore, the present work reports on the synthesis of new *N*-heterocycle-containing (1*S*)-(+)-camphor-10-sulfonamide derivatives possessing an inhibitory activity against filoviruses. It should be noted that derivatives **3a** and **3g** bearing morpholine and triazole moieties, respectively, exhibited the inhibitory activity against GP EBOV comparable to that of the reference drug. The acquired data suggest new approaches for the transformation of bicyclic terpenoids, camphor and borneol, to synthesize more efficient inhibitors of especially dangerous viral infections.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on Bruker AV-300 (operating frequencies of 300.13 and 75.47 MHz for ^{1}H and ^{13}C, respectively) and Bruker AV-400 (400.13 and 100.78 MHz, respectively) spectrometers. The residual signals of $CDCl_3$ (δ_H 7.24 and δ_C 76.90) were used as the internal standards. High-resolution mass spectra (HRMS) were recorded on DFS ThermoScientific and Agilent 7200 Accurate Mass Q-TOF spectrometers operating in the full scan mode for the *m*/*z* range of 0—500 using electron impact ionization (70 eV) during the direct sample injection. The reaction progress and purity of compounds were monitored by gas chromatography-mass spectrometry (GC-MS) on an Agilent 7890 A gas chromatograph equipped with an Agilent 5975C quadrupole mass spectrometer as the detector using HP-5MS quartz column (30000×0.25 mm) and nebulizer gas (helium). Melting points were measured on a Mettler Toledo FP900 instrument. The reaction products were isolated using column chromatography on a silica gel (60—200 μm, Masherey-Nagel). Freshly distilled solvents and reagents of the pure grade were used. The atom numbering in compounds (see Scheme 1) is given for the assignment of the NMR signals and does not match with that recommended by IUPAC. The values of specific rotation $[\alpha]_{589}$ were determined on a PolAAr 3005 spectrometer. The specific rotation is expressed in (deg mL) (g dm)$^{-1}$, and the concentration of the solution is in (g) (100 mL)$^{-1}$.

(1*S*)-(+)-Camphor-10-sulfonyl chloride (**2**) was prepared according to the known procedure.[18]

Synthesis of heterocyclic derivatives of (1*S*)-(+)-camphor-10-sulfonamide (general procedure). The corresponding *N*-nucleophile (5.0 mmol) and triethylamine (0.3 mL, 9.9 mmol) were subsequently added to a solution of (1*S*)-(+)-camphor-10-sulfonyl chloride (**2**) (0.5 g, 2.0 mmol) in dichloromethane. The reaction mixture was stirred at room temperature for 12 h, washed with brine, and extracted with chloroform (3×10 mL). The combined organic layer was dried over calcined Na_2SO_4, and the solvent was removed *in vacuo*. The product was purified by column chromatography on SiO_2 (the eluent was hexane—ethyl acetate (100 : 0→0 : 100) + methanol (1%)).

7,7-Dimethyl-1-(morpholinosulfonylmethyl)bicyclo[2.2.1]-heptan-2-one (3a). The yield was 0.45 g (75%), light yellow crystals. ^{1}H NMR ($CDCl_3$), δ: 0.85 (s, 3 H, C(9)H$_3$); 1.1 (s, 3 H, C(8)H$_3$); 1.37—1.44 (m, 1 H, H(4)$_{endo}$); 1.57—1.65 (m, 1 H, H(5)$_{endo}$); 1.92 (d, 1 H, H(2)$_{endo}$, $J_{H(2)endo,H(2)exo}$ = 18.4 Hz); 1.97—2.06 (m, 1 H, H(4)$_{exo}$); 2.09 (t, 1 H, H(3), J = 4.5 Hz); 2.36 (dt, 1 H, H(2)$_{exo}$, $J_{H(2)exo,H(2)endo}$ = 18.4 Hz, $J_{H(2)exo,H(3)}$ = = 4.5 Hz); 2.44—2.53 (m, 1 H, H(5)$_{exo}$); 2.72 (d, 1 H, H(10), J = 14.5 Hz); 3.25—3.30 (m, 4 H, 2 H(11), 2 H(12)); 3.31 (d, 1 H, H(10), J = 14.5 Hz); 3.75 (m, 4 H, 2 H(13), 2 H(14)). ^{13}C NMR ($CDCl_3$), δ: 19.84 and 19.63 (C(8) and C(9)), 25.0 (C(4)), 26.8 (C(5)), 42.4 (C(2)), 42.7 (C(3)), 44.3 (C(10)), 45.5 (C(11), C(12)), 47.7 (C(7)), 58.0 (C(6)), 66.4 (C(13), C(14)), 215.2 (C=O). The spectral characteristics are in agreement with those reported previously.[19]

