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First synthesis of α-(3-*R*-1-adamantyl)sulfoacetic acids and their derivatives

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ABSTRACT

By sulfonation of 3-*R*-1-adamantylacetic acids **1** with H_2SO_4 in trifluoroacetic anhydride (TFAA), the previously unknown α-(3-*R*-adamantyl)sulfoacetic acids **2** were obtained. In the case of 1-adamantylacetic acid **1a**, the use of ~1 equiv of H_2SO_4 led to only 1-adamantylacetic acid **2a**, while with an excess of the reactant the hydroxylation of the adamantane tertiary C–H bond also occurred. It is assumed that the bis(trifluoroacetyl)sulfate generated in situ from H_2SO_4 and TFAA is responsible both for sulfonation and oxidation steps. The adamantylated sulfoacetic acids were used for the preparation of a series of derivatives by modifications of carboxylic, sulfonic acid, and tertiary adamantane OH-groups. Due to the use of TFAA as a medium, a series of derivatives of sulfoacetic acids was obtained directly from acids **1** within one-pot procedures. Some of the synthesized compounds possess anti-HSV activity.

1. Introduction

The chemistry of adamantane derivatives has attracted considerable attention due to their wide range of application as model compounds and molecular building blocks in drug and polymer syntheses,[1] host–guest chemistry, and nanotechnology.[2] Despite the fact that a huge number of adamantane derivatives have been synthesized,[3] the published data on the synthesis of adamantane-derived sulfoacids are very limited. The parent 1-adamantanesulfonic acid and some derivatives have been obtained from adamantanes by treating with $SOCl_2/AlCl_3$ followed by hydrolysis and oxidation by H_2O_2,[4] or directly by photo-[5] or catalytic[6] sulfoxidation with SO_2/O_2. The synthesis of 3-(1-pyridinium)-1-adamantylmethanesulfonic acid by reaction of 3,7-dimethylenebicyclo[3.3.1]nonane with $Py\cdot SO_3$ in pyridine was also published.[7] Several patents concerned with the synthesis and application of 1-adamantanesulfonic acid were also observed.[8]

In line with our investigations on the synthesis and applications of adamantane derivatives,[9] we report a synthetic approach to previously unknown (3-*R*-1-adamantyl)sulfoacetic acids **2** by sulfonation of the corresponding adamantylacetic acids **1** with H_2SO_4 in trifluoroacetic acid anhydride. The motivation for this research was our recent study on the selective electrophilic reactions of adamantane derivatives in TFAA in the presence of sulfuric or triflic acids: adamantane tertiary C–H bond hydroxylation in 5-(1-adamantyl)pyrimidines by in situ generated bis(trifluoroacetyl) sulfate,[9f] and CF_3SO_3H-catalyzed self-acylation of 1-adamantylacetic acid leading to 2,4-bis(1-adamantyl)acetoacetic acid.[9g]

2. Results and discussion

2.1. Synthesis

First, the reaction of 1-adamantylacetic acid **1a** with H_2SO_4 in TFAA was studied. As sulfuric acid is easily converted to bis(trifluoroacetyl)sulfate **3** when reacted with an excess of TFAA,[10] the following stepwise procedure was used in course of the research. A mixture of sulfuric acid and TFAA was heated at reflux for 1.5 h, then the substrate **1a** was added and the reaction mixture was kept at room temperature or heated (Scheme 1). It was found that at reflux temperature, depending on the excess of H_2SO_4 used, the reaction between 1-adamantylacetic acid **1a** and bis(trifluoroacetyl)sulfate led either to selective sulfonation of CH_2CO_2H-group (~1 equiv of H_2SO_4) or to simultaneous sulfonation and hydroxylation of the adamantane tertiary C–H bond (2.2 equiv of H_2SO_4). As a result, α-(1-adamantyl)- and α-(3-hydroxy-1-adamantyl)sulfoacetic acids **2a**,**b** were synthesized for the first time. At room temperature, α-(1-adamantyl)sulfoacetic acid **2a** was the only product from the reaction of **1a** with both equimolar or

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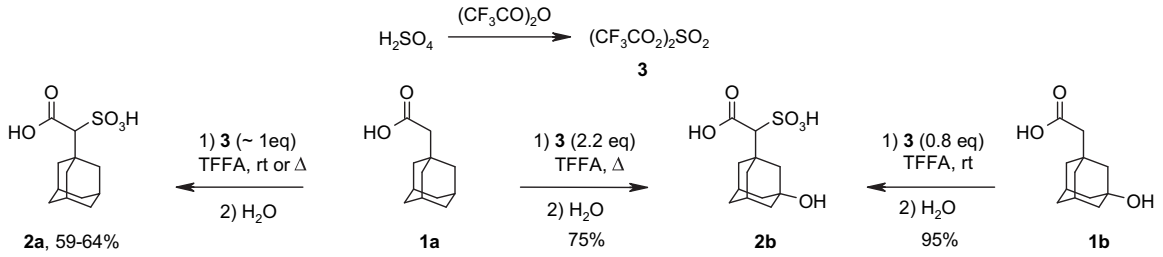
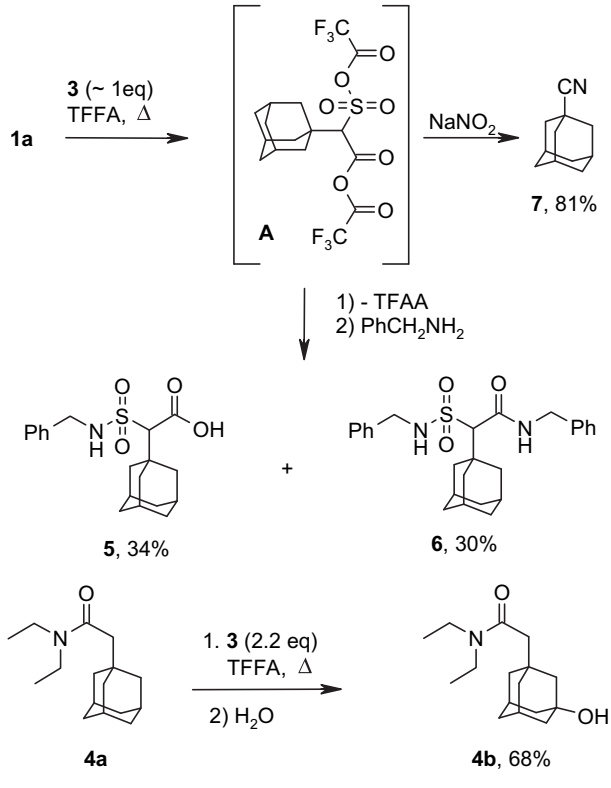


Scheme 1.

excess amount of H_2SO_4, while the acid **2b** can be obtained under these conditions from 3-hydroxy-1-adamantylacetic acid **1b**.

