Synthesis and Properties of 1,3-Disubstituted Ureas and Their Isosteric Analogs Containing Polycyclic Fragments: XVI.[1] Synthesis and Properties of 1,1'-(Alkane-1,*n*-diyl)bis-{3-[(3,5-dimethyladamantan-1-yl)methyl]ureas}

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Abstract—A one-step synthesis of 1-(isocyanatomethyl)-3,5-dimethyladamantane with a yield of 87% is described. The reaction of 1-(isocyanatomethyl)-3,5-dimethyladamantane with aliphatic diamines gave a series of symmetrical 1,3-disubstituted ureas with 63–99% yields. The synthesized ureas hold promise as human soluble epoxide hydrolase inhibitors.

Keywords: adamantane, 1,3-dimethyladamantane, isocyanate, urea, soluble epoxide hydrolase, sEH

INTRODUCTION

1,3-Disubstituted ureas are known as non-nucleoside HIV-1 reverse transcriptase inhibitors [2–4], as well as cholinesterase inhibitors for the treatment of Alzheimer's disease [5]. This class of compounds is shown to exhibit anticancer activity against breast (MCF7), colon (HCT116), and liver (Huh7) cancer cell lines [6–8], as well as bactericidal activity against *M. tuberculosis* [9–11]. 1,3-Disubstituted urea moieties are comprised in the composition of a number of drugs, including Sorafenib, Regorafenib, and Linifanib, anticancer agents and multikinase inhibitors [12–14]; Gliclazide, a glypoglycemic agent with an inhibitory activity against the SARS-CoV-2 envelope protein [15–17]; Torasemide, a diuretic [18–20]; Suramin, an antiprotozoal and anthelmintic agent [21, 22]; and Talinolol, an antiarrhythmic drug [23, 24].

Despite the wide range of biological activities, structures containing a urea moiety linked to one or more lipophilic (for example, adamantyl) fragments are of the greatest interest [25–27]. The adamantyl fragment is used in medicinal chemistry as a building block that directly affects the penetration through the blood–brain barrier [28].

Adamantyl-containing 1,3-disubstituted ureas are used as tyrosyl-DNA phosphodiesterase 1 (TDP1) inhibitors. The TDP1 enzyme is an important additional biotarget for anticancer therapy [29].

One of the promising areas of application of adamantyl-containing 1,3-disubstituted ureas is their use as target-oriented inhibitors of mammalian and human soluble epoxide hydrolase (sEH, E.C. 3.3.2.10). This enzyme is a potential target for the treatment of hypertensive [30], inflammatory [31], and pain conditions [32–34]. For example, the inhibition of sEH by an inhibitor such as t-AUCB [4-{(*trans*-4-[{(tricyclo[3.3.1.13.7]dec-1-ylamino)carbonyl}amino]-cyclohexyl)oxy}benzoic acid] protects from the type 2 diabetes-initiated oxidative stress responsible for blood–brain barrier dysfunction [35].

However, the fact that adamantane is susceptible to oxidation at the bridgehead and bridging carbon atoms, along with unsatisfactory physical properties (low water solubility and high melting point), are the key disadvantages of adamantyl-containing urea-type sEH inhibitors [36].

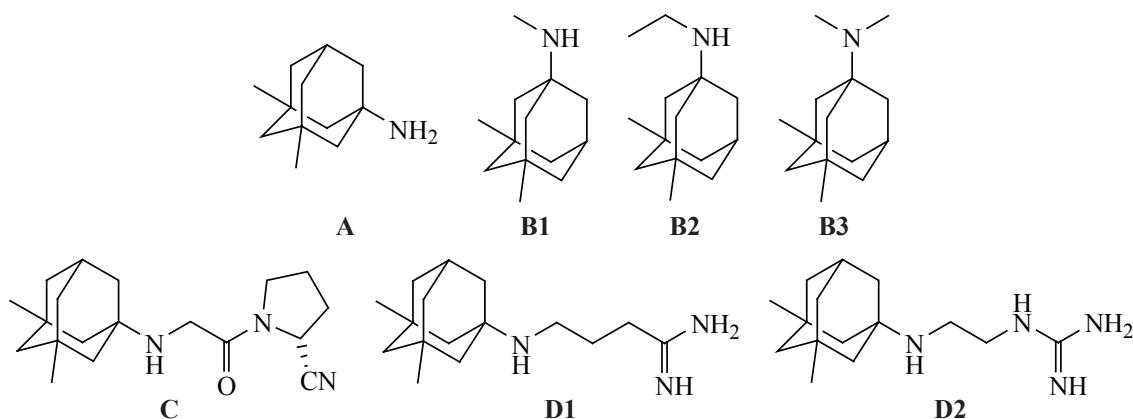
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Fig. 1. Structures of Memantine and its *N*-alkyl derivatives.