7,7-Dimethyl-1-[(4-methylpiperazin-1-ylsulfonyl)methyl]bicyclo[2.2.1]heptan-2-one (3b). The yield was 0.31 g (49%), light brown crystals, m.p. 132 °C. ^{1}H NMR ($CDCl_3$), δ: 0.85 (s, 3 H, C(9)H$_3$); 1.10 (s, 3 H, C(8)H$_3$); 1.35—1.47 (m, 1 H, H(4)$_{endo}$); 1.58—1.68 (m, 1 H, H(5)$_{endo}$); 1.91 (d, 1 H, H(2)$_{endo}$, $J_{H(2)endo,H(2)exo}$ = 18.4 Hz); 1.96—2.13 (m, 2 H, H(4)$_{exo}$, H(3)); 2.31 (s, 3 H, H(15)); 2.35—2.61 (m, 6 H, H(2)$_{exo}$, H(5)$_{exo}$, 2 H(13), 2 H(14)); 2.71 (d, 1 H, H(10), J = 14.5 Hz); 3.08—3.52 (m, 5 H, H(10), 2 H(11), 2 H(12)). ^{13}C NMR ($CDCl_3$), δ: 19.89 and 19.64 (C(8) and C(9)), 25.0 (C(4)), 26.8 (C(5)), 42.4 (C(2)), 42.7 (C(3)), 44.4 (C(10)), 45.5 (C(11), C(12)), 45.8 (C(15)), 47.8 (C(7)), 54.4 (C(13), C(14)), 58.1 (C(6)), 215.1 (C=O). HRMS, found: *m*/*z* 314.1661 [M]$^+$. Calculated for $C_{15}H_{26}N_2O_3S$: 314.1659.

1-[(4-Ethylpiperazin-1-ylsulfonyl)methyl]-7,7-dimethylbicyclo[2.2.1]heptan-2-one (3c). The yield was 0.53 g (81%), light yellow crystals, m.p. 105 °C. ^{1}H NMR ($CDCl_3$), δ: 0.85 (s, 3 H, C(9)H$_3$); 1.07 (t, 3 H, C(16)H$_3$, J = 7.2 Hz); 1.11 (s, 3 H, C(8)H$_3$); 1.35—1.45 (m, 1 H, H(4)$_{endo}$); 1.54—1.69 (m, 1 H, H(5)$_{endo}$); 1.91 (d, 1 H, H(2)$_{endo}$, J = 18.4 Hz); 1.97—2.05 (m, 1 H, H(4)$_{exo}$); 2.06—2.1 (m, 1 H, H(3)); 2.35 (dt, 1 H, H(2)$_{exo}$, $J_{H(2)exo,H(2)endo}$ = = 18.4 Hz, $J_{H(2)exo,H(3)}$ = 3.9 Hz); 2.44 (q, 2 H, 2 H(15), J = 7.0 Hz); 2.48—2.55 (m, 5 H, 2 H(13), 2 H(14), H(5)$_{exo}$); 2.70 (d, 1 H, H(10), J = 14.5 Hz); 3.22—3.39 (m, 5 H, H(10), 2 H(11), 2 H(12)). ^{13}C NMR ($CDCl_3$), δ: 11.85 (C(16)), 19.61 (C(9)), 19.91 (C(8)), 24.96 (C(4)), 26.80 (C(5)), 42.45 (C(2)), 42.65 (C(3)), 44.05 (C(10)), 45.6 (C(11), C(12)), 47.8 (C(7)), 51.91 (C(15)), 52.1 (C(13), C(14)), 57.8 (C(6)), 215.0 (C=O). HRMS, found: *m*/*z* 328.1813 [M]$^+$. Calculated for $C_{16}H_{28}N_2O_3S$: 328.1815.