The preparative syntheses of water-soluble acids **2a**,**b** were performed by selective sulfonation of **1a**,**b** with 0.8 equiv of H_2SO_4 as no free sulfuric acid remains in this case, and the excess unreacted acids **1a**,**b** are easily separated from the quenched reaction mixtures by extraction with diethyl ether.

The proposed mechanism of **1a** sulfonation involves the formation of mixed 1-adamantylacetic/trifluoroacetic anhydride with the activated α-methylene group, which is easily sulfonated with bis(trifluoroacetyl)sulfate to form the intermediate **A** (Scheme 2). The necessity to activate the methylene group is confirmed by the fact that the amide **4a** with an excess of **3** undergoes only hydroxylation of adamantane nucleus (compound **4b**), but not sulfonation of α-methylene group. The excess TFAA can be easily removed, so the mixed anhydride **A** was used as an acylating and/or sulfonating reactant to give some α-(1-adamantyl)sulfoacetic acid derivatives in a one-pot manner. The acid **1a** was first sulfonated with the slight excess of H_2SO_4 (1.05 equiv), and, after the evaporation of TFAA, treated with benzylamine in dry dichloromethane to give mono- and bis(benzylamides) **5** and **6**. While the formation of bisamide **6** proves the structure of **A**, the formation of amide **5** can be explained either by incomplete amidation of **A**, or by presence of other anhydrides in the reaction mixture after sulfonation.



Scheme 2.

The sulfamide structure of **5** was unambiguously proved by IR and NMR spectroscopic data. The IR spectrum contains characteristic absorption bands of CO_2H (1702 cm^{-1}) and SO_2NH (3467 cm^{-1} for NH and 1200 cm^{-1} for SO_2); in the ^{13}C NMR spectrum the signal of the carbonyl groups at 169.22 ppm is closer to the CO resonance of sulfoacid **2a** (169.16 ppm) than that of bisamide **6** (164.41 ppm). The structure of bisamide **6** was confirmed by X-ray analysis. A suitable crystal was obtained by crystallization from 2-propanol. The molecular structure of **6** and the crystal packing are presented in Fig. 1, the crystallographic data are collected in Table 2 (Experimental section). In the solid state the infinite rods along the *b*-axis are formed due to intermolecular hydrogen bonding (N1—H101···O2^{i} and N2—H102···O1^{i}).

Is it known that acid **1a** can be converted to 1-adamantylnitrile by treating with sodium nitrite in TFAA.[11] When sodium nitrite was added directly to the reaction mixture after the sulfonation of **1a** was complete, 1-adamantylnitrile **7** was obtained after additional heating. Thus, the action of NO^+ caused the elimination of both carboxylic and sulfo groups from anhydride **A**.

Some chemical modifications of α-(1-adamantyl)sulfoacetic acid **2a** are presented in Scheme 3. By heating with $POCl_3$, acid **2a** was converted to bis(chloroanhydride) **8**, which was reacted with nucleophiles to form bisamide **12** and diphenylester **9**. The selective hydrolysis of **9** was achieved by heating the substrate in pyridine containing 1.5 equiv of water. The X-ray data for **10** (Fig. 2, Table 2) unambiguously prove that under these conditions, hydrolysis of the sulfonate group occurs while the carboxylic ester group remains unchanged. This result is in line with the published properties of sulfoacetic acid diphenyl ester.[12] When refluxed in ethanol containing KOH, the decarboxylation of ester **9** takes place to give phenyl 1-adamantylmethylsulfonate **11** in high yield, while the parent sulfoacetic acid **2a** is resistant to heating either in alkaline (KOH) or strongly acidic (HCl) medium.

α-Sulfoacetic acids are used for the preparation of 1,2,4-thiadiazine-3,5-diones, which are of interest because of their relation to barbituric acid.[13] Following the published synthetic approach,[13b] bis(chloroanhydride) **8** was converted to bisamide **12** and then to sulfonylurea potassium salt **13**. But the ring closure step in boiling pyridine to get the desired 6-(1-adamantyl)-1,2,4-thiadiazine-3.5-dione **B** was unsuccessful due to hydrolysis of the urea.

The synthesis of sulfoacid **2b** derivatives can be also performed in a one-pot manner starting directly from 1-adamantylacetic acid **1a**. For instance, the adamantylated barbituric acid **14** was obtained from **1a** by consecutive sulfonation/hydroxylation, removal of the excess TFAA, and heating with barbituric acid in TFA (Scheme 4). It is reasonable to assume that in this case the role of the adamantylating reactant plays the bis(anhydride)-monoester **C**. Similar to intermediate **A**, after elimination of excess TFAA, intermediate **C** reacted with benzylamine to give a mixture of mono- and bisamides **15** and **16**.