It should be noted that the biological activity studies on compounds containing the lipophilic 1,3-dimethyladamantyl radical is significantly are less in number compared to compounds with an un-substituted adamantyl fragment. The most studied is 3,5-dimethyladamantane-1-amine (Fig. 1, compound **A**, Memantine), an NMDA antagonist used in the treatment of Alzheimer's disease and included in the list of vital and essential drugs of the Russian Federation.

N-Alkyl derivatives of 3,5-dimethyladamantane-1-amine (Fig. 1, compounds **B1–B3**) were also tested as antiparkinsonian, antispastic, and antidementia drugs, and compound **B3** showed high affinity for σ-sites, as measured by the competitive radioligand binding assay on postmortem human frontal cortex homogenates [37]. Compound **C** (Fig. 1) was tested as a dipeptidyl peptidase-4 (DPP4) inhibitors for the treatment of type 2 diabetes, however, methyl substitution in the adamantyl radical decreased activity, probably, on account of the overlipophilicity of this fragment [28].

The activity of *N*-[2-(3,5-dimethyladamantan-1-yl)-ethyl]guanidine (CR 3391) and *N*-[2-(3,5-dimethyl-adamantan-1-yl)ethyl]acetamidine (CR 3394) (Fig. 1, compounds **D1** and **D2**) against chemically induced parkinsonism in rodents [38] and their effect on NMDA receptors expressed in cerebral cortex neurons [39]. It was found that in vitro CR 3394 significantly reduced neuronal death induced by glutamate and NMDA, which makes it a promising candidate for the treatment of neurodegenerative disorders.

Among other compounds, noteworthy is an adamantyl retinoid (Fig. 2, compound **E**), which showed activity against H292 non-small cell lung cancer cells. However, the original unmethylated compound was significantly more active than retinoid **E**, which indicates the importance of the form of the lipophilic 3'-substituent [40].

A similar decrease in anabolic activity with methyl substitution in the adamantyl fragment was observed for 19-nortestosterone 17β-adamantoate (nandrolone adamantoate) (Fig. 2, compound **F**), which was es-tablished by an increase in rat muscle weight [41].

The information about biologically active com-pounds containing 3,5-dimethyladamantylalkyl frag-ments is scarce. Thus, 3,5-dimethyladamantylalkylami-nes (Fig. 3, compounds **G1–G3**) and dication **H** were tested as AMPA and NMDA receptor antagonists [28, 42].
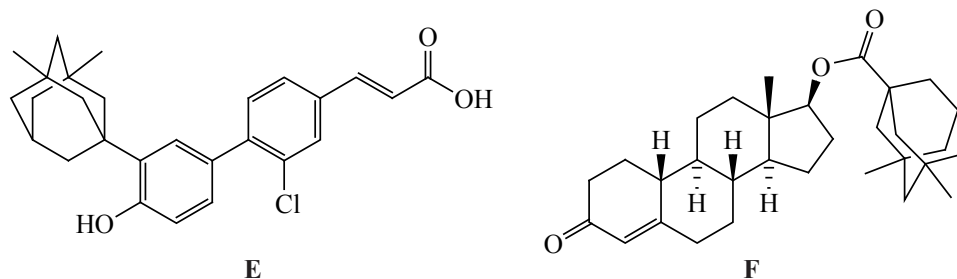

