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Synthesis and Properties of 1,3-Disubstituted Ureas and Their Isosteric Analogs Containing Polycyclic Fragments: V.[1] 1-(Bicyclo[2.2.1]heptan-2-yl)-3-R- and 1-(1,7,7-Tricyclo[2.2.1]heptan-2-yl)-3-R-ureas

D. A. Pitushkin[a,b], V. V. Burmistrov[a,b], M. H. Abbas Saeef[a], A. A. Vernigora[a], and G. M. Butov[a,b,*]

[a] *Volgograd State Technical University (VSTU), Volgograd, 400005 Russia*
[b] *Volzhsky Polytechnic Institute, VSTU Branch, Volzhsky, 404121 Russia*
**e-mail: butov@post.volpi.ru*

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Abstract—A series of 1,3-disubstituted ureas containing a bicyclic lipophilic group of natural origin were synthesized by the reactions of bicyclo[2.2.1]heptane-2-yl isocyanate with amines in yields of up to 82% and by the reactions of bicyclo[2.2.1]heptan-2-amine and 1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine with 1,1'-carbonyldiimidazole in yields of up to 94%. The synthesized ureas are potent inhibitors of RNA virus replication and soluble epoxide hydrolase.

Keywords: natural compounds, bicyclo[2.2.1]heptane, isocyanate, urea, halogenated anilines, soluble epoxide hydrolase, coronavirus, SARS-CoV

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Ureas are universal building blocks for the synthesis of various heterocyclic compounds, and they exhibit broad-range biological activity [2]. For example, 1,3-disubstituted ureas are known as the most effective inhibitors of soluble human epoxide hydrolase (sEH), a promising target in the treatment of hypertension, inflammation, and pain syndromes [3–6].

Park et al. [7] have studied a series of 1,3,3-trisubstituted ureas [ethyl 2-(4-R-1,4-diazepane-1-carboxamido)benzoates] as RNA virus replication inhibitors (Fig. 1). It has been established that useas of this series at concentrations of 250 μM decelerated replication to up to ~ 8% against control, which allowed these compounds to be considered as potential antiviral agents against such RNA viruses as SARS-CoV, HIV-1, and viruses causing ARVIs [7].

The most common method of synthesis of asymmetric ureas, known since mid-1900s, is the reaction of amines with isocyanates containing various substituents [8–11]. The main disadvantages of this method include the toxicity of the starting isocyanates and their small assortment, as well as the formation of symmetric ureas due to the reaction of isocyanates with traces of moisture inevitably present in any system. In cases where asymmetric ureas are synthesized for the purposes of medicinal chemistry, the presence of even small amounts of symmetric ureas is unacceptable, but these by-products are quite difficult to separate because of their structural similarity to the target compounds.

At present another synthetic approach to unsymmetrical 1,3-disubstituted ureas is practiced, which involves the reaction of two amines of different structures and basicities with 1,1'-carbonyldiimidazole (CDI), an analog of phosgene in the synthesis of ureas from amines. This method is a three-component one- or two-step reaction.

For example, Gray et al. [12] described the synthesis of 1-(naphthalen-1-yl)-3-(pyridin-3-yl)urea in a yield of 98% by the reaction of 3-aminopyridine with an equal amount of CDI under heating at 50°C for 1.5 h followed

[1] For communication IV, see [1].

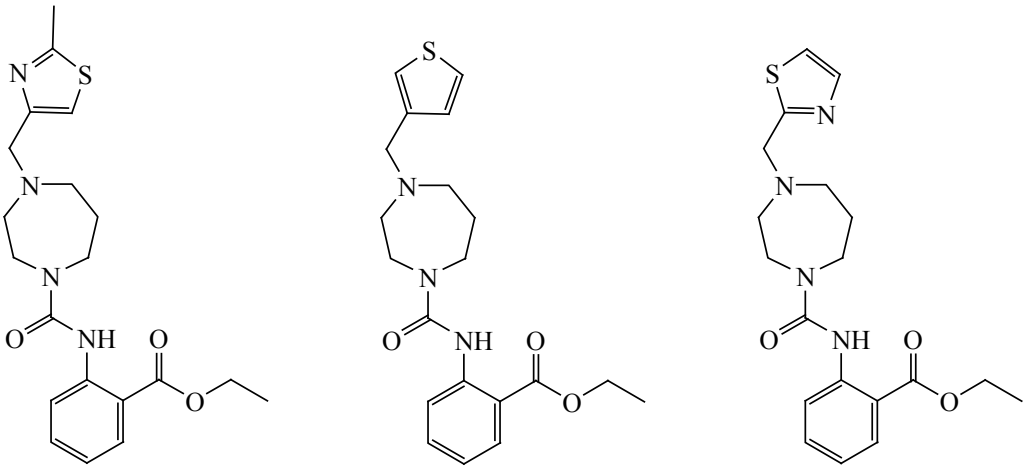


Fig. 1. Ethyl 2-(4-R-1,4-diazepane-1-carboxamido)benzoates.

by the addition of an equal amount of α-naphthylamine in THF.

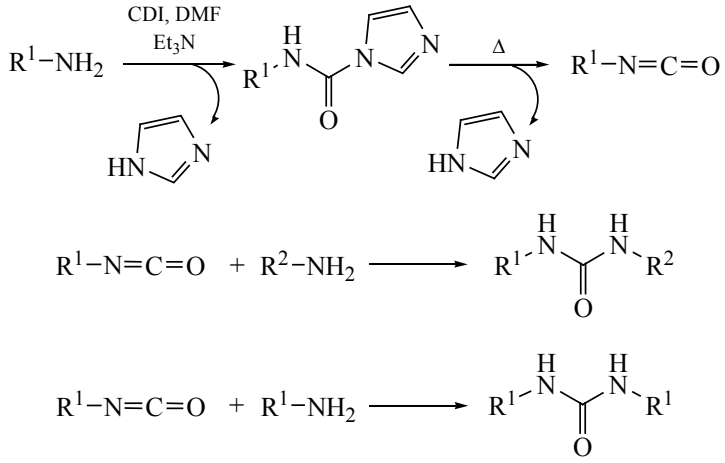
A 10% excess of CDI was used for the synthesis of [(1-methoxy-1-oxo-3-phenylpropan-2-yl)carbamoyl]-alanine at room temperature. The second amine (phenylalanine methyl ester hydrochloride) was added 5 min after the first amine (phenylalanine benzyl ester *p*-toluenesulfonate) and CDI [13].

Wang et al. [14] reported the synthesis of unsymmetrical ureas with a 3-fold excess of CDI. For example, 1-(6-bromo[1,2,4]triazole[1,5-*a*]pyridin-2-yl)-3-methylurea was synthesized in a yield of 79.6% by heating a mixture of 6-bromo[1,2,4]triazole[1,5-*a*]-pyridin-2-amine NaH and a 3-fold excess of CDI in DMF at 60°C followed by adding a 3,5-fold excess of methylamine and heating at 60°C for 6 h. The authors of the cited work did not mention whether they removed excess CDI before adding the second amine.