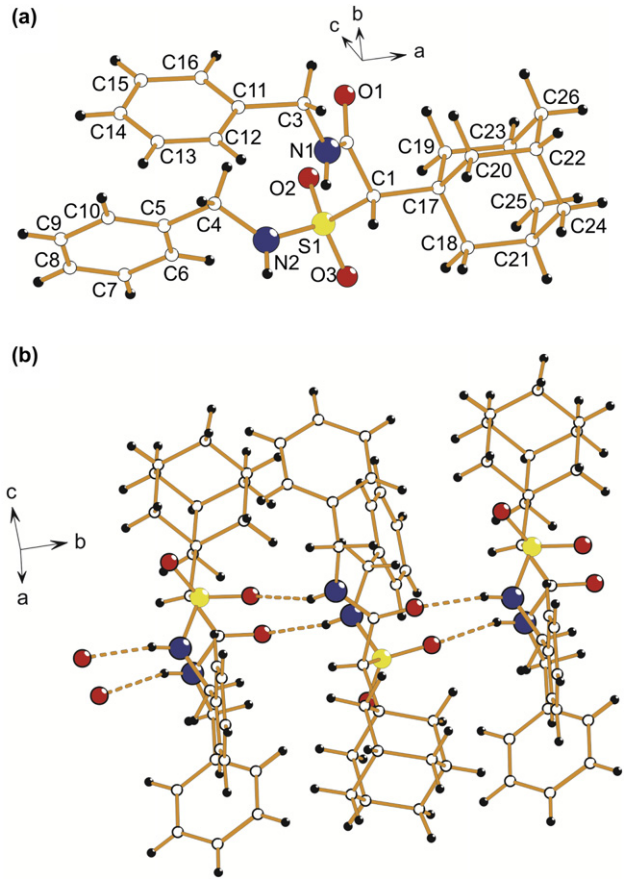
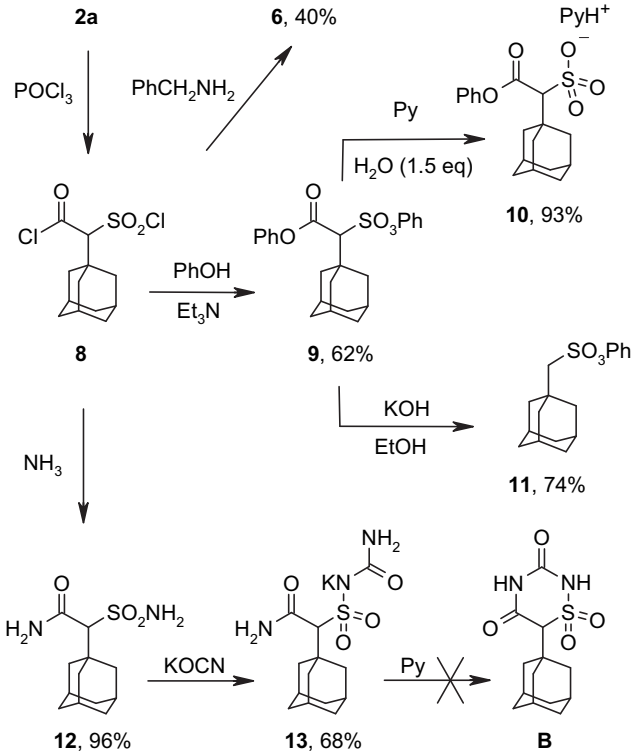


Fig. 1. Molecular structure (a) and crystal packing (b) of bisamide **6**.

As α-(3-hydroxy-1-adamantyl)sulfoacetic acid **2b** is resistant to heating in an acidic medium, it can be used for TFA-mediated adamantylation of *C*- and *N*-nucleophiles. The reaction of **2b** with



Scheme 3.

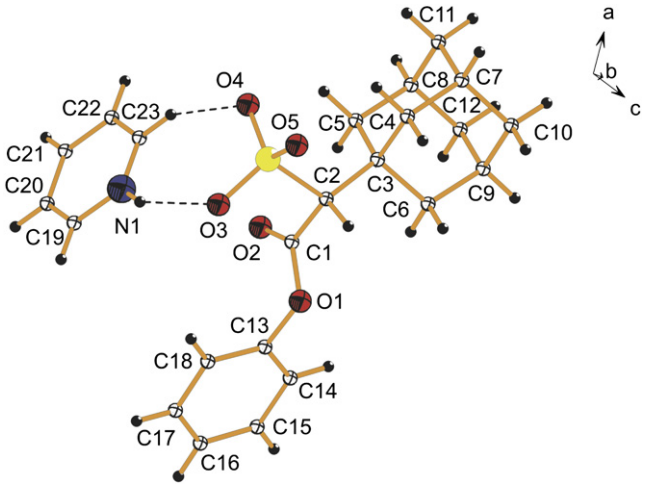
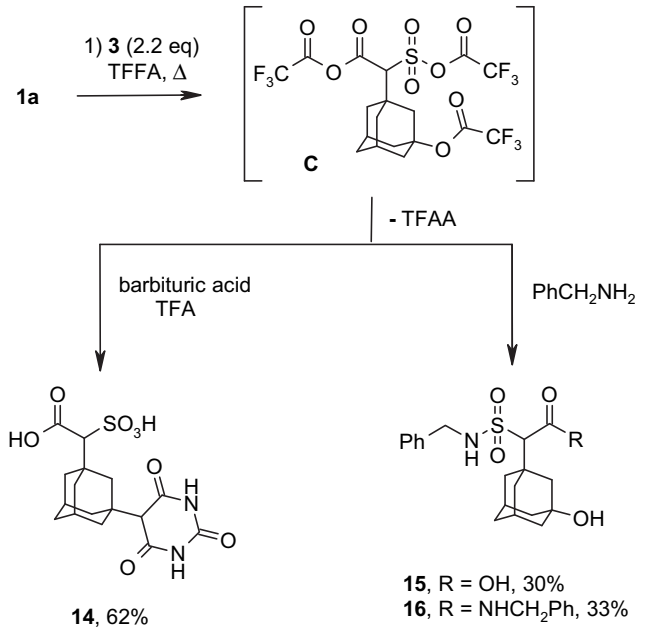


Fig. 2. Molecular structure of pyridinium salt **10**.



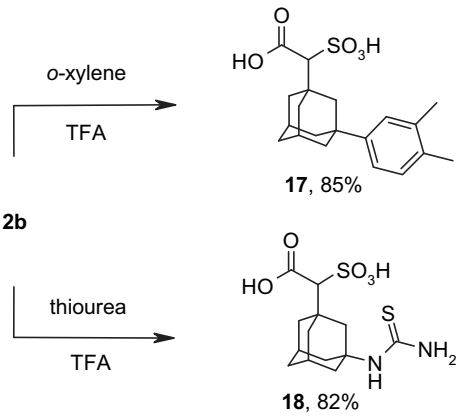
Scheme 4.

o-xylene and thiourea gave α-[3-(3,4-dimethylphenyl)-1-adamantyl]sulfoacetic acid **17** and α-(3-thioureido-1-adamantyl) sulfoacetic acid **18**, respectively (Scheme 5).

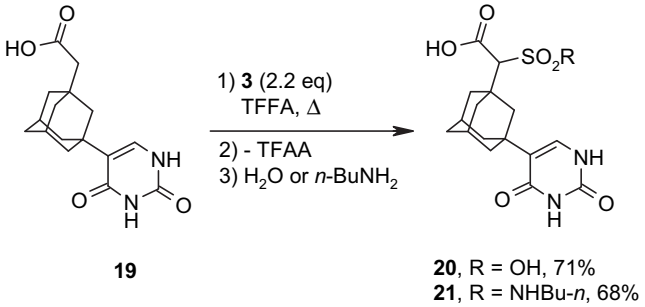
As an extension of the sulfonation/hydroxylation method, the interaction between 5-(3-carboxymethyl-1-adamantyl)uracil **19** and bis(trifluoroacetyl)sulfate was studied. Unexpectedly, even when a large excess of H_2SO_4 was used, only sulfonation occurred with no hydroxylation. The crude reaction mixture was quenched with water or *n*-butylamine to get sulfoacid **20** and sulfamide **21**, respectively (Scheme 6). Probably, the presence of two electron-withdrawing groups in the molecule (the uracil unit and the sulfoacetic unit formed during sulfonation) deactivates the adamantane tertiary C–H bond and makes the molecule resistant to hydroxylation under these conditions.