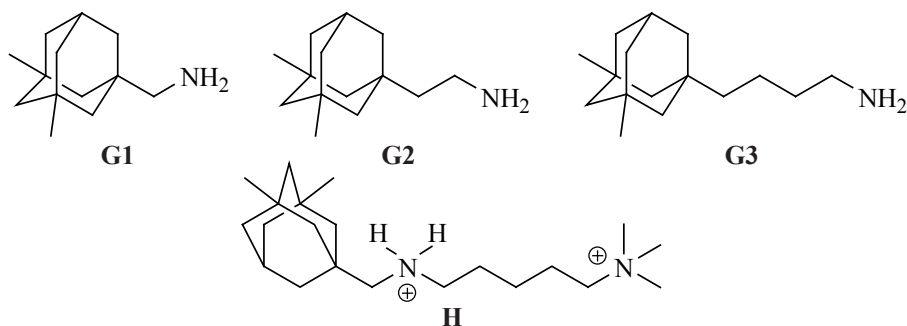**Fig. 2.** Biologically active compounds containing a 3,5-dimethyladamantan-1-yl radical.

Fig. 3. 3,5-Dimethyladamantylalkylamines.

The main route of metabolism of adamantyl-containing inhibitors in vivo and in vitro (under the action of liver microsomes) is hydroxylation of bridging and bridgehead positions in adamantane, and the rate of metabolism proportional to lipophilicity [43, 44].

The introduction of hydrophobic alkyl substituents into the adamantyl fragment of the inhibitor enhances the overall lipophilic properties of the molecule. In turn, this enhances the ability of the resulting molecule to permeate through the lipid layer, while the introduction of a methylene bridge (separating the urea and adamantyl fragments) will make the molecule more flexible, thereby increasing its inhibitory activity against sEH, decreasing the melting point, and increasing water solubility and metabolic stability [45].

In this regard, the synthesis of urea inhibitors containing a 3,5-dimethyladamantylmethyl fragment is of undoubted practical interest. This will allow evaluation of the effect of the shape of the lipophilic fragment on the efficiency of binding an adamantylurea guest molecules in the hydrophobic pockets of enzymes or in the cavities of cyclodextrins, when the conformational mobility of such molecules is increased by the presence of a methylene bridge.

RESULTS AND DISCUSSION

A two-step method of synthesis of iso-cyanates [including 1-(isocyanatomethyl)-3,5-dimethyl-adamantane, yield 90%] containing a 3,5-dimethylada-mantyl fragment is known [46, 47]. This method involves treatment of the starting adamantanoic acids

with thionyl chloride to obtain intermediate acid chlorides, which, under the action of sodium azide, are converted into adamantyl-containing isocyanates by the Curtius reaction. The disadvantage of the method is the use of toxic and explosive reagents, as well as its multistep nature.

We developed a one-step synthesis of 1-(iso-cyanatomethyl)-3,5-dimethyladamantane (**2**) with a yield of 87% by treatment of (3,5-dimethyladamantan-1-yl)acetic acid (**1**) with equimolar amounts of diphe-nylphosphoryl azide (DPPA) and triethylamine in toluene followed by extraction with diethyl ether (Scheme 1).

As starting materials for the synthesis of 1,3-di-substituted ureas **4a–4i** from isocyanate **2** we chose aliphatic diamines **3a–3h**, as well as amine **4i** [*trans*-4-amino(cyclohexyloxy)benzoic acid], which was earlied used in the synthesis of the most active sEH inhibitors (Scheme 2) [45].

The synthesis of disubstituted diureas **4a–4h** and urea **4i** was accomplished in anhydrous diethyl ether for 12 h at room temperature in the presence of triethylami-ne. The characteristics of the synthesized compounds are listed in the Table 1.

The ^{1}H NMR spectra of compounds **4a–4h** display proton signals of the urea NH group proximate to the adamantyl fragment at 5.66–5.85 ppm. The signals of the NH groups attached to the methylene groups tethering the urea fragment shift more and more downfield as n increases (from 5.78 at $n = 2$ to 5.70 at $n = 10$).

