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Synthesis and biological activity of heterocyclic borneol derivatives

Anastasiya S. Sokolova[1,2]*, Olga I. Yarovaya[1,2], Anna A. Shtro[3], Marina S. Borisova[1], Ekaterina A. Morozova[1], Tatyana G. Tolstikova[1], Vladimir V. Zarubaev[3], Nariman F. Salakhutdinov[1,2]

[1] *N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 9 Lavrentiev Ave., Novosibirsk 630090, Russia; e-mail: asokolova@nioch.nsc.ru*

[2] *Novosibirsk State University, 2 Pirogova St., Novosibirsk 630090, Russia; e-mail: ooo@nioch.nsc.ru*

[3] *Department of Chemotherapy, Research Institute of Influenza, 15/17 Prof. Popova St., Saint Petersburg 197376, Russia e-mail: zarubaev@influenza.spb.ru*

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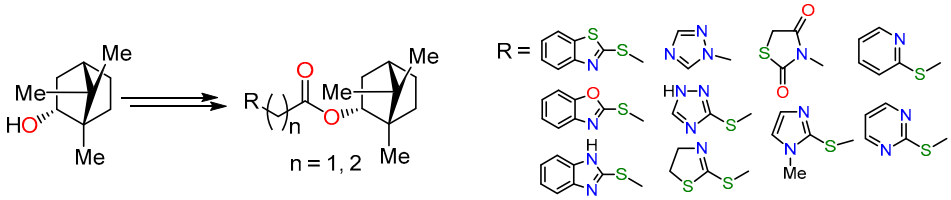


A series of novel heterocyclic derivatives of (–)-borneol has been prepared by the interaction of (1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-yl 2-chloroacetate and (1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 3-chloropropanoate with different N- and S-nucleophiles. The obtained products were screened for antiviral, antiulcer, and analgesic activity.

Keywords: 1*H*-benzimidazole-2-thiol, benzoxazole-2-thiol, benzthiazole-2-thiol, (–)-borneol, analgesic activity, antiulcer activity, antiviral activity.

Borneol (1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol) is a bicyclic monoterpenoid alcohol, which is a valuable medicinal substance used in the traditional medicine of China and India. Recent studies have shown that (–)-borneol and its derivatives possess various types of biological effects, such as antimicrobial,[1,2] anti-inflammatory,[3] and antiviral activity.[4] Some studies have shown that (–)-borneol can improve the nasal and gastrointestinal bioavailability of drugs,[5] transiently increase the permeability of the blood-brain barrier, and enhance the distribution of drugs in brain tissue.[6,7]

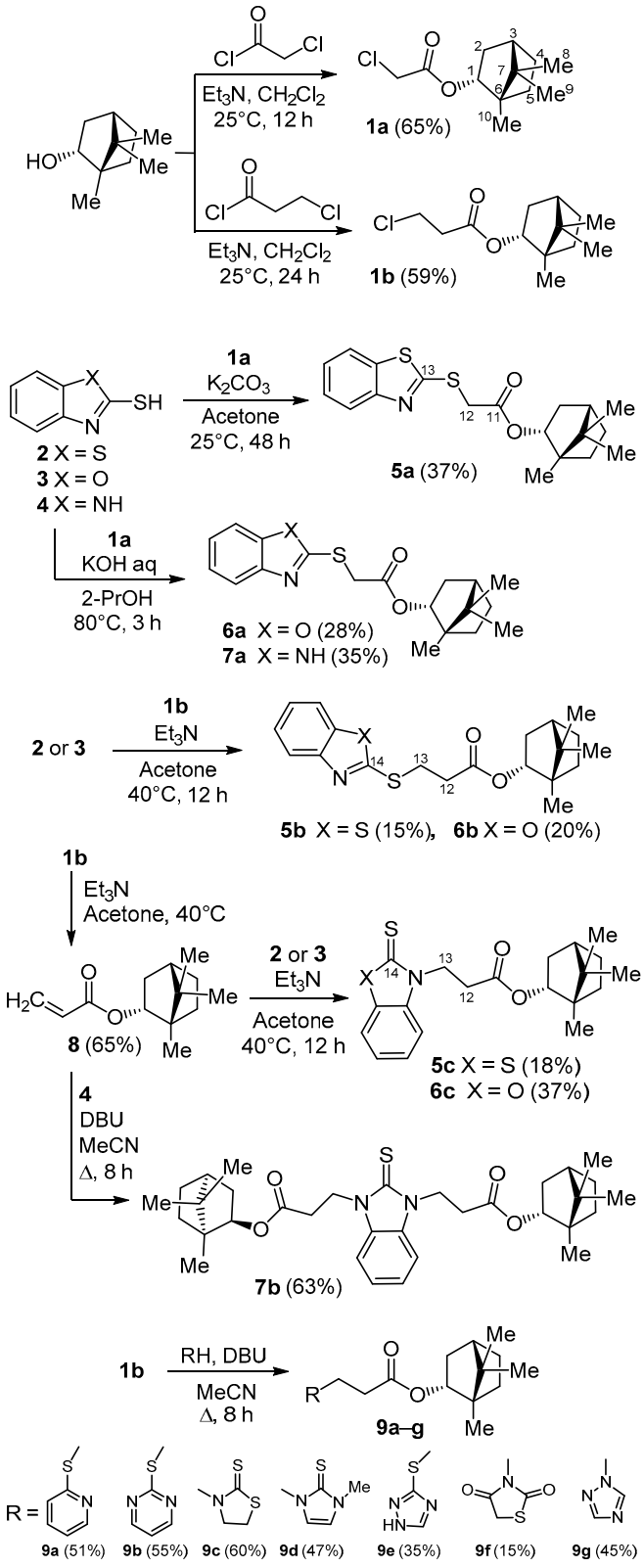
We previously demonstrated that the presence of 1,7,7-trimethylbicyclo[2.2.1]heptane scaffold was associated with high inhibitory activity of molecules on the replication of influenza A virus.[8–10] Moreover, it was reported that borneol derivatives containing the structural motif of α-truxillic acid showed analgesic activity.[11] On the other hand, heterocyclic compounds and their derivatives have attracted strong interest in the field of medicinal chemistry due to their beneficial biological and pharmacological properties. Among such compounds, derivatives of benzimidazole, benzoxazole, and benzothiazole have been shown to exhibit a wide range of biological effects, including antiulcer, antihypertensive, analgesic, anti-inflammatory, and antiviral activity.[12]

Thus, we considered it worthwhile to construct new heterocyclic (–)-borneol derivatives bearing benzothiazole, benzoxazole, benzimidazole, and other heterocycles, and to evaluate their biological properties, such as the inhibition of influenza virus replication, antiulcer action, and analgesic effect.

The synthetic strategies for obtaining the target compounds are outlined in Scheme 1. The starting (–)-borneol esters **1a**,**b** were synthesized by reactions between (–)-borneol and acyl chlorides derived from α- or β-chlorinated carboxylic acids (Scheme 1).