2.2. Pharmacology

For α-(3-*R*-1-adamantyl)sulfoacetic acids **2**, **20**, and selected derivatives, the cytotoxicity and antiviral activity against herpes simplex virus of types 1 and 2 (HSV-1 and HSV-2) in *Vero* cells were



Scheme 5.



Scheme 6.

examined according to the previously reported method.[14] From the MIC_{50} and MCC_{50} values presented in Table 1, it appears that most of substances tested possess low cytotoxicity and display moderate antiviral activity, yet significantly inferior to the reference pharmaceutical acyclovir. Pyridinium methanesulfonate **10** displayed the most pronounced antiviral activity toward HSV-2 and had a selectivity index (SI=MCC_{50}/MIC_{50}) >20, while the sulfoacetic acid **2b** showed no antiviral activity.

Table 1
Cytotoxicity and anti-HSV activity of selected compounds in *Vero* cells culture (mg/cm^{-3})[a]

Compound	MCC_{50}[b]	HSV-1		HSV-2	
		MIC_{50}[c]	SI	MIC_{50}	SI
2a[d]	1000	250	4	100	10
2b	1000	NA		NA	
5[e]	1000	100	10	100	10
10	>1000	100	>10	50	>20
12	250	250	1	50	5
20	500	500	1	100	5
Zovirax	500	0.4	1250	0.2	2500

[a] The data from three independent experiments, each duplicated; deviations below 10%.
[b] MCC_{50}—minimum cytotoxic concentration causing 50% growth inhibition of *Vero* cells.
[c] MIC_{50}—minimum inhibitory concentration reducing the cytopathogenic effect of virus by 50%.
[d] As pyridinium salt.
[e] As sodium salt.

3. Conclusions

Bis(trifluoroacetyl)sulfate prepared in situ from H_2SO_4 and TFAA was used for selective sulfonation of the α-methyl group of (3-*R*-1-adamantyl)acetic acid **1**. In the case of 1-adamantylacetic acid **1a**, under a controlled excess of H_2SO_4 used, either the selective sulfonation or simultaneous sulfonation and adamantane hydroxylation can be realized. The crude anhydridic products of sulfonation after removing of TFAA were further derivatized in a one-pot manner by interaction with different *O*-,*N*-nucleophiles or through transformations of released CO_2H and SO_3H-groups. Thus, the 2-(3-*R*-1-adamantyl)sulfoacetic acid derivatives with ester, amide, and sulfamide functionalities and also the product of decarboxylation were obtained. The product of sulfonation/hydroxylation of acetic acid **1a**—α-(3-hydroxy-1-adamantyl)sulfoacetic acid **2a**—was also used as an adamantylating reactant either in acid form or as crude anhydride-monoester form (one-pot). Some of the synthesized compounds were tested for their antiviral activity against HSV-1 and HSV-2.

4. Experimental

4.1. General

^1H and ^{13}C (APT) NMR spectra were measured with a Bruker Avance 400 spectrometer with solvent signals as internal reference. Doubled NMR signals, belonging to diastereotopic atoms, are marked with asterisks *. IR spectra were recorded with a Thermo Scientific Nicolet IR 200 FTIR spectrometer. ESI mass spectra were recorded with an Agilent 1100 LC/MS instrument. X-ray measurements were performed with an Enraf-Nonius CAD-4 diffractometer. Chemicals were of commercial grade and used without further purification. Column chromatography was performed on silica (Merck Kieselgel 60). Solvents were purified and dried according to standard procedures. TFAA was freshly distilled from P_2O_5. 1-Adamantylacetic acid **1a**,[15] 3-hydroxy-1-adamantylacetic acid **1b**,[15] and 5-(3-carboxymethyl-1-adamantyl)uracil **19**[9f] were prepared according to published procedures.

4.2. Synthesis

*4.2.1. α-(1-Adamantyl)sulfoacetic acid (**2a**). Method A*: A mixture of sulfuric acid (98%, 0.06 mL, 1.05 mmol) and TFAA (1.7 mL) was heated at reflux (oil bath, 65 °C) for 1.5 h and cooled. 1-Adamantylacetic acid **1a** (0.19 g, 1.0 mmol) was added and the resultant mixture was refluxed (oil bath, 75 °C) for 4 h. After cooling, the excess TFAA was removed under reduced pressure, the residue was treated with cold water (1 mL), the solid formed was filtered, washed with diethyl ether, and dried. Yield: 59% (0.16 g). *Method B*: A cooled TFAA-solution of bis(trifluoroacetyl)sulfate prepared from H_2SO_4 (94%, 0.045 mL, 0.8 mmol) and TFAA (0.9 mL) as described in method A, was added to the solution of 1-adamantylacetic acid **1a** (0.19 g, 1.0 mmol) in TFAA (0.9 mL). The mixture was stirred for 24 h at room temperature and then poured into water (20 mL). The resultant suspension was stirred at 95 °C for 3 h in an open flask, cooled to room temperature, extracted with diethyl ether, and the water fraction was evaporated under reduced pressure. The residue was re-evaporated twice with dry benzene. Yield: 64% (0.14 g), white solid, mp 163–167 °C. Anal. Calcd for $C_{12}H_{18}O_5S$ (274.34): C, 52.54; H, 6.61. Found: C, 52.80; H, 6.31. IR (KBr, cm^{-1}): 1715 (CO), 1172 (SO_2). ^1H NMR (400 MHz, $CDCl_3$): δ=3.11 (s, 1H, CHCO), 2.00–1.35 (m, 15H, H^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.1 (CO), 76.6 (*C*HCO), 39.8, 36.7 (CH_2^{Ad}), 35.0 (C^{Ad}), 28.2 (CH^{Ad}) ppm.