Scheme 1.

Scheme 2.

$n = 2$ (**4a**), 3 (**4b**), 4 (**4c**), 5 (**4d**), 6 (**4e**), 7 (**4f**), 8 (**4g**), 10 (**4h**).
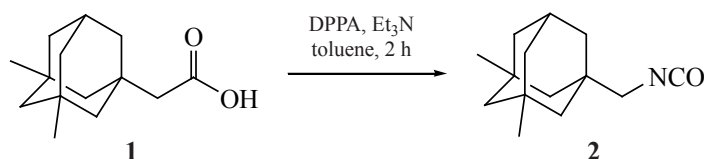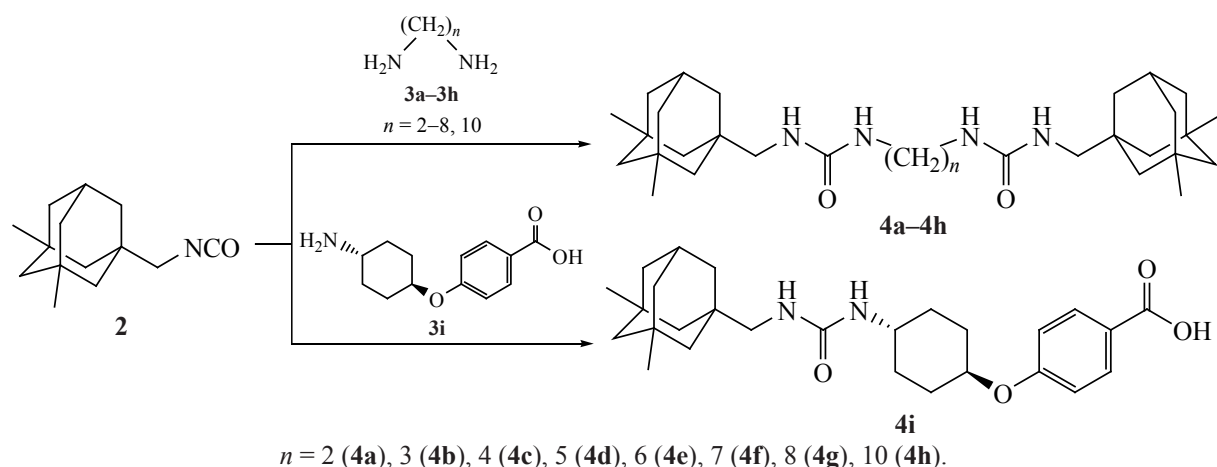
The calculated lipophilicity coefficient (log P) for compounds **4a–4h** are within 5.30–8.63, which is higher by about 0.23 than those for the series of 1,3-disubstituted diuareas (5.06–8.49), prepared from (adamantan-1-yl)methyl isocyanate. The lipophilicity coefficient of lead compound **4i** is higher by 0.12 compared to that of its analog prepared from (adamantan-1-yl)methyl isocyanate. Our earlier described closest structural analogs of lead compound **4i** have a high inhibitory activity against sEH (< 2 nM) [48]. Compound **4i** and its structural analogs have close lipophilicity coefficients and melting points, which allows us to suggest that compound **4i** will be a highly potent inhibitor.

The introduction of methylene substituents in the bridgehead positions of the adamantane core made it possible to decrease the melting point of diureas **4a–4h** by 19–115°C compared to those of analogous diureas

derived from (adamantan-1-yl)methyl isocyanate (155–243°C) (Fig. 4).

Previously, for a series of 1,3-disubstituted diureas obtained from (adamantan-1-yl)methyl isocyanate we observed a wavy dependence of the melting point on the number of methylene bridges. The melting points of diureas with an odd number of methylene bridges were higher than the melting points of diureas with an even number of methylene bridges. However, for diureas **4a–4h**, a linear decrease in the melting point is observed with increasing number of methylene bridges: from 212°C at $n = 2$ to 99°C at $n = 10$.