Ethyl 4-[(7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methylsulfonyl]piperazine-1-carboxylate (3d). The yield was 0.45 g (61%), yellow crystals, m.p. 90 °C. ^{1}H NMR ($CDCl_3$), δ: 0.85 (s, 3 H, C(9)H$_3$); 1.10 (s, 3 H, C(8)H$_3$); 1.25 (t, 3 H, C(17)H$_3$, J = 7.7 Hz); 1.36—1.47 (m, 1 H, H(4)$_{endo}$); 1.54—1.67 (m, 1 H, H(5)$_{endo}$); 1.92 (d, 1H, H(2)$_{endo}$, J = 18.2 Hz); 1.97—2.07 (m, 1 H, H(4)$_{exo}$); 2.09 (t, 1 H, H(3), J = 4.8 Hz); 2.36 (dt, 1 H, H(2)$_{exo}$, $J_{H(2)exo,H(2)endo}$ = 18.2, $J_{H(2)exo,H(3)}$ = 3.8 Hz); 2.43—2.54 (m, 1 H, H(5)$_{exo}$); 2.71 (d, 1 H, H(10), J = 14.4 Hz);

3.2—3.3 (m, 5 H, 2 H(11), 2 H(12), H(10)); 3.55 (br.s, 4 H, 2 H(13), 2 H(14)); 4.13 (q, 2 H, 2 H(16), J = 7.7 Hz). ^{13}C NMR ($CDCl_3$), δ: 14.48 (C(17)), 19.61 and 19.84 (C(8), C(9)), 25.0 (C(4)), 26.8 (C(5)), 42.4 (C(2)), 42.6 (C(3)), 43.5 (C(10)), 45.05 (C(11), C(12)), 45.4 (C(13), C(14)), 47.9 (C(7)), 58.1 (C(6)), 61.7 (C(16)), 155.1 (C=O), 215.1 (C=O). HRMS, found: m/z 372.1715 $[M]^+$. Calculated for $C_{17}H_{28}N_2O_5S$: 372.1713.

7,7-Dimethyl-1-[(piperidin-1-ylsulfonyl)methyl]bicyclo[2.2.1]-heptan-2-one (3e). The yield was 0.35 g (58%), brown viscous substance. ^{1}H NMR ($CDCl_3$), δ: 0.86 (s, 3 H, C(9)H_3); 1.12 (s, 3 H, C(8)H_3); 1.34—1.44 (m, 1 H, H(4)$_{endo}$); 1.49—1.68 (m, 7 H, H(5)$_{endo}$, 2 H(13), 2 H(14), 2 H(15)); 1.90 (d, 1 H, H(2)$_{endo}$, $J_{H(2)endo,H(2)exo}$ = 18.5 Hz); 1.97—2.04 (m, 1 H, H(4)$_{exo}$); 2.07 (t, 1 H, H(3), J = 4.5 Hz); 2.36 (dt, 1 H, H(2)$_{exo}$, $J_{H(2)exo,H(2)endo}$ = 18.5 Hz, $J_{H(2)exo,H(3)}$ = 3.8 Hz); 2.50—2.60 (m, 1 H, H(5)$_{exo}$); 2.69 (d, 1 H, H(10), J = 14.5 Hz); 3.19—3.26 (m, 4 H, 2 H(11), 2 H(12)); 3.3 (d, 1 H, H(10), J = 14.5 Hz). ^{13}C NMR ($CDCl_3$), δ: 19.84 and 19.63 (C(8) and C(9)), 23.7 (C(15)), 25.0 (C(4)), 25.5 (C(13), C(14)), 26.8 (C(5)), 42.5 (C(2)), 42.7 (C(3)), 44.3 (C(10)), 46.5 (C(11), C(12)), 47.8 (C(7)), 58.2 (C(6)), 215.4 (C=O). HRMS, found: m/z 299.1541 $[M]^+$. Calculated for $C_{15}H_{25}NO_3S$: 299.1550.