The reaction of compound **1a** with benzothiazole-2-thiol (**2**) in acetone medium in the presence of K_2CO_3 yielded derivative **5a**. Benzoxazole-2-thiol (**3**) and 1*H*-benzimidazole-2-thiol (**4**) were subjected to alkylation with (1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl chloroacetate (**1a**) in the presence of aqueous KOH in 2-PrOH,

Scheme 1



affording the required heterocyclic derivatives **6a** and 7**a**. The poor yield of compounds **5**–7 **a** can be explained by the fact that reactant **1a** was unstable under these reaction conditions. The reaction of (1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 3-chloropropanoate (**1b**) with various thiols led to the formation of a previously unknown series of heterocyclic derivatives **5b**–**c**, **6b**–**c**, **7b**, and **9a**–**g** (Scheme 1).

Due to the ambident nature of anions derived from thiols **2**–**4** in nucleophilic substitution reactions, either *N*- or *S*-substituted products can be obtained depending on the reaction conditions and the predominant mechanism. Previously, it has been shown that the ethylation of thiols **2**–**4** occurred at the nitrogen rather than the sulfur atom of thiol.[13] In all S_N2-type alkylations, e.g., with alkyl halides and dialkyl sulfates, *S*-alkylated products were obtained. In the case of ester **1b**, the reaction with benzthiazole-2-thiol (**2**) and benzoxazole-2-thiol (**3**) under basic conditions gave a mixture containing products **5b**,**c** (1:1) and **6b**,**c** (0.5:1). The ratio of products **5b**,**c** and **6b**,**c** was established by ^{1}H NMR spectroscopy. The interaction of (1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 3-chloropropanoate (**1b**) with 1*H*-benzimidazole-2-thiol (**4**) in the presence of DBU furnished only one product **7b**. The formation of *N*-substituted products can be explained by elimination process in ester **1b** that led to the electron-deficient alkene **8** with double bond activated toward nucleophilic attack. Thus, alkyl halide **1b** reacted with the thiol group, while alkene **8** was attacked by nitrogen nucleophile.

It is known that nitrogen-containing five- and six-membered heterocyclic compounds have recently attracted considerable attention due to their prominent role in the field of drug discovery.[14] In the view of this, the library of borneol propanoate derivatives was expanded by introducing pyridine, pyrimidine, imidazole, and triazole rings in the molecules of interest. The target compounds **9a**–**g** were obtained from the reactions of compound **1b** with different nucleophiles in the presence of DBU (Scheme 1).

The structures of the synthesized compounds were deduced from ^{1}H and ^{13}C NMR spectra. It is noteworthy to contrast the chemical shift observed for the methylene protons at the C-13 atom in compounds **5b**, **6b** and **5c**, **6c**. The SCH_2 proton signals in ^{1}H NMR spectra of compounds **5b**, **6b** appeared at 3.54–3.60 ppm, whereas the NCH_2 signals in ^{1}H NMR spectra of compounds **5c**, **6c** were found at 4.44–4.69 ppm. The signals of compounds **5c**, **6c** were shifted downfield due to the deshielding effect of the thiocarbonyl group. In ^{13}C NMR spectra of compounds **5b**, **6b**, the C-14 atom signals appeared at 165.8 and 164.3 ppm, respectively, whereas in their rearranged products **5c** and **6c** the C=S signals were found at 189.0 and 179.9 ppm, respectively.

The prepared compounds were studied for their antiviral activity against influenza virus A/Puerto Rico/8/34 (H1N1). The results of the investigation are presented in Table 1. Rimantadine, amantadine, and deitiforin were used as reference compounds due to a close similarity of their rigid cage fragments to those in the tested compounds.

In general, the group of studied compounds has demonstrated low-to-moderate viral inhibition activity. Among the synthesized compounds, the bis-substituted derivatives **7b** having two (–)-borneol fragments attached to 1*H*-benzimidazole-2-thiol core exhibited potent antiviral properties. High antiviral activity was also observed in the

Table 1. Antiviral activity of borneol derivatives **5**–**9** against influenza virus A/Puerto Rico/8/34 (H1N1)pdm09

Compound	CC_{50}*, μM	IC_{50}**, μM	SI***
5a	301.1 ± 26.2	69.1 ± 5.3	4
5b	Not tested	Not tested	–
5c	68.0 ± 4.4	26.7 ± 3.1	3
6a	21.4 ± 1.3	8.7 ± 1.0	2
6b	>919.2	>919.2	1
6c	231.2 ± 19.3	>91.9	3
7a	43.1 ± 3.6	8.7 ± 1.0	5
7b	530.0 ± 33.4	8.0 ± 0.5	67
8	156.3 ± 11.4	>28.8	5
9a	109.1 ± 8.7	12.2 ± 1.3	9
9b	72.2 ± 5.5	9.7 ± 0.9	7
9c	10.1 ± 0.6	6.7 ± 0.5	2
9d	329.2 ± 14.9	14.0 ± 1.5	24
9e	10.7 ± 0.6	7.1 ± 0.9	2
9f	116.9 ± 8.6	17.5 ± 2.1	7
9g	608.7 ± 42.3	41.9 ± 3.8	15
Rimantadine	335.2 ± 26.8	67.0 ± 4.9	5
Amantadine	284.1 ± 21.4	64.2 ± 4.7	4
Deitiforin	1266.2 ± 81.5	208.6 ± 15.4	6

* CC_{50} – cytotoxic concentration causing the death of 50% of cells.
** IC_{50} – the effective antiviral concentration causing 50% inhibition of viral replication.
*** SI – selectivity index (the ratio of CC_{50}/ IC_{50}).

case of compounds **9d**,**g** containing fragments of 1-methyl-1*H*-imidazole-2(3*H*)-thione and 1,2,4-triazole, respectively. The rest of the compounds showed significant antiviral activity along with high toxicity (low CC_{50} values) that resulted in low selectivity.

The antiulcer activity (AA) of some synthesized compounds was studied by applying the indomethacin-induced gastric ulcer test in rats. The AA score of the substances was determined as the ratio of the Paul's index (PI) in control group to the PI of each experimental group. The substances in question with the AA score greater than or equal to 2 were considered as effective antiulcer agents.[15] Compound **6c** synthesized from 3-chloropropanoate of borneol and containing benzoxazole-2-thiol fragment exhibited significant antiulcer activity. The observation of the gastric mucosa of the animals treated with compound **6c** prior to the indomethacin administration showed significantly reduced ulceration rate (PI 0.8) in comparison with the animals of the control group (PI 5.0). The experimental results showed that the AA score of substance **6c** (AA 6.5) was higher than the same score for the reference compound omeprazole (AA 3.8) (Fig. 1). It is also worth mentioning that the 3-chloropropanoate derivatives **9a**,**b**,**d** containing pyridine, pyrimidine-2-thiol, and 1-methyl-1*H*-imidazole-2(3*H*)-thione fragments slightly reduced the formation of gastric lesions. Compound **5a**, which was one of the bornyl acetate derivatives, exhibited antiulcer activity with the AA score of 2.0. It should be noted that (–)-borneol itself does not possess antiulcer activity.