EXPERIMENTAL

The starting 1,2-diaminoethane (≥ 99%, CAS 107-15-3), 1,3-diaminopropane (≥ 99%, CAS 109-76-2), 1,4-diaminobutane (99%, CAS 110-60-1), 1,5-diamino-pentane (≥ 97%, CAS 462-94-2), 1,6-diaminohexane

Table 1. Lipophilicity coefficients, melting points, and yield of compounds **4**

Comp. no.	n	M	log P	mp, °C	Yield, %
4a	2	498.74	5.30	212.7	98
4b	3	512.77	5.58	163.7	99
4c	4	526.81	5.84	143.5	63
4d	5	540.82	6.35	127.1	76
4e	6	554.85	6.86	128.9	98
4f	7	568.89	7.36	120.4	71
4g	8	582.92	7.87	109.9	79
4h	10	610.96	8.63	99.6	94
4i		454.6	5.32	240.1	63

(98%, CAS 124-09-4), 1,7-diaminoheptane (98%, CAS 646-19-5), 1,8-diaminooctane (98%, CAS 373-44-4), and 1,10-diaminooctane (97%, CAS 646-25-3) were purchased from Sigma-Aldrich. Diethyl ether was purified by conventional procedures. (3,5-Dimethyladamantan-1-yl)acetic acid was obtained by the procedure in [49] and 4-[(4-aminocyclohexyl)oxy]benzoic acid, by the procedure in [50].

The structure of the synthesized compounds was confirmed by ^{1}H NMR spectroscopy, gas chromatography–mass spectrometry, and elemental analysis. The ^{1}H NMR spectra were measured on a Bruker Avance 600 spectrometer in DMSO-d_6, internal standard TMS. The mass spectra were obtained on an Agilent GC 7820A/MSD 5975 system. The elemental analyses were obtained on a Perkin–Elmer Series II 2400. The melting points were determined on a Stanford Research Systems OptiMelt MPA100 automated melting point apparatus. The lipophilicity coefficients log P were calculated using Molinspiration [51].

1-(Isocyanatomethyl)-3,5-dimethyladamantane (2). Diphenylphosphoryl azide (DPPA), 6.2 g (0.023 mol), was added drowise over the course of 30 min to a solution of 5.0 g (0.023 mol) of (3,5-dimethyladamantan-1-yl)acetic acid (**1**) and 2.3 g (0.023 mol) of triethylamine in 40 mL of dry toluene at room temperature. The reaction mixture was heated under reflux for 30 min until nitrogen no longer evolved. Toluene was evaporated, and the product was extracted with dry diethyl ether. Yield 4.3 g (87%), oily liquid. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.84 s (6H, 2CH$_3$), 2.01–1.53 s (13H, Ad), 2.97 s (2H, CH$_2$). Mass spectrum, m/z (I_{rel}, %): 219 (1) [M]$^+$, 204 (2) [M – CH$_3$]$^+$, 177 (2) [M – NCO]$^+$, 163 (100) [Ad(CH$_3$)$_2$]$^+$, 148 (2), 121 (5), 107 (40), 79 (5), 56 (3) [CH$_2$NCO]$^+$. Found, %: C 76.88; H 9.73; N 6.12. C$_{14}$H$_{21}$NO. Calculated, %: C 76.67; H 9.65; N 6.39. M 219.32. The ^{1}H NMR spectrum is identical to that we reported for our earlier prepared 1-(isocyanatomethyl)-3,5-dimethyladamantane [47].

1,1'-(Ethane-1,2-diyl)bis{3-[(3,5-dimethyladamantan-1-yl)methyl]urea} (4a). 1,2-Diaminoethane (**3a**) and 0.15 mL of triethylamine were added to a solution of 0.2 g (0.91 mmol) of 1-(isocyanatomethyl)-3,5-dimethyladamantane (**2**) in 5 mL. The reaction mixture was kept at room temperature for 12 h. After adding 5 mL of 1N HCl, the mixture was stirred for 1 h. The white precipitate that formed was filtered off and washed with water. The product was purified by
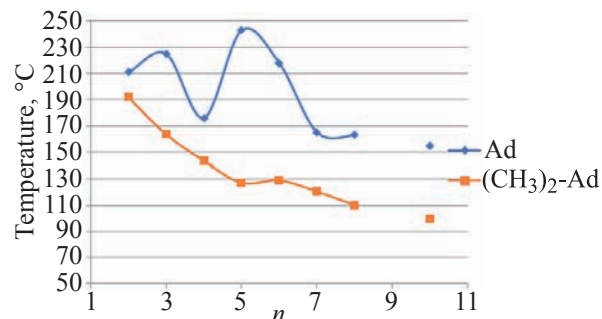