Apparently, one of the factors favoring formation of by-product symmetrical ureas is that the unreacted starting amine reacts with isocyanate formed at the second stage of the reaction (Scheme 1). Therefore, the yield of unsymmetrical ureas will be much dependent on the reaction protocol and conditions. Therewith, the basicity (nucleophilicity) and the starting amines and the reactivity of the intermediate isocyanate will determine the reaction selectivity and yield.

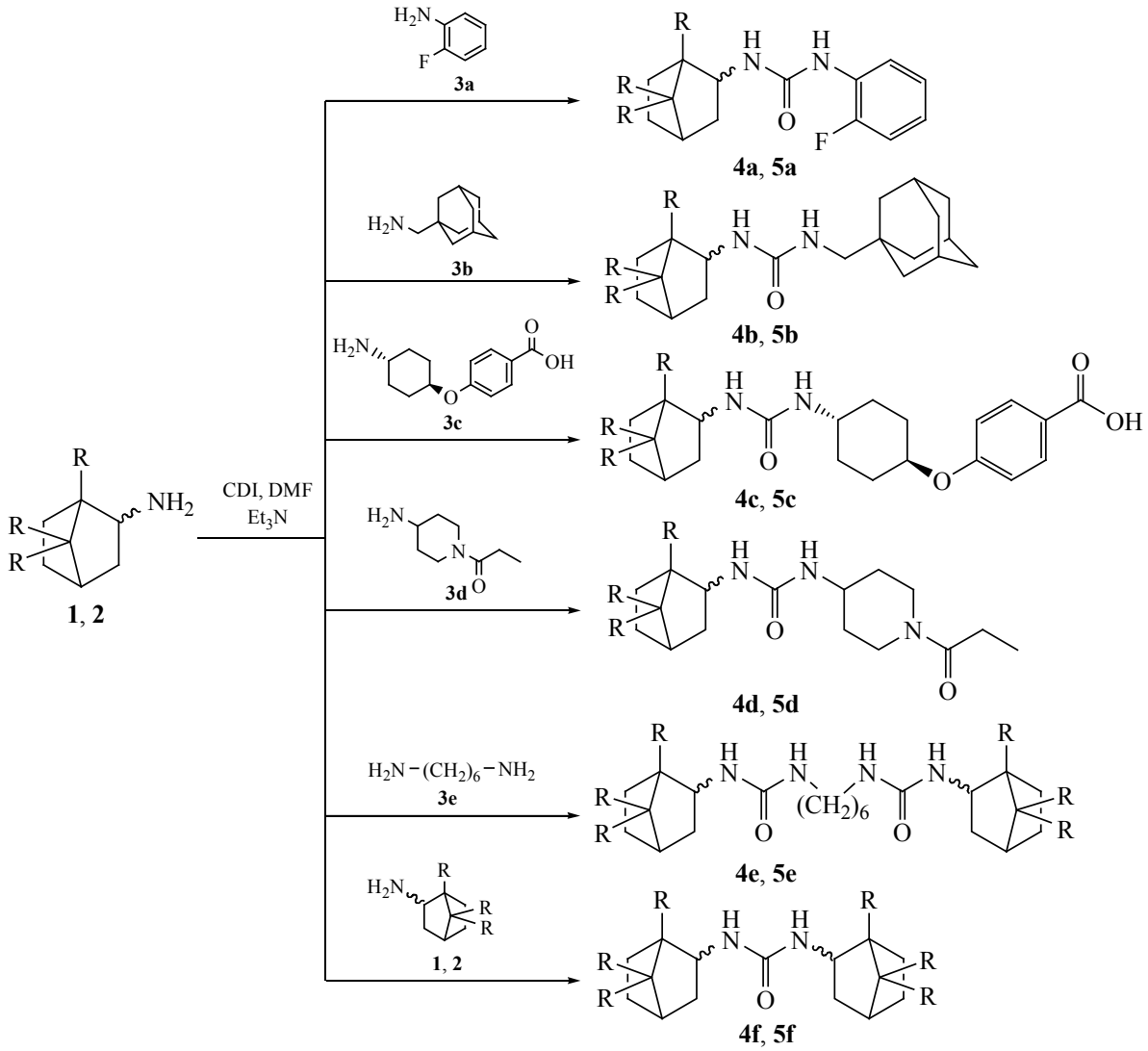
In the present work we synthesized a series of 1,3-disubstituted ureas **4a**–**4e** and **5a**–**5e** on the basis of bicyclo[2.2.1]heptan-2-amine (**1**) and 1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (**2**), as well as amines, which were previously used as starting

Scheme 1.



R^1 = alkyl, aryl; R^2 = alkyl, aryl.

Scheme 2.



R = H (**1**, **4a–4f**), R = CH_3 (**2**, **5a–5f**).

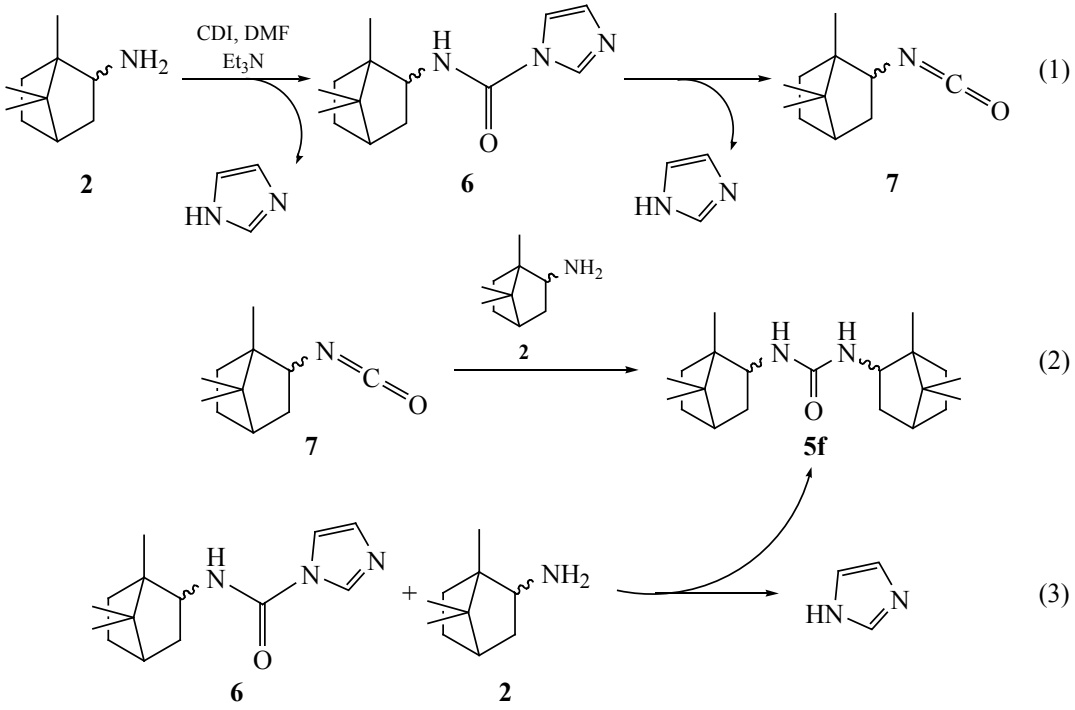
materials for preparing highly active sEH inhibitors, specifically 2-fluoroaniline (**3a**) [15], 1-(aminomethyl)-adamantane (**3b**) [16], *trans*-4-[(4-aminocyclohexyl)-oxy]benzoic acid (**3c**) [3], 1-(4-aminopiperidin-1-yl)-propan-1-one (**3d**) [4], and 1,6-diaminohexane (**3e**) [5], in the presence of CDI. In addition, symmetric ureas **4f** and **5f** were obtained from amines **1** and **2** (Scheme 2).

