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

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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 ureas of this series at concentrations of 250 $\mu$M 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...
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](https://via.placeholder.com/150)

**Scheme 1.**

R¹-NH₂ \[\xrightarrow{\text{CDI, DMF, } \text{Et₃N}}\] R¹N-H \[\xrightarrow{\Delta}\] R¹-N≡C=O

R¹-N≡C=O + R²-NH₂  \[\xrightarrow{}\] R¹-N-R²

R¹-N≡C=O + R¹-NH₂  \[\xrightarrow{}\] R¹-N-R¹

R¹ = alkyl, aryl; R² = alkyl, aryl.
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...
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.
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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 ($\geq$ 99%, CAS 348-54-9), 1,6-diaminohexane (98%, CAS 124-09-4), 1-aminomethyladamantane (98%, CAS 17768-41-1), triethylamine (BioUltra $\geq$ 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.
The structure of the synthesized compounds was confirmed by \(^1\)H, \(^{13}\)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 \(^1\)H, \(^{13}\)C, and \(^{19}\)F NMR spectra were obtained on a Bruker Avance 600 spectrometer in DMSO-\(d_6\); the \(^1\)H 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](image-url)
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           | ![Structure](image) | 248 | 3.09       | 189–190 | –/22 (35)    |
| 4b           | ![Structure](image) | 302 | 4.22       | 228–229 | –/35 (36)    |
| 4c           | ![Structure](image) | 372 | 3.79       | 324–325 | –/18 (19)    |
| 4d           | ![Structure](image) | 293 | 1.90       | 111–112 | –/3 (19)     |
| 4e           | ![Structure](image) | 390 | 3.80       | 185–186 | –/73 (82)    |
1-(Bicyclo[2.2.1]heptan-2-yl)-3-(2-fluorophenyl)-urea (4a). 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%).

Table 1. (Contd.)

| Compound no. | Structural formula | $M$ | $\log P^a$ | mp, °C | Yield, %$^b$ |
|--------------|--------------------|-----|------------|--------|-------------|
| 4f           | ![Structural formula image] | 248 | 2.81       | 258–259 | 70          |
| 5a           | ![Structural formula image] | 290 | 4.23       | 224    | 4/12        |
| 5b           | ![Structural formula image] | 344 | 5.35       | 296–297 | 25/26       |
| 5c           | ![Structural formula image] | 414 | 4.92       | 345–346 | 94/16       |
| 5d           | ![Structural formula image] | 335 | 3.03       | 290    | 3/–         |
| 5e           | ![Structural formula image] | 474 | 6.07       | 158–159 | 34/71       |
| 5f           | ![Structural formula image] | 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.
b. 1,1'-Carbonyldimidazole, 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 0.07 g (22%), mp 189–190°C. 1H NMR spectrum (DMSO-d₆), δ, ppm: 1.04–1.65 m (8H, 4CH₂), 2.17 t (1H, CH, J 4.8 Hz), 2.27 t (1H, CH, J 4.2 Hz), 3.90 td (1H, CH–NH, J₁ 8.4, J₂ 3.6 Hz), 6.75 t (1H, NH, J 6.0 Hz), 6.90 t.d.d (1H, H₄ arom, J₁ 8.4, J₂ 4.2, J₃ 1.2 Hz), 7.06 t (1H, H₃ arom, J 7.8 Hz), 7.16 d.d.d (1H, H₂ arom, J₁ 12.0, J₂ 8.4, J₃ 1.5 Hz), 8.15 t (1H, H₅ arom, J 9.6 Hz), 8.02 (1H, NH-Ph). 13C NMR spectrum (DMSO-d₆), δ, ppm: 21.70 (CH₂), 29.99 (CH₂), 36.68 (CH₂–C), 37.76 (CH), 38.11 (CH₂), 42.63 (CH–C), 50.88 (C–NCO), 115.08 (C₅ arom), 115.20 (C₁₁ arom), 120.18 (C₆ arom), 121.67 (C₇ arom), 124.80 (C₈ arom), 151.04 (C=O), 155.08 (C–F). 19F NMR spectrum (DMSO-d₆), δ, ppm: –61.32 (11F). Mass spectrum, m/z (Irel, %): 248 (5.0) [M]+, 137 (3.0) [F–Ph–NCO]+, 111 (100) [F–Ph–NH₂]+. Found, %: C 67.70; H 6.93; N 11.25; F 7.66. C₁₄H₁₇FN₂O. Calculated, %: C 67.72; H 7.58; N 7.52. 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)methylhydrochloride (3b) and 0.42 mL (2.92 mmol) of triethylamine. Yield 0.157 g (36%).

b. Similarly to compound 2a, 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. 1H NMR spectrum (DMSO-d₆), δ, ppm: 1.04–1.65 m (8H, 4CH₂), 1.40 d (6H, Ad, J 1.8 Hz), 1.63 d.d (6H, Ad, J₃ 53.4, J₂ 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, CH–NH, J₁ 8.4, J₂ 3.6 Hz), 3.78 q (2H, CH₂–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 (Irel, %): 302 (45.0) [M]+, 191 (6.0) [Ad–CH₃–NCO]⁺, 149 (12.0) [Ad–CH₃]⁺, 135 (100) [Ad]⁺, 111 (100) [C₁₉H₂₆N₂O]⁺. Found, %: C 75.47; H 10.04; N 9.22. C₁₉H₂₆N₂O. Calculated, %: C 75.45; H 10.00; N 9.26. M 302.24.