Fig. 4. Dependence of the melting points of diureas **4a–4h** and their analogs on the number of methylene units between the urea groups (n).

recrystallization from ethanol. Yield 0.219 g (98%), mp 212.7°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.79 s (12H, 4CH$_3$), 0.99–2.03 m (26H, Ad), 2.74 d (4H, 2CH$_2$NH, J 6.0 Hz), 2.97–3.01 m (4H, NHCH$_2$CH$_2$NH), 5.78 br.s (2H, NHCH$_2$CH$_2$NH), 5.85 t (2H, 2NHCH$_2$, J 6.2 Hz). Found, %: C 72.11; H 10.31; N 11.30. C$_{30}$H$_{50}$N$_4$O$_2$. Calculated, %: C 72.25; H 10.10; N 11.23. M 498.74.

1,1'-(Propane-1,3-diyl)bis{3-[(3,5-dimethyladamantan-1-yl)methyl]urea} (4b) was prepared similarly to compound **4a** from 0.2 g of compound **2** and 0.034 g of 1,3-diaminopropane (**3b**). Yield 0.232 g (99%), mp 163.5°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.79 s (12H, 4CH$_3$), 0.99–2.00 m (26H, Ad), 1.43 quintet (2H, NHCH$_2$CH$_2$CH$_2$NH, J 6.8 Hz), 2.75 d (4H, 2CH$_2$–NH, J 6.5 Hz), 2.98 t (4H, NHCH$_2$CH$_2$CH$_2$NH, J 6.7 Hz), 5.75 d (4H, 4NH, J 6.3 Hz). Found, %: C 72.55; H 10.19; N 11.77. C$_{31}$H$_{52}$N$_4$O$_2$. Calculated, %: C 72.61; H 10.22; N 11.93. M 512.77.

1,1'-(Butane-1,4-diyl)bis{3-[(3,5-dimethyladamantan-1-yl)methyl]urea} (4c) was prepared similarly to compound **4a** from 0.2 g of compound **2** and 0.04 g of 1,4-diaminobutane (**3c**). Yield 0.153 g (63%), mp 143.5°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.79 s (12H, 4CH$_3$), 0.82–2.00 m (26H, Ad), 1.07–1.14 m (4H, CH$_2$CH$_2$CH$_2$CH$_2$), 2.75 d.d (4H, 2CH$_2$–NH, J_1 16.2, J_2 6.0 Hz), 2.97 d (4H, NHCH$_2$CH$_2$CH$_2$CH$_2$NH, J 5.8 Hz), 5.70 t.d (4H, 4NH, J_1 12.2, J_2 6.2 Hz). Found, %: C 72.80; H 10.44; N 10.21. C$_{32}$H$_{54}$N$_4$O$_2$. Calculated, %: C 72.96; H 10.33; N 10.64. M 526.81.

1,1'-(Pentane-1,5-diyl)bis{3-[(3,5-dimethyladamantan-1-yl)methyl]urea} (4d) was prepared similarly to compound **4a** from 0.2 g compound **2** and 0.05 g of 1,5-diaminopentane (**3d**). Yield 0.188 g (76%), mp 127.1°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm:

0.79 s (12H, 4CH$_3$), 1.21–1.32 m (2H, CH$_2$CH$_2$C$\underline{H}_2$CH$_2$·CH$_2$), 1.35 quintet (4H, CH$_2$C$\underline{H}_2$CH$_2$C$\underline{H}_2$CH$_2$, J 7.1 Hz), 0.95–2.00 m (26H, Ad), 2.74 d (4H, 2C$\underline{H}_2$NH, J 6.2 Hz), 2.96 q (4H, NHC$\underline{H}_2$CH$_2$CH$_2$CH$_2$C$\underline{H}_2$NH, J 6.8 Hz), 5.66–5.73 m (4H, 4NH). Found, %: C 73.73; H 10.34; N 10.14. C$_{33}$H$_{56}$N$_4$O$_2$. Calculated, %: C 73.29; H 10.44; N 10.36. M 540.82.