Compounds **4a–4e** and **5a–5e** were synthesized under similar conditions. Therewith, it was found that the yield of the products depends on the structure of the starting amines (Table 1). Furthermore, symmetrical ureas **4f** and **5f** formed always, when amine **1** or **2** was the first to be reacted. If amines were charged in reverse order, symmetrical amines formed from amines **3a–3d**.

To find out how the basicity of the starting amines affects the selectivity of the reaction with CDI, we took amines **2** and **3a**, which strongly differ in basicity (pK_a 9.3 [17] and 3.2 [18], respectively). Taking into account that urea **5a** does not decompose under GC conditions (unlike its adamantane analogs [19]), we used its formation to explore the effect of different factors on the reaction.

First we studied the reaction of amine **2** with CDI in the absence of another amine. According to the GCMS data, mixing amine **2** with CDI at 25°C results in a fairly rapid (20 min) formation of intermediate carboxamide **6** [Scheme 3, reaction (1)]. However, this reaction, too, gave symmetrical urea **5f** (yield 8%), which can

Scheme 3.



be associated with the subsequent decomposition of carboxamide **6** to isocyanate **7** and its reaction with the starting amine **2** [Scheme 3, reaction (2)]. Thus, the conditions of the first stage of the three-component should exclude the decomposition of carboxamide **6** to isocyanate before the second amine has been added. Therewith, symmetrical urea **5f** may well be formed as a result of further reaction of amine **2** with carboxamide **6** [Scheme 3, reaction (3)].

Experiments with varying the order of loading the reagents established that urea **5f** (Fig. 2) did not form, when amine **2** (more basic amine) was added at the second stage (Scheme 4); instead, a symmetrical urea formed by amine **3a** (75%) and unsymmetrical urea **5a** (12%) were detected.

When the order of loading the amines was reversed, ureas **5a** and **5f** almost did not form, and the reaction mixture contained only the less basic starting amine **3a** and isocyanate **7** (Fig. 3).

However, if a more basic *tert*-butylamine (pK_a 10.86 [20]) was added to the reaction mixture, it rapidly reacted with isocyanate **7** to form urea **5h** (Fig. 4). Thus, the basicity of the amine added at the second stage plays a key role in the formation of unsymmetrical urea **5a** (Fig. 4).

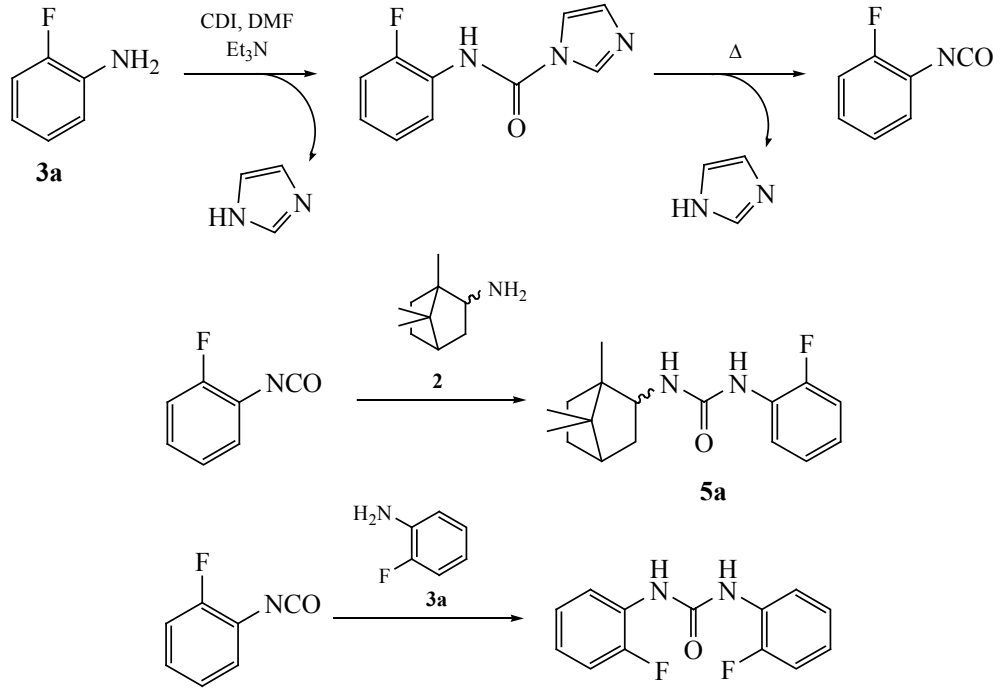
Compounds **4a**–**4f** were also prepared in an alternative way, starting from 2-isocyanatobicyclo[2.2.1]heptane **8** (Scheme 5).

Isocyanate **8** was synthesized by the reaction of bicyclo[2.2.1]heptane-2-carboxylic acid with diphenylphosphoryl azide (DPPA) in toluene in the presence of an equimolar amount of triethylamine at 110°C under stirring for 1 h (Scheme 6).

The reaction was considered complete when nitrogen no longer evolved from the reaction mixture. The solvent was removed in a vacuum, and product **8** was separated with triethylamine salt with diethyl ether.

The structure of the synthesized compounds was confirmed by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy and mass spectrometry. The ^{1}H NMR spectra contain a characteristic signal at 5.75–5.84 ppm, corresponding to the proton of the urea NH group attached to the bicyclic fragment. Therewith, methyl substituents in the bornyl radical have no effect on the chemical shift of this signal. An exception is compounds **4a** and **5a**, in the ^{1}H NMR spectra of which the proton signals of the urea NH group attached to the bicyclic fragment appear respectively at 6.75 and 6.73 ppm, apparently under the influence of the fluorine-substituted aromatic ring attached to the other NH group.

Scheme 4.



The ^{19}F NMR spectra of compounds **4a** and **5a** contain signals at –131.32 and –131.39 ppm, respectively, corresponding to the F^2 substituent.

The lipophilicity coefficients of compounds containing a bicyclo[2.2.1]heptyl fragment are lower by 1.13 compared to those of compounds with a 1,7,7-trimethylbicyclo[2.2.1]heptyl fragment (lower by 2.27 compared to compounds **4e**, **5e**, **4f**, and **5f**, which contain two lipophilic groups). The lipophilicity coefficient of compound **4c** is lower by 1.39 and 1.13 compared to those of compounds containing adamantyl and 4-(trifluoromethoxy)phenyl groups.

EXPERIMENTAL

2-Fluoroaniline (≥ 99%, CAS 348-54-9), 1,6-diaminohexane (98%, CAS 124-09-4), 1-aminomethyladamantane (98%, CAS 17768-41-1), triethylamine (BioUltra ≥ 99.5%, CAS 121-44-8), DMF (anhydrous 99.8%, CAS 68-12-2) were purchased from Sigma–Aldrich and used as received. *trans*-[4-(Aminocyclohexyl)oxy]benzoic acid [3], 1-(4-aminopiperidin-1-yl)-propan-1-one [US2013143925], bicyclo[2.2.1]heptan-2-amine [22], and 1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine [22] were prepared by known procedures.