7,7-Dimethyl-1-[(4-methylpiperidin-1-ylsulfonyl)methyl]bicyclo[2.2.1]heptan-2-one (3f). The yield was 0.62 g (84%), brown crystals, m.p. 70 °C followed by the decomposition. ^{1}H NMR ($CDCl_3$), δ: 0.86 (s, 3 H, C(9)H_3); 0.95 (d, 3 H, C(16)H_3), J = 6.6 Hz); 1.12 (s, 3 H, C(8)H_3); 1.19—1.31 (m, 2 H, H(13)$_{ax}$, H(14)$_{ax}$); 1.36—1.43 (m, 1 H, H(4)$_{endo}$); 1.51—1.64 (m, 2 H, H(5)$_{endo}$, H(15)); 1.66—1.75 (br.m, 2 H, H(13)$_{eq}$, H(14)$_{eq}$); 1.92 (d, 1 H, H(2)$_{endo}$, J = 18.5 Hz); 1.97—2.09 (m, 2 H, H(4)$_{exo}$, H(3)); 2.36 (dt, 1 H, H(2)$_{exo}$, J = 18.5 Hz, $J_{H(2)exo,H(3)}$ = 4.0 Hz); 2.49—2.58 (m, 1 H, H(5)$_{exo}$); 2.70 (d, 1 H, H(10), J = 14.4 Hz); 2.73 (m, 2 H, H(11)$_{ax}$, H(12)$_{ax}$); 3.3 (d, 1 H, H(10), J = 14.4 Hz); 3.72—3.82 (br.m, 2 H, H(11)$_{eq}$, H(12)$_{eq}$). ^{13}C NMR ($CDCl_3$), δ: 19.98 and 19.64 (C(8)), (C(9)), 21.50 (C(16)), 24.92 (C(4)), 26.77 (C(5)), 30.30 (C(15)), 33.63 (C(14), C(13)), 42.48 (C(2)), 42.65 (C(3)), 44.32 (C(10)), 46.03 and 45.9 (C(11), C(12)), 47.8 (C(7)), 58.1 (C(6)), 215.0 (C=O). HRMS, found: m/z 313.1699 $[M]^+$. Calculated for $C_{13}H_{27}NO_3S$: 313.1712.

7,7-Dimethyl-1-[(1*H*-1,2,4-triazol-1-ylsulfonyl)methyl]bicyclo[2.2.1]heptan-2-one (3g). The yield was 0.17 g (30%), light yellow crystals. ^{1}H NMR ($CDCl_3$), δ: 0.88 (s, 3 H, C(9)H_3); 1.10 (s, 3 H, C(8)H_3); 1.43—1.52 (m, 1 H, H(4)$_{endo}$); 1.77—1.88 (m, 1 H, H(5)$_{endo}$); 1.94 (d, 1 H, H(2)$_{endo}$, J = 18.2 Hz); 2.02—2.12 (m, 1 H, H(4)$_{exo}$); 2.15 (t, 1 H, H(3), J = 4.5 Hz); 2.23—2.33 (m, 1 H, H(2)$_{exo}$); 2.38 (dt, 1 H, H(5)$_{exo}$, J = 18.7 Hz, J = 3.8 Hz); 3.45 (d, 1 H, H(10), J = 15.0 Hz); 3.89 (d, 1 H, H(10), J = 15.0 Hz); 8.13 (s, 1 H, H(12)); 8.68 (s, 1 H, H(11)). ^{13}C NMR ($CDCl_3$), δ: 19.55 (C(8), C(9)), 25.07 (C(4)), 26.82 (C(5)), 42.22 (C(2)), 42.62 (C(3)), 48.30 (C(7)), 52.50 (C(10)), 58.67 (C(6)), 153.99 (C(11), C(12)), 213.1 (C=O). HRMS, found: m/z 215.0731 $[M - C_2H_2N_3]^+$. Calculated for $C_{10}H_{15}O_3S$: 215.0736.