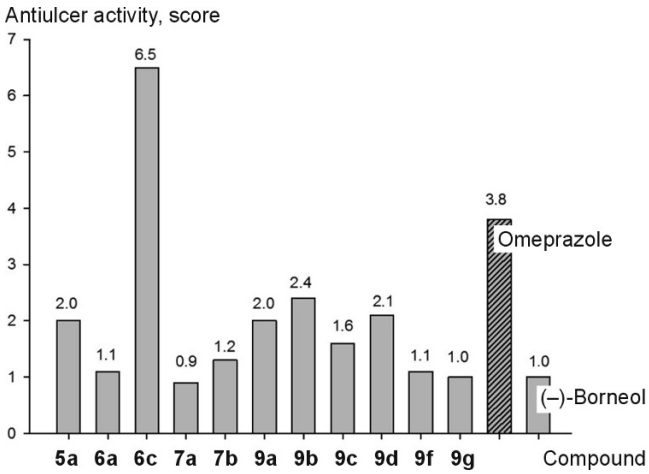


Figure 1. The antiulcer activity of the synthesized compounds in indomethacin-induced gastric ulcer test.

The investigation of analgesic activity of derivatives **9a**–**d**,**g** showed that all these compounds were inactive in the acetic acid-induced writhing test. In the hot plate test, only compound **9g** exhibited a tendency to induce hyperalgesia, reducing the time of animal pain response.

In summary, a novel series of (–)-borneol derivatives containing different heterocyclic fragments have been synthesized and screened for their antiviral, antiulcer, and analgesic activity. Some of the compounds exhibited promising antiviral and antiulcer activity. Thus, they can be considered as lead compounds for further development of more potent inhibitors of influenza virus and antiulcer agents.

Experimental

^{1}H NMR spectra were recorded on a Bruker AV400 (400 MHz) spectrometer and ^{13}C NMR JMOD spectra were recorded on a Bruker DRX 500 (125 MHz) spectrometer in $CDCl_3$. The chemical shifts are given in ppm relative to solvent signals (δ($CHCl_3$) 7.24, δ($CDCl_3$) 76.9 ppm). The atom numbering in the compounds (see Supporting information file) is given for assigning the signals in the NMR spectra and does not match the standard nomenclature of compounds. Optical rotation was measured on a PolAAr 3005 instrument. High-resolution mass spectra were recorded with a Thermo Scientific DFS mass spectrometer in a full scan mode (*m*/*z* 15–500, electron impact ionization at 70 eV, direct sample introduction). The purity of target compounds was determined by gas chromatography using an Agilent 7820A gas chromatograph with flame ionization detector, Agilent HP-5 capillary column, helium as carrier gas (flow rate 2 ml/min, flow split ratio 99:1). Column chromatography was performed on Macherey-Nagel 60–200 μm silica gel. All the target compounds reported in this publication were of at least 95% purity. Reagents and solvents were purchased from commercial suppliers and used as received. Dry solvents were obtained according to standard laboratory procedures.

(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 2-chloroacetate (1a). Chloroacetyl chloride (5.6 g, 0.05 mol) was added under argon atmosphere to a cooled (0–5°C) mixture of (−)-borneol (4.6 g, 0.03 mol) and Et_3N (3.0 g, 0.03 mol) in dry CH_2Cl_2 (20 ml), followed by stirring the mixture for 12 h at 23–25°C. Brine was added and the reaction mixture was extracted with CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4, and the solvent was removed by evaporation. The crude product was purified by vacuum distillation (bp 105°C at 5 mmHg). Yield 4.5 g (65%), colorless oil. Spectral data were in a good agreement with those reported for the same compound in the literature.[16]

(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 3-chloropropanoate (1b). A solution of 3-chloropropanoic acid (5.0 g, 46 mmol) in anhydrous CH_2Cl_2 (10 ml) was treated with an excess of oxalyl chloride (8.7 g, 69 mmol), and one drop of *N*,*N*-dimethylformamide was added. The mixture was stirred under argon atmosphere at room temperature for 4 h. The excess of the oxalyl chloride was removed on a rotary evaporator. The resulting 3-chloropropanoyl chloride was immediately used in the further reaction. 3-Chloropropanoyl chloride (3.8 g, 0.05 mol) solution in CH_2Cl_2 (5 ml) was added to a solution of (−)-borneol (4.6 g, 0.03 mol) and Et_3N (3.0 g, 0.03 mol) in CH_2Cl_2 (10 ml) at 0–5°C, and the mixture was stirred under argon atmosphere at room temperature for 24 h. The resulting precipitate was removed by filtration. The filtrate was washed with brine and extracted with CH_2Cl_2. The combined organic phase was dried over anhydrous Na_2SO_4, and the solvent was removed by evaporation. The crude product was purified by flash column chromatography (eluent hexane – ethyl acetate, 100:0→70:30). Yield 4.3 g (59%), yellow oil. $[\alpha]_D^{27}$ –36.2 ($CHCl_3$, *c* 0.7). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.80 (3H, s, 9-CH_3); 0.84 (3H, s, 10-CH_3); 0.87 (3H, s, 8-CH_3); 0.97 (1H, dd, ^2J = 13.7, $J_{2endo,1exo}$ = 3.5, 2-CH_{endo}); 1.16–1.33 (2H, m, 4-CH_{endo}, 5-CH_{exo}); 1.65 (1H, dd, $J_{3,2exo}$ = 4.6, $J_{3,4exo}$ = 4.6, 3-CH); 1.67–1.77 (1H, m, 4-CH_{exo}); 1.89 (1H, ddd, ^2J = 12.9, $J_{5endo,4endo}$ = 9.3, $J_{5endo,4exo}$ = 4.4, 5-CH_{endo}); 2.30–2.39 (1H, m, 2-CH_{exo}); 2.77 (2H, t, *J* = 6.6, 12-CH_2); 3.74 (2H, t, *J* = 6.6, 13-CH_2); 4.91 (1H, ddd, $J_{1exo,2exo}$ = 10.0, $J_{1exo,2endo}$ = 3.5, $J_{1exo,5exo}$ = 2.2, 1-CH_{exo}). ^{13}C NMR spectrum, δ, ppm: 170.4 (s); 80.5 (d); 48.7 (s); 47.7 (s); 44.7 (d); 39.2 (d); 37.8 (d); 36.5 (t); 27.9 (t); 27.0 (t); 19.6 (q); 18.7 (q); 13.3 (q). Found, *m*/*z*: 244.1225 $[M]^+$. $C_{13}H_{21}O_2Cl$. Calculated, *m*/*z*: 244.1222.