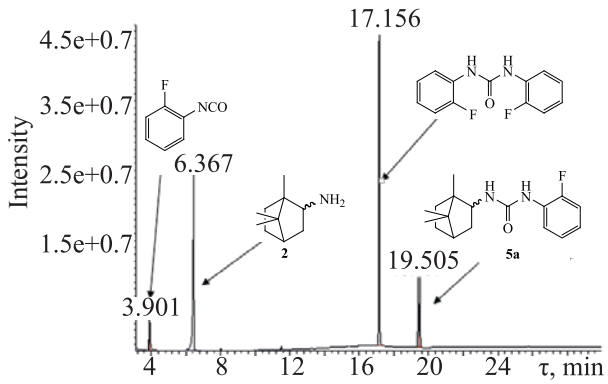


Fig. 2. Mass chromatogram of the reaction mixture. First stage: 2-fluoroaniline (**3a**), CDI, and Et_3N in DMF, 3 h, 25°C. Second stage: 1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (**2**), 8 h, 60°C.

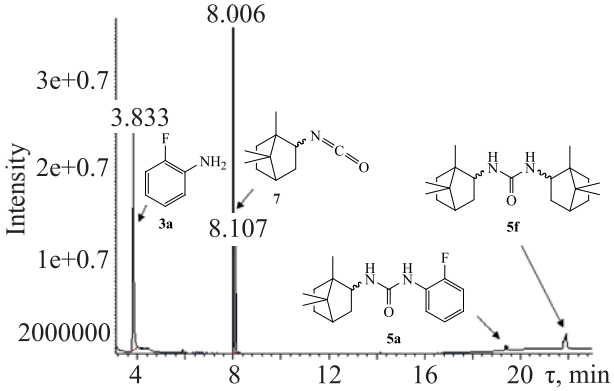


Fig. 3. Mass chromatogram of the reaction mixture. First stage: 1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (**2**), CDI, and Et_3N in DMF, 3 h, 25°C. Second stage: 2-fluoroaniline (**3a**), 8 h, 60°C.

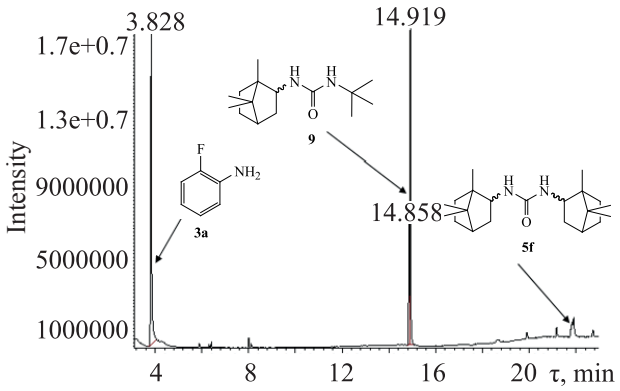
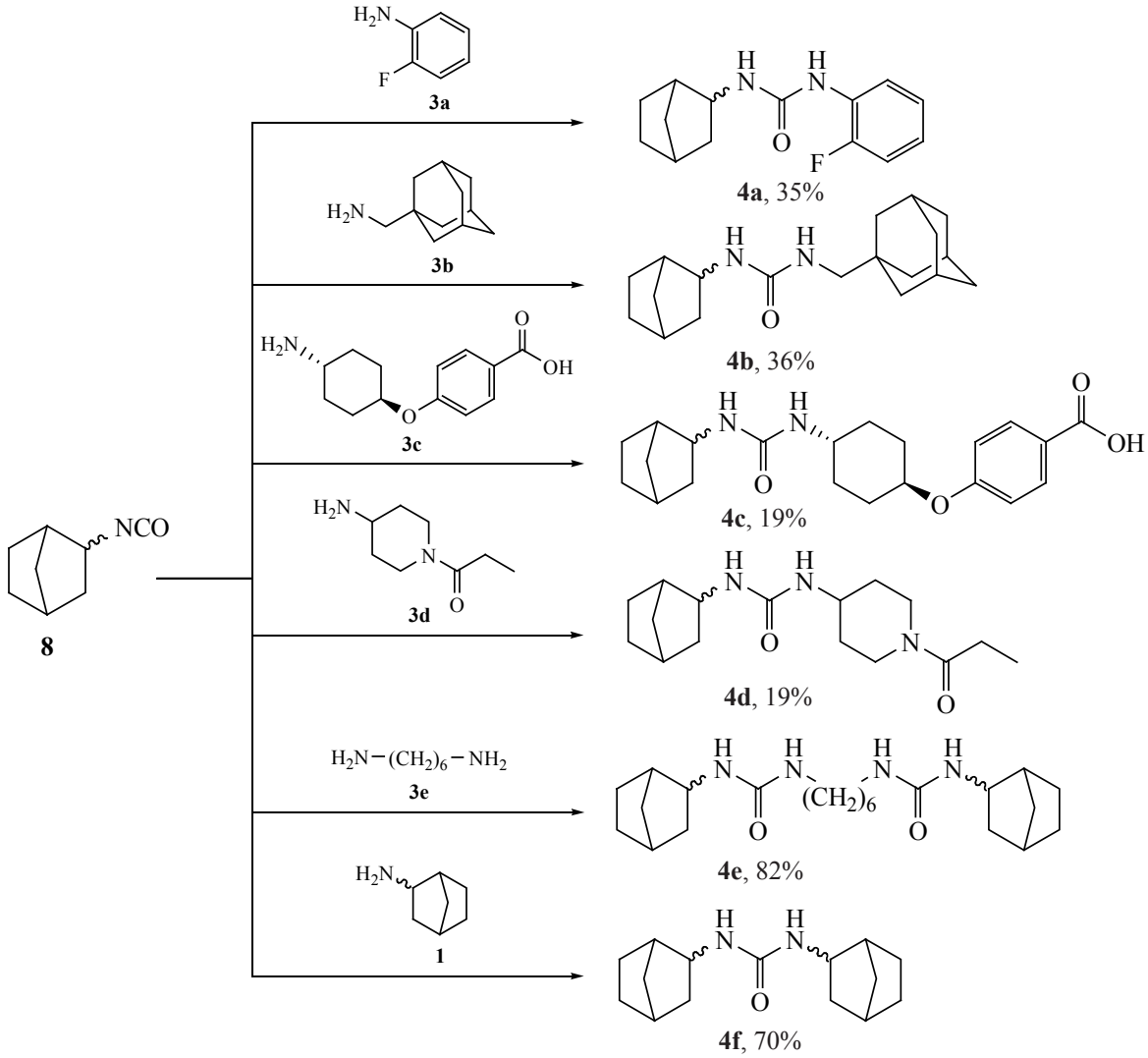


Fig. 4. Mass chromatogram of the reaction mixture. First stage: 1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (**2**), CDI, and Et_3N in DMF, 3 h, 25°C. Second stage: 2-fluoroaniline (**3a**), 8 h, 60°C. Third stage: *tert*-butylamine, 1 h, 25°C.