*4.2.2. α-(3-Hydroxy-1-adamantyl)sulfoacetic acid (**2b**). Method A*: Acid **2b** was obtained from 1-adamantylacetic acid **1a** (0.39 g, 2.0 mmol), H_2SO_4 (98%, 0.23 mL, 4.3 mmol), and TFAA (3.4 mL) as described for **2a** (method A). After removal of TFAA, the residue was dissolved in water and allowed to stay overnight. The clear water solution was decanted and treated with 0.5 M $BaCl_2$ until precipitation was complete, and then treated with Na_2CO_3 to pH 8. The solution was filtered and acidified with HCl to pH 2. The water was

removed under reduced pressure, and the dry solid residue was extracted repeatedly by dry methanol. The methanol solution was evaporated to dryness. Yield: 75% (0.44 g). *Method B*: Acid **2b** was obtained from 3-hydroxy-1-adamantylacetic acid **1b** (0.42 g, 2.0 mmol), H_2SO_4 (94%, 0.09 mL, 1.6 mmol), and TFAA (3.4 mL) as described for **2a** (method B). Yield: 95% (0.44 g), light yellow solid (hygroscopic), mp 200–203 °C (decomp.). Anal. Calcd for $C_{12}H_{18}O_6S\cdot H_2O$ (308.36): C, 46.74; H, 6.54. Found: C, 46.99; H, 6.34%. IR (KBr, cm^{-1}): 1708 (CO), 1170 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ=3.17 (s, 1H, CHCO), 2.04 (br s, 2H, CH^{Ad}), 1.95–1.30 (m, 12H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=170.0 (CO), 75.5 (*C*HCO), 66.9 (C^{Ad}), 48.0, 44.7 (CH_2^{Ad}), 38.3 (C^{Ad}), 38.0, 35.4 (CH_2^{Ad}), 30.1*, 30.0* (CH^{Ad}) ppm. MS (ESI): m/z=288.9 $[M-H]^-$, for $C_{12}H_{17}O_6S$ (289.07).

*4.2.3. N,N-Diethyl-α-(1-adamantyl)acetamide (**4a**).* A mixture of 1-adamantylacetic acid **1a** (0.78 g, 4.0 mmol) and $SOCl_2$ (5 mL) was heated at reflux for 3 h and cooled. The excess $SOCl_2$ was removed under reduced pressure and the residue was re-evaporated twice with dry benzene. The resultant oil was dissolved in dry benzene (10 mL), and diethylamine (2.1 mL, 20 mmol) was added dropwise at stirring, and the mixture was allowed to stay overnight at room temperature. The solvent was evaporated under reduced pressure and the residue treated with 2 M HCl (15 mL) and extracted with dichloromethane. The organic fraction was washed with water, dried with $MgSO_4$, and the solvent evaporated. Yield: 79% (0.79 g), colorless oil. Anal. Calcd for $C_{16}H_{27}NO$ (249.40): C, 77.06; H, 10.91; N, 5.62. Found: C, 77.23; H, 10.82; N, 5.81. IR (KBr, cm^{-1}): 1621 (CO). ^1H NMR (400 MHz, $CDCl_3$): δ=3.28 (m, 4H, NCH_2), 2.02 (m, 2H, CH_2CO), 1.88 (br s, 3H, CH^{Ad}), 1.67–1.51 (m, 12H, CH_2^{Ad}), 1.06 (m, 6H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.3 (CO), 45.7 (CH_2CO), 42.6 (CH_2^{Ad}), 39.8 (NCH_2), 36.7 (CH_2^{Ad}), 33.4 (C^{Ad}), 28.6 (CH^{Ad}), 14.3, 13.2 (CH_3) ppm.

*4.2.4. N,N-Diethyl-α-(3-hydroxy-1-adamantyl)acetamide (**4b**).* Obtained from acetamide **4a** (0.25 g, 1.0 mmol), H_2SO_4 (98%, 0.12 mL, 2.2 mmol), and TFAA (1.7 mL) as described for **2a** (method A). The residue formed after removal of TFAA was heated with 1 M NaOH at 50 °C for 2 h, cooled, acidified with HCl to pH 2, and the solution extracted with dichloromethane. The organic solution was dried by $MgSO_4$ and the solvent evaporated. Yield: 68% (0.18 g), colorless oil. Anal. Calcd for $C_{16}H_{27}NO_2$ (265.40): C, 72.41; H, 10.25; N, 5.28. Found: C, 72.02; H, 9.96; N. 5.15. IR (KBr, cm^{-1}): 1623 (CO). ^1H NMR (400 MHz, $CDCl_3$): δ=4.44 (br s, 1H, OH), 3.35–3.25 (m, 4H, NCH_2), 2.16–2.09 (br s, 4H, CH_2CO+CH^{Ad}), 1.70–1.45 (m, 12H, CH_2^{Ad}), 1.14–1.02 (m, 6H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.3 (CO), 68.7 (C^{Ad}), 50.0 (CH_2^{Ad}), 44.5 (CH_2CO), 44.2 (CH_2^{Ad}), 42.8 (NCH_2), 41.2 (CH_2^{Ad}), 40.1 (NCH_2), 36.7 (C^{Ad}), 35.2 (CH_2^{Ad}), 30.5 (CH^{Ad}), 14.2, 13.1 (CH_3) ppm.

*4.2.5. α-(1-Adamantyl)-α-(benzylsulfamoyl)acetic acid (**5**).* The reaction mixture obtained after sulfonation of 1-adamantylacetic acid **1a** (0.39 g, 2.0 mmol) with H_2SO_4 (98%, 0.12 mL, 2.2 mmol) in TFAA (3.4 mL) as described for **2a** (method A) was concentrated to dryness under reduced pressure. The residue was dissolved in dry dichloromethane (20 mL), and a solution of benzylamine (0.66 mL, 6.0 mmol) and triethylamine (0.84 mL, 6.0 mmol) in dichloromethane (4 mL) was added with cooling (0–5 °C). The mixture was allowed to stay overnight at room temperature and quenched with 2 M HCl. After 24 h, the water fraction (as suspension) was separated and filtered, the solid was washed with water and dried. Yield: 34% (0.25 g), white solid, mp 175–179 °C. Anal. Calcd for $C_{19}H_{25}NO_4S$ (363.48): C, 62.79; H, 6.93; N, 3.85. Found: C, 62.50; H, 6.85; N, 3.71. IR (KBr, cm^{-1}): 3467 (NH), 1702 (CO), 1200 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ=7.50–7.35 (m, 5H, ArH), 4.07–3.97 (m, 2H, NCH_2), 3.08 (s, 1H, CHCO), 2.00–1.50 (m, 15H, H^{Ad}) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=169.2 (CO), 134.0 (C^{Ar}), 128.9, 128.7, 128.5 (CH^{Ar}), 76.4 (*C*HCO), 42.4 (NCH_2), 39.7, 36.6 (CH_2^{Ad}), 34.7 (C^{Ad}), 28.1 (CH^{Ad}) ppm.