(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 2-(benzothiazol-2-ylsulfanyl)acetate (5a). 2-Benzothiazole-2-thiol **2** (0.7 g, 4 mmol) and K_2CO_3 (1.1 g, 8 mmol) were added to a solution of compound **1a** (0.9 g, 4 mmol) in acetone (30 ml). The reaction mixture was stirred at room temperature for 48 h. After completion of the reaction, the mixture was treated with brine, extracted with ethyl acetate (3×10 ml), dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane – diethyl ether, 100:0→50:50) to yield 0.5 g (37%) of ester **5a** as white powder, mp 50–51°C. $[\alpha]_D^{27}$ –20.7 ($CHCl_3$, *c* 0.8). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.77 (3H, s, 9-CH_3); 0.82 (3H, s, 10-CH_3); 0.85 (3H, s, 8-CH_3); 0.99 (1H, dd, ^2J = 13.7, $J_{2endo,1exo}$ = 3.5, 2-CH_{endo}); 1.04–1.12 (1H, m, 4-CH_{endo}); 1.17–1.27 (1H, m, 5-CH_{exo}); 1.60–1.64 (1H, m, 3-CH); 1.64–1.72 (1H, m, 4-CH_{exo}); 1.83–1.93 (1H, m, 5-CH_{endo}); 2.30–2.39 (1H, m, 2-CH_{exo}); 4.13 (1H, d, *J* = 16.0) and 4.16 (1H, d, *J* = 16.0, 12-CH_2); 4.94 (1H, ddd, $J_{1exo,2exo}$ = 10.0, $J_{1exo,2endo}$ = 3.5, $J_{1exo,5exo}$ = 2.2, 1-CH_{exo}); 7.23–7.29 (1H, m, H-16); 7.35–7.41 (1H, m, H-15); 7.70–7.75 (1H, m, H-17); 7.80–7.84 (1H, m, H-18). ^{13}C NMR spectrum, δ, ppm: 168.3 (s); 164.7 (s); 152.8 (s); 135.3 (s); 125.9 (d); 124.3 (d); 121.5 (d); 120.9 (d); 81.7 (d); 48.8 (s); 47.7 (s); 44.7 (d); 36.2 (t); 35.2 (t); 27.7 (t); 26.8 (t); 19.5 (q); 18.7 (q); 13.3 (q). Found, *m*/*z*: 361.1165 $[M]^+$. $C_{19}H_{23}O_2NS_2$. Calculated, *m*/*z*: 361.1165.

Synthesis of compounds 6a and 7a (General method). Aqueous 18 M KOH solution (0.2 ml) was added to a solution of benzoxazole-2-thiol (**3**) (0.5 g, 3.3 mmol) or 1*H*-benzimidazole-2-thiol (**4**) (0.5 g, 3.3 mmol) in 2-PrOH (5 ml). The mixture was heated to 40°C, and compound **1a** (0.7 g, 3 mmol) was added, followed by stirring of the reaction mixture at 80°C for 3 h. After the completion of the reaction, the mixture was cooled to room temperature and poured into water. The product was extracted several times with EtOAc, the extract was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexane – diethyl ether, 100:0→50:50) to yield ester **6a** or **7a**.

(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 2-(benzoxazol-2-ylsulfanyl)acetate (6a). Yield 0.30 g (28%), white powder. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.78 (3H, s, 9-CH_3); 0.82 (3H, s, 10-CH_3); 0.86 (3H, s, 8-CH_3); 0.99 (1H, dd, ^2J = 13.7, $J_{2endo,1exo}$ = 3.5, 2-CH_{endo}); 1.05–1.14 (1H, m, 4-CH_{endo}); 1.17–1.27 (1H, m, 5-CH_{exo}); 1.61–1.65 (1H, m, 3-CH); 1.65–1.71 (1H, m, 4-CH_{exo}); 1.81–1.90 (1H, m, 5-CH_{endo}); 2.27–2.37 (1H, m, 2-CH_{exo}); 4.07 (1H, d, *J* = 16.0) and 4.13 (1H, d, *J* = 16.0, 12-CH_2); 4.94 (1H, ddd, $J_{1exo,2exo}$ = 10.0, $J_{1exo,2endo}$ = 3.5, $J_{1exo,5exo}$ = 2.2, 1-CH_{exo}); 7.19–7.28 (2H, m, H-16,17); 7.39–7.43 (1H, m, H-18); 7.54–7.57 (1H, m, H-15). ^{13}C NMR spectrum, δ, ppm: 167.9 (s); 163.1 (s); 151.8 (s); 141.6 (s); 124.2 (d); 123.8 (d); 118.4 (d); 109.8 (d); 81.9 (d); 48.8 (s); 47.7 (s); 44.6 (d); 36.2 (t); 34.3 (t); 27.7 (t); 26.7 (t); 19.4 (q); 18.6 (q); 13.2 (q). Found, *m*/*z*: 345.1398 $[M]^+$. $C_{19}H_{23}NO_3S$. Calculated, *m*/*z*: 345.1393.

(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 2-(1*H*-benzimidazol-2-ylsulfanyl)acetate (7a). Yield 0.36 g (35%), white powder. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.81 (3H, s, 9-CH_3); 0.85 (3H, s, 10-CH_3); 0.88 (3H, s, 8-CH_3); 1.01 (1H, dd, ^2J = 13.7, $J_{2endo,1exo}$ = 3.5, 2-CH_{endo}); 1.12–1.32 (2H, m, 4-CH_{endo}, 5-CH_{exo}); 1.64–1.76 (2H, m, 3-CH, 4-CH_{exo}); 1.84–1.92 (1H, m, 5-CH_{endo}); 2.31–2.40 (1H, m, 2-CH_{exo}); 3.94 (2H, s, 12-CH_2); 4.97 (1H, ddd, $J_{1exo,2exo}$ = 10.0, $J_{1exo,2endo}$ = 3.5, $J_{1exo,5exo}$ = 2.2, 1-CH_{exo}); 7.16–7.21 (2H, m, H-16,17); 7.36–7.72 (2H, m, H-15,18). ^{13}C NMR spectrum, δ, ppm: 171.0 (s); 148.2 (s), 122.3 (d); 82.3 (d); 48.8 (s); 47.8 (s); 44.6 (d); 36.3 (t); 34.5 (t); 27.7 (t); 26.8 (t); 19.5 (q); 18.6 (q); 13.3 (q). Found, *m*/*z*: 344.1550 $[M]^+$. $C_{19}H_{24}O_2N_2S$. Calculated, *m*/*z*: 344.1550.

Preparation of compounds 5b,c and 6b,c (General method). Benzothiazole-2-thiol (**2**) or 1*H*-benzimidazole-2-thiol (**3**) (1.2 mmol) in acetone (5 ml) and Et_3N (0.3 ml, 2 mmol) were added to a solution of compound **1b** (0.3 g, 1.4 mmol) in acetone (30 ml). The reaction mixture was

heated at 40°C for 12 h. After completion of the reaction, acetone was removed and brine was added, the mixture was extracted with ethyl acetate (3×10 ml), the extract was dried over anhydrous Na_2SO_4, and then the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane–EtOAc, 100:0→70:30 + 1% MeOH) to yield esters **5b**,**c** or **6b**,**c**.