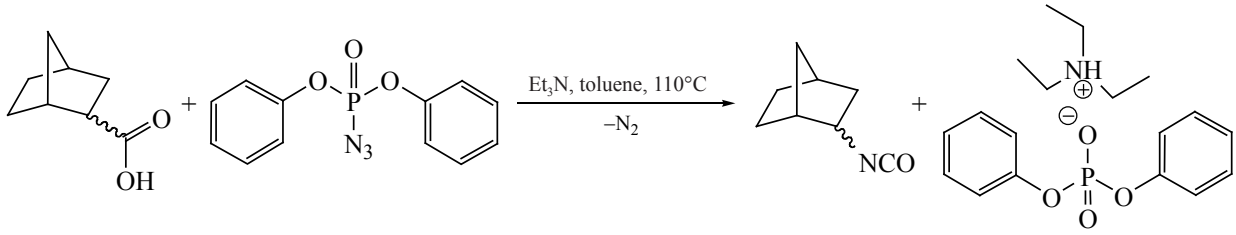
The structure of the synthesized compounds was confirmed by ^1H, ^{13}C, and ^{19}F NMR spectroscopy, gas chromatography–mass spectrometry, and elemental analysis. The mass spectra were obtained on an Agilent GC 5975/MSD 7820 system and an Advion Expression compact mass spectrometer in the full scan mode (ESI). The ^1H, ^{13}C, and ^{19}F NMR spectra were obtained on a Bruker Avance 600 spectrometer in DMSO-d_6; the ^1H chemical shifts were measured against internal TMS. The elemental analyses were obtained on a Perkin-Elmer Series II 2400 analyzer.

Bicyclo[2.2.1]heptane-2-yl isocyanate (8). Triethylamine, 5.15 mL (35.71 mmol), and 9.82 g (35.71 mmol) of DPPA were added to a solution of 5.0 g (35.71 mmol) of bicyclo[2.2.1]heptane-2-carboxylic acid in 50 mL

Scheme 5.



Scheme 6.



of toluene. The reaction mixture was slowly heated to reflux under stirring and then refluxed for 1 h. The reaction completion was established, when nitrogen no longer evolved from the reaction mixture. After cooling to room temperature, the solvent was removed in a vacuum to leave a yellow oily material. The target product was obtained after treatment of the latter diethyl ether (2 × 15 mL) and removal of the solvent from the extract. Yield 4.20 g (86%), transparent oily liquid. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.02–1.11 m (2H,

Table 1. Lipophilicity coefficients, melting points, and yields of compounds **3a–3f** and **4a–4f**

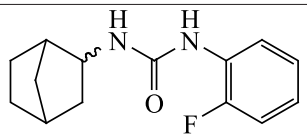
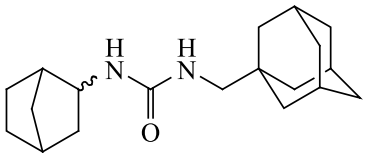
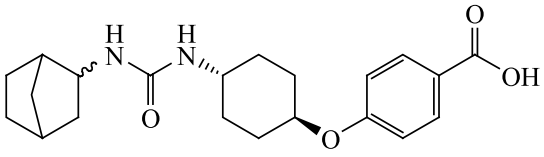
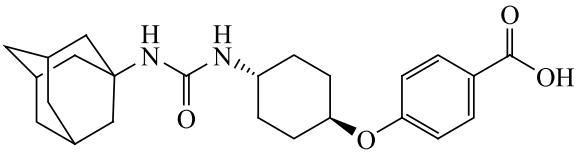
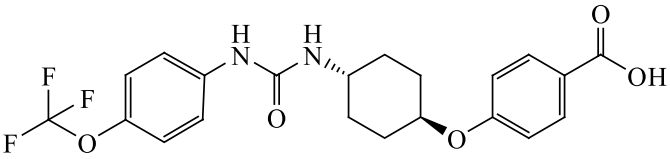
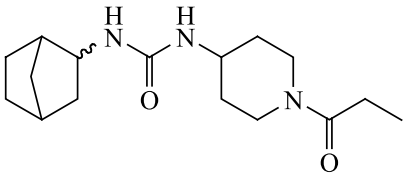
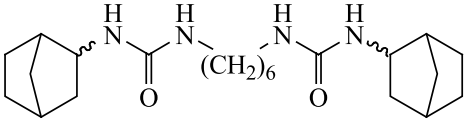
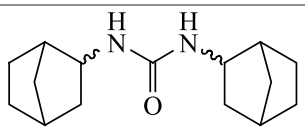
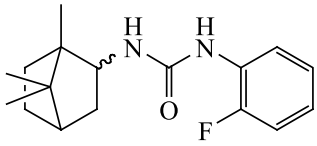
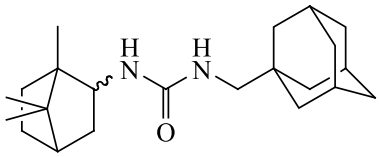
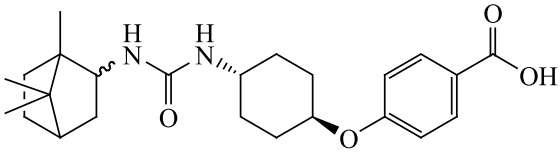
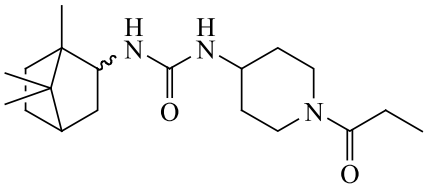
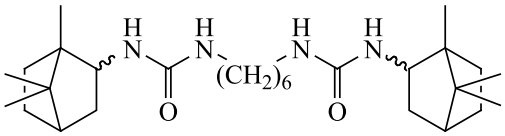
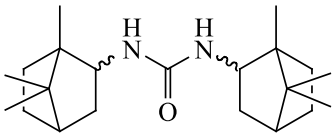
Compound no.	Structural formula	*M*	log *P*[a]	mp, °C	Yield, %[b]
4a		248	3.09	189–190	–/22 (35)
4b		302	4.22	228–229	–/35 (36)
4c		372	3.79	324–325	–/18 (19)
		412	5.18	250–255 [21]	
		438	4.92	244–273 [21]	
4d		293	1.90	111–112	–/3 (19)
4e		390	3.80	185–186	–/73 (82)

Table 1. (Contd.)

Compound no.	Structural formula	*M*	log *P*[a]	mp, °C	Yield, %[b]
4f		248	2.81	258–259	70
5a		290	4.23	224	4/12
5b		344	5.35	296–297	25/26
5c		414	4.92	345-346	94/16
5d		335	3.03	290	3/–
5e		474	6.07	158–159	34/71
5f		332	5.08	332–333	64

[a] Calculated by Molinspiration (http://www.molinspiration.com).
[b] Yield according to Scheme 1: decreasing basicity order/increasing basicity order.