*4.2.6. N-Benzyl-α-(1-adamantyl)-α-(benzylsulfamoyl)acetamide (**6**). Method A*: Obtained by chromatographic purification (dichloromethane/methanol, 99:1) of the dichloromethane fraction from the synthesis of **5**. Yield: 30% (0.27 g). *Method B*: A mixture of 2-(1-adamantyl)sulfoacetic acid **2a** (0.14 g, 0.5 mmol) and $POCl_3$ (2 mL) was heated at 125 °C for 5 h. The excess $POCl_3$ was removed under reduced pressure, and the residue was dissolved in dry dichloromethane (4 mL). After cooling to 0–5 °C, a solution of benzylamine (0.16 mL, 1.5 mmol) and triethylamine (0.21 mL, 1.5 mmol) in dichloromethane (3 mL) was added. The mixture was stirred at room temperature for 24 h, diluted with dichloromethane, and washed with 2 M HCl. The organic fraction was dried by $MgSO_4$, concentrated, and the residue was purified by column chromatography (dichloromethane/methanol, 99:1). Yield: 40% (0.09 g), white solid, mp 154–156 °C. Anal. Calcd for $C_{26}H_{32}N_2O_3S$ (452.62): C, 69.00; H, 7.13; N, 6.19. Found: C, 69.32; H, 7.01; N, 6.50. IR (KBr, cm^{-1}): 3370, 3210 (NH), 1660 (CO), 1149 (SO_2). ^1H NMR (400 MHz, $CDCl_3$): δ=7.38–7.17 (m, 10H, ArH), 6.88 (br s, 1H, $NHSO_2$), 4.79 (br s, 1H, NHCO), 4.50 (dd, ^2J=14.4 Hz, ^3J=6.2 Hz, 1H, NCH_2), 4.40 (dd, ^2J=14.4 Hz, ^3J=5.6 Hz, 1H, NCH_2), 4.21 (dd, ^2J=13.9 Hz, ^3J=6.5 Hz, 1H, NCH_2), 4.16 (dd, ^2J=13.9 Hz, ^3J=5.5 Hz, 1H, NCH_2), 3.64 (s, 1H, CHCO), 2.15–1.55 (m, 15H, H^{Ad}) ppm. ^{13}C NMR ($CDCl_3$): δ=164.4 (CO), 137.6, 136.5 (C^{Ar}), 128.8, 128.7, 128.0, 128.0, 127.9, 127.7 (CH^{Ar}), 79.9 (*C*HCO), 47.5 (CH_2NCO), 43.9 (CH_2NSO_2), 40.4 (CH_2^{Ad}), 37.0 (C^{Ad}), 36.3 (CH_2^{Ad}), 28.5 (CH^{Ad}) ppm.

*4.2.7. 1-Adamantylnitrile (**7**).* The reaction mixture obtained after sulfonation of 1-adamantylacetic acid **1a** (0.19 g, 1.0 mmol) with H_2SO_4 (98%, 0.06 mL, 1.1 mmol) in TFAA (3.4 mL) as described for **2a** (method A) was cooled to room temperature and $NaNO_2$ (0.15 g, 2.2 mmol) was added. The mixture was refluxed (oil bath, 55 °C) for 4 h, cooled, and the solvent evaporated under reduced pressure. The residue was washed with water, methanol and dried. Yield: 81% (0.13 g), white solid, mp 191–193 °C (lit. 193–196 °C[11]). ^1H NMR (400 MHz, $CDCl_3$): δ=2.10–1.85 (m, 9H, CH^{Ad}+CH_2^{Ad}), 1.80–1.65 (m, 6H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=125.3 (CN), 39.9, 35.8 (CH_2^{Ad}), 34.1 (C^{Ad}), 27.2 (CH^{Ad}) ppm.

*4.2.8. Diphenyl-α-(1-adamantyl)sulfoacetate (**9**).* Obtained from 2-(1-adamantyl)sulfoacetic acid **2a** (0.27 g, 1.0 mmol), $POCl_3$ (2 mL), phenol (0.38 g, 4.0 mmol), and triethylamine (0.83 mL, 6.0 mmol) in dichloromethane (6 mL) as described for **6** (method B). The crude product was purified with column chromatography (dichloromethane/hexane, 1:1). Yield: 62% (0.26 g), colorless needles, mp 138–142 °C (decomp.). Anal. Calcd for $C_{24}H_{26}O_5S$ (426.54): C, 67.58; H, 6.14. Found: C 67.99, H 6.31. IR (KBr, cm^{-1}): 1758–1745 (CO), 1135 (SO_2). ^1H NMR (400 MHz, $CDCl_3$): δ=7.45–7.13 (m, 10H, ArH), 4.20 (s, 1H, CHCO), 2.30–1.90 (m, 6H, CH_2^{Ad}), 2.11 (br s, 3H, CH^{Ad}), 1.82–1.68 (m, 6H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.8 (CO), 150.1, 148.9 (C^{Ar}), 129.9, 129.6, 127.3, 126.5, 122.1, 121.2 (CH^{Ar}), 76.7 (*C*HCO), 34.9 (CH_2^{Ad}), 37.8 (C^{Ad}), 36.2 (CH_2^{Ad}), 28.4 (CH^{Ad}) ppm.

*4.2.9. α-(Phenoxycarbonyl)-α-(1-adamantyl)methanesulfonic acid, pyridinium salt (**10**).* A mixture of ester **9** (0.21 g, 0.5 mmol), water (0.014 mL, 0.75 mmol), and dry pyridine (3 mL) was heated at 120 °C for 12 h. The solvent was evaporated and the resultant solid was washed with diethyl ether. Yield: 93% (0.20 g), colorless crystals, mp 119–123 °C (decomp.). Anal. Calcd for $C_{18}H_{21}O_5S\cdot C_5H_6N$ (429.54): C, 64.31; H, 6.34; N, 3.26. Found: C, 63.95; H, 6.11; N, 3.45. IR (KBr, cm^{-1}): 1748 (CO), 1253–1164 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ=8.85 (br s, 2H, ArH^{Py}), 8.36 (br s, 1H, ArH^{Py}), 7.90 (br s, 2H, ArH^{Py}), 7.40–6.95 (m, 5H, ArH^{Ph}), 3.94 (s, 1H, CHCO), 2.25–1.95

(m, 9H, CH^{Ad}+CH_2^{Ad}), 1.80–1.60 (m, 6H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=167.8 (CO), 150.6 ($C^{Ar,Ph}$), 145.6, 142.1 ($CH^{Ar,Py}$), 129.3 ($CH^{Ar,Ph}$), 127.1 ($CH^{Ar,Py}$), 125.8, 121.5 ($CH^{Ar,Ph}$), 76.2 (*C*HCO), 40.0, 36.6 (CH_2^{Ad}), 36.5 (C^{Ad}), 28.5 (CH^{Ad}) ppm.