4-{(4-[(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. 1H NMR spectrum (DMSO-d₆), δ, ppm: 1.02–2.05 m (16H, 8CH₂), 2.11 t (1H, CH, J 4.8 Hz), 2.17 t (1H, CH, J 4.2 Hz), 3.76–3.81 m (2H, 2CH–NH), 4.40–4.45 m (1H, CHO), 5.79 t (1H, 2NH, J 8.4 Hz), 7.02 d (2H, 2CH₂ arom, J 9.0 Hz), 7.86 d (2H, 2CH₂ arom, J 9.0 Hz), 12.56 br.s (1H, COOH). Mass spectrum, m/z (Irel, %): 371 (71.8) [M]+. Found, %: C 67.75; H 7.60; N 7.49. C₁₂H₁₅N₃O₄. Calculated, %: C 67.72; H 7.58; N 7.52. M 372.47.

1-(Bicyclo[2.2.1]heptan-2-yl)-3-(1-propionylpiperidin-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. 1H NMR spectrum (DMSO-d₆), δ, ppm: 0.98 t (3H, CH₃, J 7.8 Hz), 1.05–1.92 m (12H, 6CH₂), 2.11 t (1H, CH, J 4.8 Hz), 2.18 t (1H, CH, J 4.2 Hz), 2.30 q [2H, CH₂–C(O), J 7.5 Hz], 2.77 t (1H, CH₂–N, J 11.4 Hz), 3.09 t (1H, CH₂–N, J 12.6 Hz), 3.53–3.61 m (1H, CH₂–N), 3.71 d (1H, CH–NH, J 14.4 Hz), 3.77–3.81 m (1H, CH₂–N), 4.12 d (1H, CH–NH, J 13.8 Hz), 5.75 s (2H, 2NH). Mass spectrum, m/z (Irel, %): 293 (18.0) [M]+. Found, %: C 65.54; H 9.31; N 14.29. C₁₆H₂₁N₃O₂. 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-\(d_6\)), \(\delta\) 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, 2CH-NH), 5.65 t (1H, \(J \) 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\(_4\)O\(_2\). Calculated, %: C 70.65; H 9.69; N 9.65. C\(_{22}\)H\(_{38}\)N\(_4\)O\(_2\). 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-\(d_6\)), \(\delta\) 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), 5.52 d (2H, 2NH, \(J \) 8.4 Hz), 5.86 d (1H, NH, \(J \) 8.2 Hz), 7.16 t (1H, \(J \) 9.0 Hz). Mass spectrum, \(m/z\) \((I_{rel}, \%)\): 248 (37.0) \([M]^+\), 137 (4.0) \([C_6H_{11}-\text{NCO}]^+\), 111 (100), \([C_6H_{11}-\text{NH}_2]^+\), 94 (70.0) \([C_6H_{12}]^+\). Found, %: C 72.51; H 9.76; N 11.32. C\(_{15}\)H\(_{24}\)N\(_2\)O. 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'-Carbonyldiimidazo-1-

C\(_{22}\)H\(_{38}\)N\(_4\)O\(_2\). Calculated, %: C 70.32; H 7.98; N 9.65; F 6.54. C\(_{17}\)H\(_{23}\)F\(_3\)N\(_2\). Calculated, %: C 70.32; H 7.98; N 9.65; F 6.54. M 290.38.

1-[(Adamant-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-\(d_6\)), \(\delta\) 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 (1H, CH, \(J \) 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, 2CH–NH), 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) \([\text{Ad}–\text{CH}_2–\text{NCO}]^+\), 153 (33.0) \([\text{C}_11\text{H}_{17}–\text{NH}_2]^+\), 135 (100) \([\text{Ad}]^+\). Found, %: C 76.72; H 10.55; N 8.09. C\(_{22}\)H\(_{38}\)N\(_2\)O. Calculated, %: C 76.69; H 10.53; N 8.13. M 344.54.
SYNTHESIS AND PROPERTIES OF 1,3-DISUBSTITUTED UREAS

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. 1H NMR spectrum (DMSO-d6), δ, ppm: 0.69 s (6H, 2CH3), 0.83 s (6H, 2CH3), 0.88 s (6H, 2CH3), 1.05–1.71 m (12H, 6CH2), 1.21–1.27 m (4H, 2CH2), 1.34 d (4H, 2CH2, J 8.4 Hz), 2.16 t.t (2H, 2CH, J1 112.0, J2 3.9 Hz), 2.93–3.01 m (4H, 2CH2–NH), 3.85–3.91 m (2H, 2CH–NH), 5.44 t (1H, NH, J 8.4 Hz), 5.79 d (1H, NH, J 6.6 Hz). Mass spectrum, m/z (Irel, %): 510 (100) [M + Cl]+. Found, %: C 70.86; H 10.60; N 11.83. C28H50N4O2. 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. 1H NMR spectrum (DMSO-d6), δ, ppm: 0.69 d (6H, 2CH3, J 3.0 Hz), 0.83 s (6H, 2CH3), 0.88 s (6H, 2CH3), 1.04–1.76 m (12H, 6CH2), 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 (Irel, %): 332 (68.0) [M]+, 180 (8.0) [C11H17–NCO]+, 153 (56.0) [C11H17–NH2]+, 136 (22.0) [C11H17–NH2H]+, 82 (100). Found, %: C 75.81; H 8.46. C21H36N2O. Calculated, %: C 75.85; H 8.91; 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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