CH_2), 1.44–1.63 m (2H, CH_2), 1.77–1.82 m (1H, CH), 2.01–2.07 m (1H, CH), 2.25 t (1H, CH_2, *J* 4.8 Hz), 2.35 t (1H, CH_2, *J* 4.8 Hz), 3.87 d.t.d (1H, CH–NCO, J_1 10.8, J_2 4.2, J_3 3.0 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.86 (CH_2), 29.53 (CH_2), 36.79 ($\underline{C}H_2$–C), 37.36 (CH), 39.32 (CH_2), 42.30 ($\underline{C}$H–C), 55.11 ($\underline{C}$–NCO), 129.08 (N$\underline{C}$O). Mass spectrum, *m/z* (I_{rel}, %): 137 (15.0) $[M]^+$, 95 (100) $[M - NCO]^+$. Found, %: C 70.08; H 8.05; N 10.22. $C_8H_{11}NO$. Calculated, %: C 70.04; H 8.08; N 10.21. *M* 137.08.

1-(Bicyclo[2.2.1]heptan-2-yl)-3-(2-fluorophenyl)-urea (4a). *a*. 2-Fluoroaniline (**3a**), 0.162 g (1.46 mmol), and 0.21 mL (1.46 mmol) of triethylamine were added to a solution of 0.2 g (1.46 mmol) of compound **8** in 5 mL of anhydrous diethyl ether. The reaction mixture was stirred at room temperature for 12 h, and the solvent was removed at reduced pressure. The residual reaction mixture was diluted with 5 mL of 1 N HCl and stirred for 30 min. The precipitate that formed was filtered off and washed with water. Yield 0.13 g (35%).

b. 1,1'-Carbonyldiimidazole, 0.22 g (1.36 mmol), and 0.27 g (2.72 mmol) of triethylamine were added to a solution of 0.15 g (1.36 mmol) of compound **3a** in 5 mL of DMF. The reaction mixture was stirred for 3 h at room temperature and then 0.2 g (1.36 mmol) of bicyclo[2.2.1]heptan-2-amine hydrochloride (**1**) was added. The reaction mixture was stirred at 60°C for 8 h, cooled, diluted with 5 mL of 1 N HCl, and stirred for an additional 30 min. The precipitate that formed was filtered off and washed with water. Yield 0.074 g (22%), mp 189–190°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.04–1.65 m (8H, 4CH_2), 2.17 t (1H, CH, *J* 4.8 Hz), 2.27 t (1H, CH, *J* 4.2 Hz), 3.90 td (1H, C<u>H</u>–NH, J_1 8.4, J_2 3.6 Hz), 6.75 t (1H, NH, *J* 6.0 Hz), 6.90 t.d.d (1H, H^4_{arom}, J_1 8.4, J_2 4.2, J_3 1.2 Hz), 7.06 t (1H, H^5_{arom}, *J* 7.8 Hz), 7.16 d.d.d (1H, H^3_{arom}, J_1 12.0, J_2 8.4, J_3 1.5 Hz), 8.15 t (1H, H^6_{arom}, *J* 9.6 Hz), 8.02 (1H, NH-Ph). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.70 (CH_2), 29.99 (CH_2), 36.68 (<u>C</u>H_2–C), 37.76 (CH), 38.11 (CH_2), 42.63 (<u>C</u>H–C), 50.88 (<u>C</u>–NCO), 115.08 (C^3_{arom}), 115.20 (C^1_{arom}), 120.18 (C^6_{arom}), 121.67 (C^4_{arom}), 124.80 (C^5_{arom}), 151.04 (C=O), 155.08 (C–F). ^{19}F NMR spectrum (DMSO-d_6), δ, ppm: –131.32 (1F). Mass spectrum, *m/z* (I_{rel}, %): 248 (5.0) $[M]^+$, 137 (3.0) $[F–Ph–NCO]^+$, 111 (100) $[F–Ph–NH_2]^+$. Found, %: C 67.70; H 6.93; N 11.25; F 7.66. $C_{14}H_{17}FN_2O$. Calculated, %: C 67.72; H 6.90; N 11.28; F 7.65. *M* 248.30.

1-[(Adamantan-1-yl)methyl]-3-(bicyclo[2.2.1]-heptan-2-yl)urea (4b). *a*. Similarly to compound **4a**, from 0.2 g (1.46 mmol) of compound **8**, 0.293 g (1.46 mmol) of (adamantan-1-yl)methylamine hydrochloride (**3b**) and 0.42 mL (2.92 mmol) of triethylamine. Yield 0.157 g (36%).

b. Similarly to compound **4a**, from 0.27 g (1.36 mmol) of compound **3b**, 0.22 g (1.36 mmol) of CDI, 0.41 g (4.08 mmol) of triethylamine, and 0.2 g (1.36 mmol) of compound **1**. Yield 0.144 g (35%), mp 228–229°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.04–1.65 m (8H, 4CH_2), 1.40 d (6H, Ad, *J* 1.8 Hz), 1.63 d.d (6H, Ad, J_1 53.4, J_2 10.8 Hz), 1.91 s (3H, Ad), 2.11 t (1H, CH, *J* 4.8 Hz), 2.18 t (1H, CH, *J* 4.2 Hz), 2.69 t.d (1H, C<u>H</u>–NH, J_1 8.4, J_2 3.6 Hz), 3.78 q (2H, C<u>H</u>$_2$–Ad, *J* 4.8 Hz), 5.65 t (1H, NH–Ad, *J* 6.0 Hz), 5.84 d (1H, NH-norbornyl, *J* 7.8 Hz). Mass spectrum, *m/z* (I_{rel}, %): 302 (45.0) $[M]^+$, 191 (6.0) $[Ad–CH_2–NCO]^+$, 149 (12.0) $[Ad–CH_2]^+$, 135 (100) $[Ad]^+$, 111 (100) $[C_7H_{11}–NH_2]^+$. Found, %: C 75.47; H 10.04; N 9.22. $C_{19}H_{30}N_2O$. Calculated, %: C 75.45; H 10.00; N 9.26. *M* 302.24.

4-([4-{3-(Bicyclo[2.2.1]heptan-2-yl)ureido}-cyclohexyl]oxy)benzoic acid (4c). *a*. Similarly to compound **4a**, from 0.2 g (1.46 mmol) of compound **8**, 0.343 g (1.46 mmol) of 4-[(4-aminocyclohexyl)-oxy]benzoic acid (**3c**) and 0.42 mL (2.92 mmol) of triethylamine. Yield 0.103 g (19%).

b. Similarly to compound **4a**, from 0.32 g (1.36 mmol) of compound **3c**, 0.22 g (1.36 mmol) of CDI, 0.41 g (4.08 mmol) of triethylamine, and 0.2 g (1.36 mmol) of compound **1**. Yield 0.091 g (18%), mp 324–325°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.02–2.05 m (16H, 8CH_2), 2.11 t (1H, CH, *J* 4.8 Hz), 2.17 t (1H, CH, *J* 4.2 Hz), 3.76–3.81 m (2H, 2C<u>H</u>–NH), 4.40–4.45 m (1H, CHO), 5.79 t (1H, 2NH, *J* 8.4 Hz), 7.02 d (2H, 2CH_{arom}, *J* 9.0 Hz), 7.86 d (2H, 2CH_{arom}, *J* 9.0 Hz), 12.56 br.s (1H, COOH). Mass spectrum, *m/z* (I_{rel}, %): 371 (71.8) $[M]^+$. Found, %: C 67.75; H 7.60; N 7.49. $C_{21}H_{28}N_2O_4$. Calculated, %: C 67.72; H 7.58; N 7.52. *M* 372.47.