*4.2.10. Phenyl α-(1-adamantyl)methanesulfonate (**11**).* A mixture of ester **9** (0.15 g, 0.35 mmol), NaOH (0.02 g, 0.5 mmol), water (1 mL), and ethanol (2 mL) was heated at 85 °C for 20 h and then stirred at room temperature for 12 h. The solid formed was filtered off, and the filtrate acidified with HCl to pH 2, and concentrated to dryness. The residue was washed with water (1 mL) and dried. Yield: 74% (0.07 g), white solid, mp 159–162 °C (decomp.). Anal. Calcd for $C_{17}H_{22}O_3S$ (306.43): C, 66.64; H, 7.24. Found: C, 66.90; H, 7.40. ^1H NMR (400 MHz, DMSO-d_6): δ=7.50–7.10 (m, 5H, ArH), 3.09 (br s, 2H, CH_2S), 2.20–1.50 (m, 15H, H^{Ad}) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=149.3 (C^{Ar}), 129.9, 127.0, 122.0 (CH^{Ar}), 63.0 (CH_2S), 41.7, 36.3 (CH_2^{Ad}), 33.4 (C^{Ad}), 28.3 (CH^{Ad}) ppm.

*4.2.11. α-Carbamoyl-α-(1-adamantyl)methanesulfonamide (**12**).* A mixture of 2-(1-adamantyl)sulfoacetic acid **2a** (0.14 g, 0.5 mmol) and $POCl_3$ (1 mL) was heated at 125 °C for 4 h, cooled, and the solvent evaporated under reduced pressure. The residue was dissolved in dry 1,4-dioxane (2 mL) and added to a cold 1,4-dioxane saturated with gaseous NH_3 (15 mL). The mixture was stirred at room temperature for 12 h, and the solvent evaporated. The residual solid was stirred with water (3 mL) for 6 h, the solid formed was collected, washed with water, acetone, and dried. Yield: 96% (0.13 g), white solid, mp 194–199 °C (decomp.). Anal. Calcd for $C_{12}H_{20}N_2O_3S$ (272.37): C, 52.92; H, 7.40; N, 10.29. Found: C, 52.57; H, 7.59; N, 10.31. IR (KBr, cm^{-1}): 1674 (CO), 1150 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ=7.47 (br s, 1H, $CONH_2$), 7.25 (br s, 1H, $CONH_2$), 6.75 (br s, 2H, SO_2NH_2), 3.52 (s, 1H, CHCO), 2.10–1.50 (m, 15H, H^{Ad}) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=167.3 (CO), 77.9 (*C*HCO), 39.5, 36.3 (CH_2^{Ad}), 35.6 (C^{Ad}), 28.0 (CH^{Ad}) ppm.

*4.2.12. α-Carbamoyl-α-(1-adamantyl)methanesulfonylurea, potassium salt (**13**).* A mixture of bisamide **12** (0.14 g, 0.5 mmol), KOCN (0.045 g, 0.55 mmol), and dry ethanol (2.5 mL) was refluxed (oil bath, 95 °C) for 5 h. The reaction mixture was cooled and allowed to stay at 0 °C for 12 h. The solid formed was filtered, washed with cold ethanol, and dried. Yield: 68% (0.12 g), white solid, mp 96–99 °C (decomp.). Anal. Calcd for $C_{13}H_{20}KN_3O_4S$ (353.49): C, 44.17; H, 5.70; N, 11.89. Found: C, 43.85; H, 6.09; N, 11.55. IR (KBr, cm^{-1}): 1673 (CO), 1137 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ=7.09 (br s, 1H, $CONH_2$), 6.79 (br s, 1H, $CONH_2$), 5.20–4.90 (br s, 2H, $KNCONH_2$), 3.71 (s, 1H, CHCO), 2.05–1.65 (m, 6H, CH_2^{Ad}), 1.89 (br s, 3H, CH^{Ad}), 1.65–1.50 (m, 6H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=169.2 (*C*HCO), 162.4 ($KNCONH_2$), 76.5 (*C*HCO), 39.8, 36.6 (CH_2^{Ad}), 35.0 (C^{Ad}), 28.2 (CH^{Ad}) ppm.

*4.2.13. 5-[3-(α-Sulfocarboxymethyl)-1-adamantyl]barbituric acid (**14**).* The reaction mixture obtained after sulfonation/hydroxylation of 1-adamantylacetic acid **1a** (0.19 g, 1.0 mmol) with H_2SO_4 (98%, 0.12 mL, 2.2 mmol) in TFAA (1.7 mL) as described for **2a** (method A) was concentrated to dryness under reduced pressure. TFA (2 mL) and barbituric acid (0.19 g, 1.5 mmol) were added and the reaction mixture was refluxed (oil bath, 95 °C) for 15 h. After cooling, the solvent was removed under reduced pressure, water was added, and the mixture was allowed to stay at 0 °C for 12 h. The solution was filtered, and the solvent evaporated. The residue was extracted with ethanol (2 mL), the solvent evaporated, and the solid residue washed with diethyl ether. Yield: 62%, yellow solid, mp >300 °C. Anal. Calcd for $C_{16}H_{20}N_2O_8S$ (400.41): C, 48.00; H, 5.03; N, 7.00. Found: C, 48.32; H, 5.26; N, 6.75. IR (KBr, cm^{-1}): 1757–1678 (CO), 1241–1147 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ=11.07 (br s, 2H, NH), 3.11 (s, 1H, CHCO), 2.66 (s, 1H, CH^{Pyr}), 2.05–1.35 (m, 14H, H^{Ad}) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=168.95 (COOH), 168.7 (C^{Pyr}), 151.5 (C^{Pyr}), 76.1 (*C*HCO), 61.4 (CH^{Pyr}), 42.8, 38.9 (CH_2^{Ad}), 38.1 (C^{Ad}), 36.2 (CH_2^{Ad}), 35.5 (CH_2^{Ad}), 28.6*, 28.5* (CH^{Ad}) ppm.