(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 3-(benzothiazol-2-ylsulfanyl)propanoate (5b). Yield 0.07 g (15%), colorless oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.82 (3H, s, 9-CH_3); 0.84 (3H, s, 10-CH_3); 0.88 (3H, s, 8-CH_3); 0.99 (1H, dd, ^2J = 13.7, $J_{2endo,1exo}$ = 3.5, 2-CH_{endo}); 1.16–1.32 (2H, m, 4-CH_{endo}, 5-CH_{exo}); 1.64–1.77 (2H, m, 3-CH, 4-CH_{exo}); 1.85–1.94 (1H, m, 5-CH_{endo}); 2.30–2.40 (1H, m, 2-CH_{exo}); 2.92 (2H, t, *J* = 6.9, 12-CH_2); 3.60 (2H, t, *J* = 6.9, 13-CH_2); 4.93 (1H, ddd, $J_{1exo,2exo}$ = 10.0, $J_{1exo,2endo}$ = 3.5, $J_{1exo,5exo}$ = 2.2, 1-CH_{exo}); 7.23–7.29 (1H, m, H-16); 7.36–7.42 (1H, m, H-19); 7.70–7.74 (1H, m, H-17); 7.83–7.86 (1H, m, H-18). ^{13}C NMR spectrum, δ, ppm: 171.5 (s); 165.8 (s); 153.0 (s); 135.1 (s); 125.8 (d); 124.1 (d); 121.4 (d); 120.8 (d); 80.4 (d); 48.6 (s); 47.6 (s); 44.7 (d); 36.6 (t); 34.6 (t); 28.2 (t); 27.8 (t); 26.9 (t); 19.5 (q); 18.6 (q); 13.3 (q). Found, *m*/*z*: 375.1320 $[M]^+$. $C_{20}H_{25}NO_2S_2$. Calculated, *m*/*z*: 375.1321.

(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 3-(benzoxazol-2-ylsulfanyl)propanoate (6b). Yield 0.09 g (20%), yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.82 (3H, s, 9-CH_3); 0.85 (3H, s, 10-CH_3); 0.88 (3H, s, 8-CH_3); 0.99 (1H, dd, ^2J = 13.7, $J_{2endo,1exo}$ = 3.5, 2-CH_{endo}); 1.16–1.32 (2H, m, 4-CH_{endo}, 5-CH_{exo}); 1.64–1.76 (2H, m, 3-CH, 4-CH_{exo}); 1.84–1.93 (1H, m, 5-CH_{exo}); 2.30–2.40 (1H, m, 2-CH_{exo}); 2.94 (2H, t, *J* = 6.8, 12-CH_2); 3.54 (2H, t, *J* = 6.8, 13-CH_2); 4.93 (1H, ddd, $J_{1exo,2exo}$ = 10.0, $J_{1exo,2endo}$ = 3.5, $J_{1exo,5exo}$ = 2.2, 1-CH_{exo}); 7.19–7.29 (2H, m, H-16,19); 7.39–7.43 (1H, m, H-17); 7.56–7.60 (1H, m, H-18). ^{13}C NMR spectrum, δ, ppm: 171.5 (s); 164.3 (s); 151.8 (s); 141.7 (s); 124.2 (d); 123.8 (d); 118.3 (d); 109.8 (d); 80.6 (d); 48.7 (s); 47.5 (s); 44.7 (d); 36.6 (t); 34.5 (t); 27.9 (t); 27.1 (t); 27.0 (t); 19.6 (q); 18.7 (q); 13.4 (q). Found, *m*/*z*: 359.1553 $[M]^+$. $C_{20}H_{25}NO_3S$. Calculated, *m*/*z*: 359.1550.

(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 3-(2-thioxobenzothiazol-3(2*H*)-yl)propanoate (5c). Yield 0.08 g (18%), white powder. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.74 (3H, s, 9-CH_3); 0.83 (3H, s, 10-CH_3); 0.85 (3H, s, 8-CH_3); 0.84–0.90 (1H, m, 2-CH_{endo}); 1.09–1.30 (2H, m, 4-CH_{endo}, 5-CH_{exo}); 1.61–1.65 (1H, m, 3-CH); 1.65–1.74 (1H, m, 4-CH_{exo}); 1.77–1.87 (1H, m, 5-CH_{endo}); 2.24–2.34 (1H, m, 2-CH_{exo}); 2.88 (2H, t, *J* = 7.4, 12-CH_2); 4.69 (2H, t, *J* = 6.8, 13-CH_2); 4.82–4.87 (1H, m, 1-CH_{exo}); 7.25–7.34 (2H, m, H-16,19); 7.36–7.48 (2H, m, H-17,18). ^{13}C NMR spectrum, δ, ppm: 189.0 (s); 171.0 (s); 141.0 (s); 127.6 (s); 126.9 (d); 124.7 (d); 121.3 (d); 112.3 (d); 80.7 (d); 48.6 (s); 47.6 (s); 44.6 (d); 41.9 (t); 36.4 (t); 31.4 (t); 27.8 (t); 26.9 (t); 19.5 (q); 18.6 (q); 13.3 (q). Found, *m*/*z*: 375.1323 $[M]^+$. $C_{20}H_{25}NO_2S_2$. Calculated, *m*/*z*: 375.1321.

(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 3-(2-thioxobenzoxazol-3(2*H*)-yl)propanoate (6c). Yield 0.16 g (37%), white powder, mp 159.7°C. $[\alpha]_D^{25}$ –26.5 ($CHCl_3$, *c* 0.74). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.71 (3H, s, 9-CH_3); 0.82 (3H, s, 10-CH_3); 0.84 (3H, s, 8-CH_3); 0.84–0.90 (1H, m, 2-CH_{endo}); 1.09–1.18 (1H, m, 4-CH_{endo}); 1.19–1.28 (1H, m, 5-CH_{exo}); 1.61–1.65 (1H, m, 3-CH); 1.64–1.74 (1H, m, 4-CH_{exo}); 1.76–1.85 (1H, m, 5-CH_{endo}); 2.22–2.32 (1H, m, 2-CH_{exo}); 2.96 (2H, t, *J* = 6.7, 12-CH_2); 4.44 (2H, t, *J* = 6.7, 13-CH_2); 4.81–4.87 (1H, m, 1-CH_{exo}); 7.20–7.34 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 179.9 (s); 171.1 (s); 147.0 (s); 131.7 (s); 124.8 (d); 124.2 (d); 110.2 (d); 109.9 (d); 80.8 (d); 48.6 (s); 47.6 (s); 44.6 (d); 41.4 (t); 36.4 (t); 31.4 (t); 27.8 (t); 26.8 (t); 19.5 (q); 18.6 (q); 13.2 (q). Found, *m*/*z*: 359.1550 $[M]^+$. $C_{20}H_{25}O_3NS$. Calculated, *m*/*z*: 359.1546.