1-(Bicyclo[2.2.1]heptan-2-yl)-3-(1-propionyl-piperidin-4-yl)urea (4d). *a*. Similarly to compound **4a**, from 0.2 g (1.46 mmol) of compound **8**, 0.228 g (1.46 mmol) of 1-(4-aminopiperidin-1-yl)propan-1-one (**3d**), and 0.21 mL (1.46 mmol) of triethylamine. Yield 0.081 g (19%).

b. Similarly to compound **4a**, from 0.21 g of compound **3d**, 0.22 g (1.36 mmol) of CDI, 0.27 g (2.72 mmol) of triethylamine, and 0.2 g (1.36 mmol) of compound **1**. Yield 0.01 g (3%), mp 111–112°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.98 t (3H, CH_3, *J* 7.8 Hz), 1.05–1.92 m (12H, 6CH_2), 2.11 t (1H, CH, *J* 4.8 Hz), 2.18 t (1H, CH, *J* 4.2 Hz), 2.30 q [2H, CH_2–C(O), *J* 7.5 Hz], 2.77 t (1H, CH_2–N, *J* 11.4 Hz), 3.09 t (1H, CH_2–N, *J* 12.6 Hz), 3.55–3.61 m (1H, CH_2–N), 3.71 d (1H, CH–NH, *J* 14.4 Hz), 3.77–3.81 m (1H, CH_2–N), 4.12 d (1H, CH–NH, *J* 13.8 Hz), 5.75 s (2H, 2NH). Mass spectrum, *m/z* (I_{rel}, %): 293 (18.0) $[M]^+$. Found, %: C 65.54; H 9.31; N 14.29. $C_{16}H_{27}N_3O_2$. Calculated, %: C 65.50; H 9.28; N 14.32. *M* 293.41.

1,1'-(1,6-Hexan-1,1-diyl)bis{3-(bicyclo[2.2.1]-heptan-2-yl)urea} (4e). *a*. Similarly to compound **4a**, from 0.2 g (1.46 mmol) of compound **8**, 0.085 g (0.73 mmol) hexane-1,6-diamine (**3e**), and 0.21 mL (1.46 mmol) of triethylamine. Yield 0.236 g (82%).

b. Similarly to compound **4a**, from 0.08 g (1.36 mmol) of compound **3e**, 0.22 g (1.36 mmol) of CDI, 0.41 g (4.08 mmol) of triethylamine, and 0.2 g (1.36 mmol) of

compound **1**. Yield 0.193 g (73%), mp 185–186°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.02–1.92 m (12H, 6CH_2), 1.22–1.26 m (4H, 2CH_2), 1.33 d (4H, 2CH_2, *J* 8.4 Hz), 2.11 t (2H, 2CH, *J* 4.8 Hz), 2.18 t (2H, 2CH, *J* 4.2 Hz), 2.92–3.00 m (4H, 2CH_2–NH), 3.75–3.81 m (2H, 2C<u>H</u>–NH), 5.65 t (1H, NH, *J* 5.4 Hz), 5.82 d (1H, NH, *J* 7.4 Hz). Mass spectrum, *m/z* (I_{rel}, %): 425 (100) [*M* + Cl]$^+$. Found, %: C 67.69; H 9.80; N 14.34. $C_{22}H_{38}N_4O_2$. Calculated, %: C 67.66; H 9.81; N 14.35. *M* 390.57.

1,3-Bis(bicyclo[2.2.1]heptan-2-yl)urea (4f). Similarly to compound **4a**, from 0.4 g (2.72 mmol) of compound **1**, 0.22 g (1.36 mmol) of CDI, and 0.41 g (4.08 mmol) of triethylamine. Yield 0.236 g (70%), mp 258–259°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.06–1.59 m (16H, 8CH_2), 1.99 t (2H, 2CH, *J* 4.8 Hz), 2.18 t (2H, 2CH, *J* 4.2 Hz), 3.35 t.d (2H, 2CH–NH, J_1 8.4, J_2 3.6 Hz), 5.52 d (2H, 2NH, *J* 9.0 Hz). Mass spectrum, *m/z* (I_{rel}, %): 248 (37.0) [*M*]$^+$, 137 (4.0) [C_7H_{11}–NCO]$^+$, 111 (100), [C_7H_{11}–NH_2]$^+$, 94 (70.0) [C_7H_{12}]. Found, %: C 72.51; H 9.76; N 11.32. $C_{15}H_{24}N_2O$. Calculated, %: C 72.54; H 9.74; N 11.28. *M* 248.37.

1-(2-Florophenyl)-3-(1,7,7-trimethylbicyclo-[2.2.1]heptan-2-yl)urea (5a). 1,1'-Carbonyldiimidazole, 0.256 g (1.58 mmol), and 0.32 g (3.16 mmol) of triethylamine were added to a solution of 0.175 g (1.58 mmol) of compound **3a** in 7 mL of DMF. The reaction mixture was stirred at room temperature for 3 h, after which 0.3 g (1.58 mmol) of 1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine hydrochloride (**2**) was added. The reaction mixture was stirred at 60°C for 8 h, cooled to room temperature, diluted with 5 mL of 1 N HCl, and stirred for an additional 30 min. The precipitate that formed was filtered off and washed with water. Yield 0.054 g (12%), mp 224°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.76 s (3H, CH_3), 0.81 s (3H, CH_3), 0.86 s (3H, CH_3), 1.11–1.79 m (6H, 3CH_2), 2.22–2.28 m (1H, CH), 3.95–3.99 m (1H, C<u>H</u>–NH), 6.73 d (1H, NH, *J* 8.4 Hz), 7.00–7.08 m (1H, H^4_{arom}), 7.15 t (1H, H^5_{arom}, *J* 7.8 Hz), 7.16 d.d (1H, H^3_{arom}, J_1 11.7, J_2 8.4, J_3 1.2 Hz), 8.18 t (1H, H^6_{arom}, *J* 8.2 Hz), 9.02 s (1H, N<u>H</u>–Ph). ^{19}F NMR spectrum (DMSO-d_6), δ, ppm: –131.39 (1F). Mass spectrum, *m/z* (I_{rel}, %): 290 (5.0) [*M*]$^+$, 179 (3.0) [$C_{11}H_{17}$–NCO]$^+$, 153 (2.0) [$C_{11}H_{17}$–NH_2]$^+$, 137 (3.0) [F–Ph–NCO]$^+$, 111 (100) [F–Ph–NH_2]$^+$. Found, %: C 70.35; H 8.01; N 9.69; F 6.59. $C_{17}H_{23}FN_2O$. Calculated, %: C 70.32; H 7.98; N 9.65; F 6.54. *M* 290.38.