1-(7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-*N*-(3-morpholinopropyl)methanesulfonamide (3h). The yield was 0.54 g (87%), brown crystals. ^{1}H NMR ($CDCl_3$), δ: 0.87 (s, 3 H, C(9)H_3); 1.02 (s, 3 H, C(8)H_3); 1.36—1.45 (m, 1 H, H(4)$_{endo}$); 1.64—1.85 (m, 3 H, 2 H(16), H(5)$_{endo}$); 1.89 (d, 1 H, H(2)$_{endo}$, J = 18.5 Hz); 1.95—2.07 (m, 1 H, H(4)$_{exo}$); 2.10 (m, 1 H, H(3)); 2.28—2.60 (m, 8 H, 2 H(17), 2 H(11), 2 H(12), H(5)$_{exo}$, H(2)$_{exo}$); 2.85 (d, 1 H, H(10), J = 15.2 Hz); 3.25 (t, 2 H, 2 H(15), J = 6.2 Hz); 3.39 (d, 1 H, H(10), J = 15.2 Hz); 3.69 (t, 4 H, 2 H(13), 2 H(14), J = 4.7 Hz); 5.83 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 19.73 and 19.50 (C(8)), (C(9)), 25.12 (C(16)), 25.75 (C(4)), 26.90 (C(5)), 42.60 (C(3)), 42.76 (C(2)), 43.10 (C(10)), 48.43 (C(15)), 48.6 (C(7)), 53.33 (C(11), C(12)), 57.17 (C(17), 58.74 (C(6)), 66.58 (C(13), C(14)), 216.3 (C=O). HRMS, found: m/z 357.1849 $[M]^+$. Calculated for $C_{17}H_{30}N_2O_4S$: 358.1921.

Estimation of the cytotoxicity of compounds 3a—h against 293FT cells. Standardized solutions of the compounds in DMSO (at the concentration of 100 mmol L^{-1}) were added to a growth medium containing the target cells of the 293FT line at concentrations from 10 to 500 μmol L^{-1}. The cells were incubated for 48 h, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added to the cell cultures to the final concentration of 0.5 mg mL^{-1}, and cells were incubated for additional 4 h. The resulting precipitate of formazan was dissolved by addition of sodium dodecyl sulfate solution (10%) in 0.01 *M* hydrochloric acid to the growth medium. The amount of formazan (proportional to the number of viable cells) was determined spectrophotometrically measuring the absorption at λ = 570 nm. The 293FT cells incubated in the growth medium containing DMSO without the tested compounds was used as the reference. The percentage of viable cells in cultures containing the tested compounds at different concentrations was estimated according to the following equation:

$$\text{Viable cells (\%)} = A/A_0 \cdot 100\%,$$

wherein A and A_0 are the absorption of experimental (in the presence of the tested compound) and control samples, respectively.

The concentration of a tested compound causing the 50% survival of the cells as compared to the control sample was assumed as the CC_{50} value.

Production of pseudoviruses based on the recombinant vesicular stomatitis virus (VSV) exposing on their surface either Ebola or Marburg virus glycoprotein. To obtain pseudoviruses exposing either the Ebola virus glycoprotein (Mayinga strain) or Marburg virus glycoprotein (Popp strain) on its surface, the production cells of 293FT line were initially transfected with a plasmid containing the gene sequence of this glycoprotein (ph-GPE or ph-GPM) (5 μg of plasmid per 60 mm plate with the production cells). After 24 h from the transfection, the production cells were infected with pVSV-ΔG-G (5 μL, ~10^6 of the transducing units). Four hours after the infection, the infecting pseudovirus was washed off, and the medium was replaced with the fresh one. The pseudovirus preparation exposing either the Ebola virus glycoprotein (pVSV-ΔG-GPE) or the Marburg virus glycoprotein (pVSV-ΔG-GPM) was harvested 24 h after the infection. The pseudovirus preparations were stored at −80 °C.

Determination of half inhibitory concentrations of the compounds against the pVSV-ΔG-GPE and pVSV-ΔG-GPM pseudoviruses and calculation of therapeutic index (SI) values. To estimate the contagious ability of pseudoviruses, the targeting cells of HEK293 line seeded into 96-well plates at a monolayer density of 80–90% were used. The infectivity of pseudoviruses in the presence of inhibitors and in the control (non-inhibited) samples was determined according to the luminescence index measured 24 h after the infection. All the measurements were performed three times determining the average value and standard deviation. The half maximal inhibitory concentrations (IC_{50}) against the pVSV-ΔG-GPE and pVSV-ΔG-GPM pseudoviruses were deter-

mined for all the studied compounds. For the each compound, the selectivity index (SI) was consequently calculated as the ratio of cytotoxicity of the compound and its inhibitory activity against the virus (CC_{50}/IC_{50}). Sertraline ((1*S*,4*S*)-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine) was selected as the reference drug inhibiting the Ebola virus infection.

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