(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl acrylate (8). (1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]-heptan-2-yl 3-chloropropanoate (**1b**) (0.30 g, 1.4 mmol) was dissolved in acetone, Et_3N (0.3 ml, 2 mmol) was added, and the mixture was stirred at 40°C for 18 h. After completion of the reaction, acetone was removed under reduced pressure and brine was added, the mixture was extracted with ethyl acetate (3×10 ml), the extract was dried over anhydrous Na_2SO_4, and then the solvent was removed under reduced pressure. Yield 0.19 g (65%), colorless oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.82 (3H, s, 9-CH_3); 0.85 (3H, s, 10-CH_3); 0.89 (3H, s, 8-CH_3); 0.99 (1H, dd, ^2J = 13.7, $J_{2endo,1exo}$ = 3.5, 2-CH_{endo}); 1.18–1.34 (2H, m, 4-CH_{endo}, 5-CH_{exo}); 1.63–1.78 (2H, m, 3-CH, 4-CH_{exo}); 1.9–2.0 (1H, m, 5-CH_{endo}); 2.30–2.42 (1H, m, 2-CH_{exo}); 4.90–4.95 (1H, m, 1-CH_{exo}); 5.78 (1H, dd, ^2J = 1.6, ^3J = 10.5, CH=C$\underline{H}_{cis}$); 6.12 (1H, dd, $^3J_{trans}$ = 17.3, $^3J_{cis}$ = 10.5, C$\underline{H}$=CH_2); 6.36 (1H, dd, ^2J = 1.6, ^3J = 17.3, CH=C$\underline{H}_{trans}$). ^{13}C NMR spectrum, δ, ppm: 166.4 (s); 129.9 (t); 128.9 (d); 79.9 (d); 48.7 (s); 47.7 (s); 44.8 (d); 36.6 (t); 28.2 (t); 27.9 (t); 27.0 (t); 19.6 (q); 18.7 (q); 13.4 (q). Found, *m*/*z*: 208.3015 $[M]^+$. $C_{13}H_{20}O_2$. Calculated, *m*/*z*: 208.3010.

Preparation of compounds 7b, 9a–g (General method). DBU (0.40 g, 2.5 mmol) was added to a solution of the appropriate heterocycle (2.5 mmol) in MeCN (15 ml), and the mixture was gently heated for 15 min. Then compound **1b** (0.60 g, 2.5 mmol) was added, and the mixture was refluxed for 8 h. After the completion of reaction, MeCN was removed under reduced pressure, brine was added, the mixture was extracted with ethyl acetate (3×10 ml), the combined extracts were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane–EtOAc, 100:0→70:30 + 1% MeOH)**.**

Bis((1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl) 3,3'-(2-thioxo-1*H*-benzimidazole-1,3(2*H*)-diyl)dipropanoate (7b). Yield 0.78 g (63%), white powder, mp 115°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.72 (6H, s, 9,9'-CH_3); 0.81 (6H, s, 10,10'-CH_3); 0.84 (6H, s, 8,,8'-CH_3); 0.82–0.88 (2H, m, 2,2'-CH_{endo}); 1.07–1.26 (4H, m, 4,4'-CH_{endo}, 5,5'-CH_{exo}); 1.59–1.63 (2H, m, 3,3'-CH); 1.63–1.71 (2H, m, 4,4'-CH_{exo}); 1.76–1.85 (2H, m, 5,5'-CH_{endo}); 2.22–2.32 (2H, m, 2,2'-CH_{exo}); 2.90 (4H, t, *J* = 7.2, 12,12'-CH_2); 4.57 (4H, t, *J* = 7.2, 13,13'-CH_2); 4.79–4.85 (2H, m, 1,1'-CH); 7.20–7.23 (2H, m, H-16,19); 7.27–7.32 (2H, m, H-17,18). ^{13}C NMR spectrum, δ, ppm: 171.5 (s); 168.8 (s); 131.6 (s); 123.0 (d); 109.3 (d); 80.5 (d); 48.6 (s); 47.8 (s); 44.7 (d); 40.3 (t); 36.5 (t); 32.5 (t); 27.8 (t); 26.9 (t); 19.5 (q), 18.7 (q), 13.3 (q). Found, *m*/*z*: 566.3170 $[M]^+$. $C_{33}H_{46}O_4N_2S$. Calculated, *m*/*z*: 566.3173.

(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 3-(pyridin-2-ylsulfanyl)propanoate (9a). Yield 0.4 g (51%), colorless oil. $[\alpha]_D^{27}$ –30.7 ($CHCl_3$, *c* 0.84). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.79 (3H, s, 9-CH_3); 0.82 (3H, s, 10-CH_3); 0.86 (3H, s, 8-CH_3); 0.96 (1H, dd, ^2J = 13.7, $J_{2endo,1exo}$ = 3.5, 2-CH_{endo}); 1.13–1.29 (2H, m, 4-CH_{endo}, 5-CH_{exo}); 1.59–1.64 (1H, m, 3-CH); 1.65–1.75 (1H, m, 4-CH_{exo}); 1.83–1.93 (1H, m, 5-CH_{endo}); 2.23–2.41 (1H, m, 2-CH_{exo}); 2.75 (2H, t, *J* = 6.9, 12-CH_2); 3.41 (2H, t, *J* = 6.9, 13-CH_2); 4.88 (1H, ddd, $J_{1exo,2exo}$ = 10.0, $J_{1exo,2endo}$ = 3.5, $J_{1exo,5exo}$ = 2.2, 1-CH_{exo}); 6.88–6.95 (1H, m, H-17); 7.08–7.13 (1H, m, H-15); 7.38–7.44 (1H, m, H-16); 8.33–8.41 (1H, m, H-18). ^{13}C NMR spectrum, δ, ppm: 172.1 (s); 158.0 (s); 149.2 (d); 135.7 (d); 122.2 (d); 119.2 (d); 80.0 (d); 48.6 (s); 47.6 (s); 44.6 (d); 36.5 (t); 34.8 (t); 27.8 (t); 26.9 (t); 24.8 (t); 19.5 (q); 18.6 (q); 13.3 (q). Found, *m*/*z*: 319.1606 $[M]^+$. $C_{18}H_{25}O_2NS$. Calculated, *m*/*z*: 319.1601.