1,1'-(Hexane-1,6-diyl)bis{3-[(3,5-dimethyladamantan-1-yl)methyl]urea} (4e) was prepared similarly to compound **4a** from 0.2 g compound **2** and 0.055 g 1,6-diaminohexane (**3e**). Yield 0.247 g (98%), mp 128.9°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.78 s (12H, 4CH$_3$), 1.06–1.11 m (4H, CH$_2$CH$_2$C$\underline{H}_2$·C$\underline{H}_2$CH$_2$CH$_2$), 0.98–2.01 m (26H, Ad), 1.34 quintet (4H, CH$_2$C$\underline{H}_2$CH$_2$CH$_2$C$\underline{H}_2$CH$_2$, J 7.1 Hz), 2.72 d (4H, 2C$\underline{H}_2$–NH, J 5.9 Hz), 2.96 q (4H, NHC$\underline{H}_2$CH$_2$CH$_2$·CH$_2$CH$_2$C$\underline{H}_2$NH, J 6.3 Hz), 5.70 t (4H, 4NH, J 5.7 Hz). Found, %: C 73.54; H 10.23; N 10.09. C$_{34}$H$_{58}$N$_4$O$_2$. Calculated, %: C 73.60; H 10.54; N 10.10. M 554.85.

1,1'-(Heptane-1,7-diyl)bis{3-[(3,5-dimethyladamantan-1-yl)methyl]urea} (4f) was prepared similarly to compound **4a** from 0.2 g compound **2** and 0.06 g 1,7-diaminoheptane (**3f**). Yield 0.184 g (71%), mp 120.4°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.79 s (12H, 4CH$_3$), 1.21–1.28 m (6H, CH$_2$CH$_2$C$\underline{H}_2$·C$\underline{H}_2$C$\underline{H}_2$CH$_2$CH$_2$), 0.98–2.09 m (26H, Ad), 1.35 quintet (4H, CH$_2$C$\underline{H}_2$CH$_2$CH$_2$CH$_2$C$\underline{H}_2$CH$_2$, J 6.9 Hz), 2.74 d (4H, 2C$\underline{H}_2$NH, J 6.5 Hz), 2.96 t.d (4H, NHC$\underline{H}_2$CH$_2$·CH$_2$CH$_2$CH$_2$C$\underline{H}_2$NH, J_1 6.8, J_2 4.0 Hz), 5.70 t (4H, 4NH, J 5.7 Hz). Found, %: C 73.81 0; H 10.46; N 9.58. C$_{35}$H$_{60}$N$_4$O$_2$. Calculated, %: C 73.90; H 10.63; N 9.85. M 568.89.

1,1'-(Octane-1,8-diyl)bis{3-[(3,5-dimethyladamantan-1-yl)methyl]urea} (4g) was prepared similarly to compound **4a** from 0.2 g of compound **2** and 0.066 g of 1,8-diaminooctane (**3g**). Yield 0.210 g (79%), mp 109.9°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.79 s (12H, 4CH$_3$), 1.21–1.28 m (8H, CH$_2$·CH$_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$CH$_2$), 1.34 d (4H, CH$_2$C$\underline{H}_2$·CH$_2$CH$_2$CH$_2$CH$_2$C$\underline{H}_2$CH$_2$, J 7.2 Hz), 0.98–2.01 m (26H, Ad), 2.71–2.78 m (4H, 2C$\underline{H}_2$NH), 2.96 t (4H, NHC$\underline{H}_2$·CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$C$\underline{H}_2$NH, J 6.8 Hz), 5.68 d (4H, 4NH, J 6.7 Hz). Found, %: C 74.36; H 10.23; N 9.73. C$_{36}$H$_{62}$N$_4$O$_2$. Calculated, %: C 74.18; H 10.72; N 9.61. M 582.92.