1-[(Adamantan-1-yl)methyl]-3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)urea (5b) was prepared similarly to compound **5a** from 0.317 g (1.58 mmol) of compound **3b**, 0.256 g (1.58 mmol) of CDI, 0.48 g (4.74 mmol) of triethylamine, and 0.3 g (1.58 mmol) of compound **2**. Yield 0.14 g (26%), mp 296–297°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.69 s (3H, CH_3), 0.83 s (3H, CH_3), 0.88 s (3H, CH_3), 1.05–1.65 m (6H, 3CH_2), 1.40 d (6H, Ad, *J* 1.8 Hz), 1.63 d.d (6H, Ad, J_1 53.4, J_2 10.8 Hz), 1.93 s (3H, Ad), 2.17 t.t (1H, CH, J_1 11.4, J_2 3.9 Hz), 2.69 t.d (1H, CH–NH, J_1 8.4, J_2 3.6 Hz), 3.85–3.91 m (2H, C<u>H</u>$_2$–Ad), 5.67 t (1H, NH–Ad, *J* 6.0 Hz), 5.82 d (1H, NH-bornyl, *J* 8.7 Hz). Mass spectrum, *m/z* (I_{rel}, %): 344 (85.0) [*M*]$^+$, 191 (17.0) [Ad–CH_2–NCO]$^+$, 153 (33.0) [$C_{11}H_{17}$–NH_2]$^+$, 135 (100) [Ad]$^+$. Found, %: C 76.72; H 10.55; N 8.09. $C_{22}H_{36}N_2O$. Calculated, %: C 76.69; H 10.53; N 8.13. *M* 344.54.

4-([4-{3-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)ureido}cyclohexyl]oxy)benzoic acid (5c) was prepared similarly to compound **5a** from 0.3 g (1.58 mmol) of compound **2**, 0.256 g (1.58 mmol) of CDI, 0.48 g (4.74 mmol) of triethylamine, and 0.37 g (1.58 mmol) of compound **3c**. Yield 0.43 g (94%), mp 345–346°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.70 s (3H, CH_3), 0.83 s (3H, CH_3), 0.88 s (3H, CH_3), 1.04–1.72 m (6H, 3CH_2), 1.88 d (4H, 2CH_2, *J* 13.2 Hz), 2.03 d (4H, 2CH_2, *J* 13.2 Hz), 2.18 t (1H, CH, *J* 4.2 Hz), 3.85–3.91 m (2H, 2C<u>H</u>–NH), 4.40–4.47 m (1H, CHO), 5.86 d (1H, NH, *J* 7.8 Hz), 5.76 d (1H, NH, *J* 9.0 Hz), 7.02 d (2H, 2CH_{arom}, *J* 9.0 Hz), 7.86 d (2H, 2CH_{arom}, *J* 9.0 Hz), 12.55 br.s (1H, COOH). Mass spectrum, *m/z* (I_{rel}, %): 449 (69.6) [*M* + Cl]$^+$, 413 (34.6) [*M* – 1]$^+$. Found, %: C 69.50; H 8.23; N 6.80. $C_{24}H_{34}N_2O_4$. Calculated, %: C 69.54; H 8.27; N 6.76. *M* 414.55.

1-(1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)-3-(1-propionylpiperidin-4-yl)urea (5d) was prepared similarly to compound **5a** from 0.3 g (1.58 mmol) of compound **2**, 0.256 g (1.58 mmol) of CDI, 0.32 g (3.16 mmol) of triethylamine, and 0.24 g (1.58 mmol) of compound **3d**. Yield 0.015 g (3%), mp 290°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.74 s (3H, CH_3), 0.83 s (3H, CH_3), 0.88 s (3H, CH_3), 0.88 t (3H, CH_3, *J* 7.8 Hz), 1.05–1.72 m (10H, 5 CH_2), 2.17 t (1H, CH, *J* 4.2 Hz), 2.30 q [2H, CH_2–C(O), *J* 7.5 Hz], 2.77 t (1H, CH_2–N, *J* 11.4 Hz), 3.08–3.13 m (1H, CH_2–N), 3.55–3.62 m (1H, CH_2–N), 3.71 d (1H, CH–NH, *J* 14.4 Hz), 3.85–3.91 m (1H, CH_2–N), 4.12 d (1H, CH–NH, *J* 13.8 Hz), 5.79 s (2H, 2NH). Mass spectrum, *m/z*

(I_{rel}, %): 370 (100) [M + Cl]$^+$. Found, %: C 68.22; H 9.88; N 12.55. $C_{19}H_{33}N_3O_2$. Calculated, %: C 68.20; H 9.91; N 12.53. M 335.49.

1,1'-(1,6-Hexane-1,1-diyl)bis{3-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)urea} (5e) was prepared similarly to compound **5a** from 0.092 g (1.58 mmol) of compound **3e**, 0.256 g (1.58 mmol) of CDI, 0.32 g (3.16 mmol) of triethylamine, and 0.3 g (1.58 mmol) of compound **2**. Yield 0.26 g (71%), mp 158–159°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.69 s (6H, 2CH$_3$), 0.83 s (6H, 2CH$_3$), 0.88 s (6H, 2CH$_3$), 1.05–1.71 m (12H, 6CH$_2$), 1.21–1.27 m (4H, 2CH$_2$), 1.34 d (4H, 2CH$_2$, J 8.4 Hz), 2.16 t.t (2H, 2CH, J_1 12.0, J_2 3.9 Hz), 2.93–3.01 m (4H, 2C<u>H</u>$_2$–NH), 3.85–3.91 m (2H, 2C<u>H</u>–NH), 5.44 t (1H, NH, J 8.4 Hz), 5.79 d (1H, NH, J 6.6 Hz). Mass spectrum, m/z (I_{rel}, %): 510 (100) [M + Cl]$^+$. Found, %: C 70.86; H 10.60; N 11.83. $C_{28}H_{50}N_4O_2$. Calculated, %: C 70.84; H 10.62; N 11.80. M 474.73.

1,3-Bis(1,7,7-bicyclo[2.2.1]heptan-2-yl)urea (5f) was prepared similarly to compound **5a** from 0.6 g (3.16 mmol) of compound **2**, 0.256 g (1.58 mmol) of CDI, and 0.48 g (4.74 mmol) of triethylamine. Yield 0.33 g (64%), mp 332–333°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.69 d (6H, 2CH$_3$, J 3.0 Hz), 0.83 s (6H, 2CH$_3$), 0.88 s (6H, 2CH$_3$), 1.04–1.76 m (12H, 6CH$_2$), 2.17 br.s (2H, 2CH), 3.84–3.91 m (2H, 2CH–NH), 5.80 t (2H, 2NH, J 9.0 Hz). Mass spectrum, m/z (I_{rel}, %): 332 (68.0) [M]$^+$, 180 (8.0) [$C_{11}H_{17}$–NCO]$^+$, 153 (56.0) [$C_{11}H_{17}$–NH$_2$]$^+$, 136 (22.0) [$C_{11}H_{17}$–NH$_2$], 82 (100). Found, %: C 75.81; H 10.88; N 8.46. $C_{21}H_{36}N_2O$. Calculated, %: C 75.85; H 10.91; N 8.42. M 332.53.

CONCLUSIONS

Thus, we synthesized two series of 1,3-disubstituted ureas containing lipophilic bicyclic groups of natural origin: bicyclo[2.2.1]heptan-2-yl and 1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl. The synthesized ureas show promise as inhibitors of RNA virus replication and soluble human epoxide hydrolase.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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