(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 3-(pyrimidin-2-ylsulfanyl)propanoate (9b). Yield 0.4 g (55%), pale yellow oil. $[\alpha]_D^{30}$ –30.5 ($CHCl_3$, *c* 0.76). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.79 (3H, s, 9-CH_3); 0.82 (3H, s, 10-CH_3); 0.85 (3H, s, 8-CH_3); 0.96 (1H, dd, ^2J = 13.7, $J_{2endo,1exo}$ = 3.5, 2-CH_{endo}); 1.14–1.29 (2H, m, 4-CH_{endo}, 5-CH_{exo}); 1.60–1.65 (1H, m, 3-CH); 1.65–1.74 (1H, m, 4-CH_{exo}); 1.81–1.92 (1H, m, 5-CH_{endo}); 2.27–2.36 (1H, m, 2-CH_{exo}); 2.79 (2H, t, *J* = 7.1, 12-CH_2); 3.36 (2H, t, *J* = 7.1, 13-CH_2); 4.88 (1H, ddd, $J_{1exo,2exo}$ = 10.0, $J_{1exo,2endo}$ = 3.5, $J_{1exo,5exo}$ = 2.2, 1-CH_{exo}); 6.91–6.96 (1H, m, H-16); 8.44–8.52 (2H, m, H-15,17). ^{13}C NMR spectrum, δ, ppm: 172.0 (s); 171.7 (s); 157.1 (d), 116.4 (d); 80.1 (d); 48.6 (s); 47.6 (s); 44.7 (d); 36.6 (t); 34.5 (t); 27.8 (t); 26.9 (t); 25.9 (t); 19.5 (q); 18.6 (q); 13.4 (q). Found, *m*/*z*: 320.1563 $[M]^+$. $C_{17}H_{24}O_2N_2S$. Calculated, *m*/*z*: 320.1553.

(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 3-(2-thioxothiazolidin-3-yl)propanoate (9c). Yield 0.42 g (60%), white powder, mp 105°C. $[\alpha]_D^{30}$ –25.4 ($CHCl_3$, *c* 0.52). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.80 (3H, s, 9-CH_3); 0.85 (3H, s, 10-CH_3); 0.87 (3H, s, 8-CH_3); 0.95 (1H, dd, ^2J = 13.7, $J_{2endo,1exo}$ = 3.5, 2-CH_{endo}); 1.17–1.33 (2H, m, 4-CH_{endo}, 5-CH_{exo}); 1.65–1.68 (1H, m, 3-CH); 1.68–1.77 (1H, m, 4-CH_{exo}); 1.84–1.93 (1H, m, 5-CH_{endo}); 2.28–2.38 (1H, m, 2-CH_{exo}); 2.80 (2H, t, *J* = 6.5, 12-CH_2); 3.26 (2H, t, *J* = 6.5, 13-CH_2); 3.99 (2H, t, *J* = 6.2, 16-CH_2); 4.18 (2H, t, *J* = 6.2, 15-CH_2); 4.87 (1H, ddd, $J_{1exo,2exo}$ = 10.0, $J_{1exo,2endo}$ = 3.5, $J_{1exo,5exo}$ = 2.2, 1-CH_{exo}). ^{13}C NMR spectrum, δ, ppm: 196.9 (s); 171.9 (s); 80.6 (d); 57.9 (t); 48.6 (s); 47.7 (s); 44.9 (t); 44.6 (d); 36.5 (t); 31.8 (t); 27.8 (t); 27.6 (t); 26.9 (t); 19.5 (q); 18.6 (q); 13.4 (q). Found, *m*/*z*: 327.1325 $[M]^+$. $C_{16}H_{25}NO_2S_2$. Calculated, *m*/*z*: 327.1321.

(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 3-(3-methyl-2-thioxoimidazolidin-1-yl)propanoate (9d). Yield 0.30 g (47%), white powder, mp 95°C. $[\alpha]_D^{30}$ –26.9 ($CHCl_3$, *c* 0.52). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.77 (3H, s, 9-CH_3); 0.83 (3H, s, 10-CH_3); 0.86 (3H, s, 8-CH_3); 0.90 (1H, dd, ^2J = 13.7, $J_{2endo,1exo}$ = 3.5, 2-CH_{endo}); 1.26–1.29 (2H, m, 4-CH_{endo}, 5-CH_{exo}); 1.61–1.65 (1H, m, 3-CH); 1.66–1.75 (1H, m, 4-CH_{exo}); 1.80–1.88 (1H, m, 5-CH_{endo}); 2.25–2.35 (1H, m, 2-CH_{exo}); 2.88 (2H, t, *J* = 6.0, 12-CH_2); 3.57 (3H, s, 17-CH_3); 4.29 (2H, t, *J* = 6.0, 13-CH_2); 4.84 (1H, ddd, $J_{1exo,2exo}$ = 10.0, $J_{1exo,2endo}$ = 3.5, $J_{1exo,5exo}$ = 2.2, 1-CH_{exo}); 6.62 (1H, br. s, H-15); 6.82 (1H, br. s, H-16). ^{13}C NMR spectrum, δ, ppm: 171.8 (s); 161.9 (s); 117.9 (d); 117.2 (d); 80.5 (d); 48.6 (s); 47.7 (s); 44.7 (d); 43.6 (t); 36.5 (t); 34.9 (q); 33.1 (t); 27.8 (t); 26.9 (t); 19.5 (q); 18.7 (q); 13.4 (q). Found, *m*/*z*: 322.1716 $[M]^+$. $C_{17}H_{26}N_2O_2S$. Calculated, *m*/*z*: 322.1710.

(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 3-[(1*H*-1,2,4-triazol-3-yl)sulfanyl]propanoate (9e). Yield 0.20 g (35%), colorless oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.79 (3H, s, 9-CH_3); 0.83 (3H, s, 10-CH_3); 0.85 (3H, s, 8-CH_3); 0.95 (1H, dd, ^2J = 13.7, $J_{2endo,1exo}$ = 3.5, 2-CH_{endo}); 1.13–1.30 (2H, m, 4-CH_{endo}, 5-CH_{exo}); 1.61–1.65 (1H, m, 3-CH); 1.65–1.75 (1H, m, 4-CH_{exo}); 1.80–1.89 (1H, m, 5-CH_{endo}); 2.26–2.36 (1H, m, 2-CH_{exo}); 2.81 (2H, t, *J* = 6.9, 12-CH_2); 3.38 (2H, t, *J* = 6.9, 13-CH_2); 4.88 (1H, ddd, $J_{1exo,2exo}$ = 10.0, $J_{1exo,2endo}$ = 3.5, $J_{1exo,5exo}$ = 2.2, 1-CH_{exo}); 8.18 (1H, s, H-15). ^{13}C NMR spectrum, δ, ppm: 172.1 (s); 156.6 (br. s); 146.9 (br. d); 80.6 (d); 48.6 (s); 47.6 (s); 44.6 (d); 36.49 (t); 35.0 (t); 27.8 (t); 27.5 (t); 26.9 (t); 19.5 (q); 18.6 (q); 13.3 (q). Found, *m*/*z*: 309.1504 $[M]^+$. $C_{15}H_{23}N_3O_2S$. Calculated, *m*/*z*: 309.1506.