1,1'-(Decane-1,10-diyl)bis{3-[(3,5-dimethyladamantan-1-yl)methyl]urea} (4h) was prepared similarly to compound **4a** from 0.2 g compound **2** and 0.08 g of 1,10-diaminodecane (**3h**). Yield 0.263 g (94%), mp 99.6°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.79 s (12H, 4CH$_3$), 1.26 d (12H, CH$_2$CH$_2$·C$\underline{H}_2$CH$_2$CH$_2$CH$_2$CH$_2$C$\underline{H}_2$CH$_2$CH$_2$), 1.34 quintet (4H, CH$_2$C$\underline{H}_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$C$\underline{H}_2$CH$_2$, J 7.0 Hz), 0.98–2.09 m (26H, Ad), 2.73 d (4H, 2C$\underline{H}_2$NH, J 6.2 Hz), 2.96 t (4H, NHC$\underline{H}_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$·CH$_2$CH$_2$C$\underline{H}_2$NH, J 6.7 Hz), 5.68 d (4H, 4NH, J 6.7 Hz). Found, %: C 74.50; H 10.98; N 9.03. C$_{38}$H$_{66}$N$_4$O$_2$. Calculated, %: C 74.70; H 10.89; N 9.17. M 610.96.

4-[(4-{3-[(3,5-Dimethyladamantan-1-yl)methyl]ureido}cyclohexyl)oxy]benzoic acid (4i) was prepared similarly to compound **4a** from 0.2 g compound **2** and 0.22 g of *trans*-4-(cyclohexyloxy)benzoic acid (**3i**). Yield 0.260 g (63%), mp 240.1°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.79 s (12H, 4CH$_3$), 1.25 d (2H, cyclohexane CH$_2$, J 7.2 Hz), 0.98–2.15 m (26H, Ad), 1.47 d (2H, cyclohexane CH$_2$, J 7.0 Hz), 1.86–1.90 m (2H, cyclohexane CH$_2$ cyclohexane), 2.01–2.03 m (2H, cyclohexane CH$_2$), 2.74 d (2H, C$\underline{H}_2$NH, J 6.6 Hz), 3.07 s (1H, C$\underline{H}$NH), 4.40 s (1H, CHO), 5.70 d (1H, N$\underline{H}$CH, J 7.58 Hz), 5.81 t (1H, N$\underline{H}$CH$_2$, J 6.2 Hz), 7.03 d (2H, 2CH$_{arom}$, J 8.5 Hz), 7.87 d (2H, 2CH$_{arom}$, J 8.4 Hz), 12.45 br.s (1H, COOH). Found, %: C 71.23; H 8.55; N 6.22. C$_{27}$H$_{38}$N$_2$O$_4$. Calculated, %: C 71.33; H 8.43; N 6.16. M 454.60.

CONCLUSIONS

A one-step method has been developed for the synthesis of 1-(isocyanatomethyl)-3,5-dimethyladamantane with a yield of 87% under mild conditions. 1-(Isocyanatomethyl)-3,5-dimethyladamantane was reacted with aliphatic diamines to synthesize a series of 1,3-disubstituted diurea derivatives in 63–99% yields and with *trans*-4-amino(cyclohexyloxy)benzoic acid to synthesized a 1,3-disubstituted urea derivative in 63% yield. The melting points of the synthesized 1,3-disubstituted diureas span the range 99–212°C vs 240.1°C for the lead compound obtained from *trans*-4-amino(cyclohexyloxy)benzoic acid. The lipophilicity coefficients of the series of 1,3-disubstituted diureas span the range 5.30–8.63 and that of the urea derivative obtained from *trans*-4-amino(cyclohexyloxy)benzoic acid is 5.32. The resulting ureas are promising inhibitors of human soluble epoxide hydrolase.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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