(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 3-(2,4-dioxothiazolidin-3-yl)propanoate (9f). Yield 0.10 g (15%), colorless oil. $[\alpha]_D^{29}$ –30.4 ($CHCl_3$, *c* 0.54). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.79 (3H, s, 9-CH_3); 0.83 (3H, s, 10-CH_3); 0.86 (3H, s, 8-CH_3); 0.92–0.97 (1H, m, 2-CH_{endo}); 1.15–1.32 (2H, m, 4-CH_{endo}, 5-CH_{exo}); 1.63–1.66 (1H, m, 3-CH); 1.66–1.76 (1H, m, 4-CH_{exo}); 1.79–1.89 (1H, m, 5-CH_{endo}); 2.27–2.36 (1H, m, 2-CH_{exo}); 2.59–2.69 (2H, m, 12-CH_2); 3.84–3.97 (2H, m, 13-CH_2); 3.93 (2H, s, 15-CH_2); 4.84 (1H, ddd, $J_{1exo,2exo}$ = 10.0, $J_{1exo,2endo}$ = 3.5, $J_{1exo,5exo}$ = 2.2, 1-CH_{exo}). ^{13}C NMR spectrum, δ, ppm: 171.7 (s); 171.4 (s); 170.9 (s); 81.0 (d); 49.0 (s); 48.1 (s); 45.1 (d); 37.9 (t); 36.9 (t), 34.0 (t); 32.4 (t); 28.3 (t); 27.4 (t); 20.0 (q); 19.1 (q); 13.8 (q). Found, *m*/*z*: 325.1344 $[M]^+$. $C_{16}H_{23}NO_4S$. Calculated, *m*/*z*: 325.1342.

(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 3-(1*H*-1,2,4-triazol-1-yl)propanoate (9g). Yield 0.30 g (45%), white powder. $[\alpha]_D^{27}$ –33.6 ($CHCl_3$, *c* 0.66). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.72 (3H, s, 9-CH_3); 0.80 (3H, s, 10-CH_3); 0.83 (3H, s, 8-CH_3); 0.81–0.85 (1H, m, 2-CH_{endo}); 1.07–1.27 (2H, m, 4-CH_{endo}, 5-CH_{exo}); 1.58–1.62 (1H, m, 3-CH); 1.62–1.80 (2H, m, 4-CH_{exo}, 5-CH_{endo}); 2.20–2.32 (1H, m, 2-CH_{exo}); 2.82–2.95 (2H, m, 12-CH_2); 2.35–2.48 (2H, m, 13-CH_2); 4.82 (1H, ddd, $J_{1exo,2exo}$ = 10.0, $J_{1exo,2endo}$ = 3.5, $J_{1exo,5exo}$ = 2.2, 1-CH_{exo}); 7.88 (1H, s, H-15); 8.08 (1H, s, H-14). ^{13}C NMR spectrum, δ, ppm: 170.6 (s); 151.9 (d); 143.4 (d); 80.7 (d); 48.5 (s); 47.6 (s); 44.9 (t); 44.5 (d); 36.4 (t); 34.2 (t); 27.7 (t); 26.8 (t); 19.4 (q); 18.6 (q); 13.3 (q). Found, *m*/*z*: 277.1788 $[M]^+$. $C_{15}H_{23}N_3O_2$. Calculated, *m*/*z*: 277.1785.

Biological studies. *Cytotoxicity assessment*. Microtetrazolium test (MTT) was used to study the cytotoxicity of the compounds.[17] A series of threefold dilutions of each compound (300–3 μg/ml) in minimal essential medium (MEM) were prepared. MDCK cells were incubated for 48 h at 37°C under 5% CO_2 atmosphere in the presence of dissolved study compounds. The degree of destruction of the cell monolayer was then evaluated by the microtetrazolium test (MTT). The cells were washed twice with saline, and a solution of 3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide (ICN Biochemicals Inc.,

Aurora, OH, USA) (0.5 mg/ml) in phosphate-buffered saline was added to the wells. After 1 h incubation, the wells were washed and the formazan residue dissolved in DMSO (0.1 ml per well). The optical density of cells was then measured on a Victor 2 1440 multifunctional reader (Perkin Elmer, Finland) at 535 nm and plotted against the concentration of the compounds. Each concentration was tested in three parallel tests. The 50% cytotoxic dose (CC_{50}) of each compound (i.e., the compound concentration that caused the death of 50% cells in a culture, or decreasing the optical density to one half of the value in control wells) was calculated from the data obtained.

Antiviral activity. To assess the antiviral activity, cells were infected with 100 $TCID_{50}$ of influenza virus A/Puerto Rico/8/34 (H1N1) in the presence of threefold dilutions of compounds, and the virus titer was further measured by $TCID_{50}$ titration. Based on the data obtained, 50% cytotoxic concentration CC_{50} (the concentration resulting in the death of 50% of cells), 50% inhibiting concentration IC_{50} (the concentration resulting in a decrease of virus titer by 50%) and the selectivity index SI (the ratio of CC_{50} to IC_{50}) were calculated.

Antiulcer activity. Female Wistar rats weighing 180–200 g were obtained from the Laboratory of Experimental Animal Breeding of the Institute of Cytology and Genetics, Novosibirsk, Russia. The animals were kept in environmentally controlled rooms (21°C, 12 h light and dark cycle) with free access to water. The animals were fasted for approximately 24 h prior to the experiment. The agents were suspended in distilled water containing 0.5% of Tween 80 and were administered to the animals *per os* in the dose of 100 mg/kg. Omeprazole in the dose of 100 mg/kg was used as a reference compound. The animals in the control group were treated with distilled water containing Tween 80. Indomethacin aqueous suspension was administered to the rats *per os* in the dose of 25 mg/kg 1 h later to induce ulceration.[18] All the animals were sacrificed 24 h after the administration of indomethacin, their stomachs were excised and observed for lesions. The Pauls' index (PI) representing the degree of ulceration was calculated for every experimental group using the following formula: PI = (A × B)/100%, where A is the mean number of ulcers per animal and B is the percent of animals with ulcerations in the group. The substances in question with the AA score greater than or equal to 2 were considered as effective antiulcer agents.

Analgesic tests. The studies were carried out on outbred albino mice weighing 20–25 g obtained from the Laboratory of Experimental Animal Breeding of the Institute of Cytology and Genetics, Novosibirsk, Russia. The agents were dissolved in distilled water containing 0.5% of Tween 80 just before use and were administered *per os* in the dose of 10 mg/kg for compound **9g** and in the dose of 20 mg/kg for compounds **9a**–**d** 1 h before the acetic acid-induced writhing test and hot plate test. In the acetic acid-induced writhing test, the pain reaction was determined by the number of abdominal convulsions, recorded from the 5th to 8th min following the acetic acid injection (0.75 %, 0.1 ml/10 g of body weight).[19] In the hot plate test, animals were placed individually on a metallic plate warmed to 54 ± 0.5°C, and the time until either licking of the hind paw or jumping occurred was recorded by a stopwatch.[20]

The Supplementary information file, containing ^{1}H and ^{13}C NMR spectra of compounds **2**–**3 a**–**c**, **4a**,**b**, **6a**–**g**, is available from the journal website at http://link.springer.com/journal/10593.

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