*4.2.14. α-(3-Hydroxy-1-adamantyl)-α-(benzylsulfamoyl)acetic acid (**15**) and N-benzyl α-(3-hydroxy-1-adamantyl)-α-(benzylsulfamoyl) acetamide (**16**).* The reaction mixture obtained after sulfonation/hydroxylation of 1-adamantylacetic acid **1a** (0.39 g, 2.0 mmol) with H_2SO_4 (98%, 0.23 mL, 4.4 mmol) in TFAA (3.4 mL) as described for **2a** (method A) was concentrated to dryness under reduced pressure. The residue was dissolved in dry dichloromethane (10 mL), and a solution of benzylamine (2.18 mL, 20.0 mmol) in dichloromethane (5 mL) was added at cooling (0–5 °C). The mixture was allowed to stay for 24 h at room temperature and washed with 1 M HCl, water, and dried by $MgSO_4$. The solvent was evaporated and the residue was subjected to column chromatography (dichloromethane/ethanol, 20:1). Compound **15**: Yield: 30% (0.23 g), white solid, mp 198–203 °C. Anal. Calcd for $C_{19}H_{25}NO_5S$ (379.48): C, 60.14; H, 6.64; N, 3.69. Found: C, 60.43; H, 6.78; N, 3.57. ^1H NMR (400 MHz, acetone-d_6): δ=7.60–7.45 (m, 5H, ArH), 4.95 (br s, 1H, NH), 4.40–4.30 (m, 2H, NCH_2), 3.73 (s, 1H, CHCO), 2.21 (br s, 2H, CH^{Ad}), 2.00–1.40 (m, 12H, CH_2^{Ad}) ppm. Compound **16:** Yield: 33% (0.31 g), white needles, mp 174–177 °C. Anal. Calcd for $C_{26}H_{32}N_2O_4S$ (468.62): C, 66.64; H, 6.88; N, 5.98. Found: C, 66.25; H, 6.63; N, 6.35. ^1H NMR (400 MHz, $CDCl_3$): δ=7.35–7.15 (m, 10H, ArH), 6.92 (br s, 1H, $NHSO_2$), 4.86 (br s, 1H, NHCO), 4.55–4.10 (m, 4H, NCH_2), 3.67 (s, 1H, CHCO), 2.05–1.45 (m, 14H, H^{Ad}) ppm. ^{13}C NMR ($CDCl_3$): δ=164.2 (CO), 137.6, 136.6 (C^{Ar}), 128.8, 128.7, 128.0, 127.9, 127.8 (CH^{Ar}), 78.6 (*C*HCO), 68.5 (C^{Ad}), 47.9 (CH_2NCO), 47.5 (CH_2^{Ad}), 44.0 (CH_2NSO_2), 43.9 (CH_2^{Ad}), 39.9 (C^{Ad}), 39.1, 39.0, 34.8 (CH_2^{Ad}), 30.4*, 30.3* (CH^{Ad}) ppm.

*4.2.15. α-[3-(3,4-Dimethylphenyl)-1-adamantyl]sulfoacetic acid (**17**).* A mixture of 2-(3-hydroxy-1-adamantyl)sulfoacetic acid **2b** (0.15 g, 0.5 mmol), *o*-xylene (0.08 mL, 0.65 mmol), and TFA (1 mL) was refluxed (oil bath, 90 °C) for 6 h, cooled, and the solvent evaporated under reduced pressure. The solid formed upon addition of water was collected, washed with water, methanol, and dried. Yield: 85% (0.16 g), white solid, mp 164–169 °C. Anal. Calcd for $C_{20}H_{26}O_5S$ (378.49): C, 63.47; H, 6.92. Found: C, 63.09; H, 6.69. IR (KBr, cm^{-1}): 1712 (CO), 1239 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ=7.08–6.95 (m, 3H, ArH), 3.18 (s, 1H, CHCO), 2.18 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.06 (br s, 3H, CH^{Ad}), 2.03–1.50 (m, 12H, CH_2^{Ad}) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=169.8 (CO), 148.4, 135.7, 133.3 (C^{Ar}), 129.4, 126.2, 122.2 (CH^{Ar}), 76.3 (*C*HCO), 45.7, 42.3, 39.0 (CH_2^{Ad}), 36.3 (C^{Ad}), 36.1 (CH_2^{Ad}), 35.9 (C^{Ad}), 28.9 (CH^{Ad}), 20.0, 19.1 (CH_3) ppm. MS (ESI): m/z=378.7 $[M+H]^+$, for $C_{20}H_{26}O_5S\cdot H$ (379.16).

*4.2.16. α-(3-Thioureido-1-adamantyl)sulfoacetic acid (**18**).* Obtained from 2-(3-hydroxy-1-adamantyl)sulfoacetic acid **2b** (0.29 g, 1.0 mmol), thiourea (0.23 g, 3.0 mmol), and TFA (2 mL) as described for **14** with prolonged (15 h) heating. Yield: 82% (0.27 g), white solid, mp 223–226 °C. Anal. Calcd for $C_{13}H_{20}N_2O_5S_2$ (348.44): C, 44.81; H, 5.79; N, 8.04. Found: C, 44.45; H, 5.58; N, 8.49. ^1H NMR (400 MHz, DMSO-d_6): δ=9.31 (s, 1H, $CONH_2$), 9.13 (s, 1H, $CONH_2$), 3.24 (s, 1H, CHCO), 2.15–1.40 (m, 14H, H^{Ad}) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=169.4 (CO), 164.5 (CS), 75.3 (*C*HCO), 54.2 (C^{Ad}), 44.8, 42.9, 42.8, 37.5 (CH_2^{Ad}), 36.6 (C^{Ad}), 34.5 (CH_2^{Ad}), 30.0 (CH^{Ad}) ppm.

*4.2.17. 5-[3-(α-Sulfocarboxymethyl)-1-adamantyl]uracil (**20**).* Obtained from 5-(3-carboxymethyl-1-adamantyl)uracil **19** (0.15 g, 0.5 mmol), H_2SO_4 (98%, 0.06 mL, 1.1 mmol), and TFAA (0.9 mL) as described for **2a** (method A). The residue formed after removal of TFAA was dissolved in 1 M NaOH (5 mL) and allowed to stay for 12 h at room temperature. The solid formed upon addition

of HCl was collected, washed with water, diethyl ether, and dried. Yield: 71% (0.14 g), white solid, mp >300 °C. Anal. Calcd for $C_{16}H_{20}N_2O_7S$ (384.41): C, 49.99; H, 5.24; N, 7.29. Found: C, 49.60; H, 5.51; N, 7.35. ^{1}H NMR (400 MHz, DMSO-d_6): δ=10.84 (br s, 1H, NH), 10.67–10.58 (m, 1H, NH), 6.85 (d, J=5.8 Hz, 1H, CH^{Pyr}), 3.14 (s, 1H, CHCO), 2.10–1.45 (m, 15H, H^{Ad}) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=169.7 (COOH), 163.4, 151.0 (C^{Pyr}), 136.3 (CH^{Pyr}), 119.7 (C^{Pyr}), 76.0 (*C*HCO), 42.5, 39.0, 38.9 (CH_2^{Ad}), 35.9, 35.6 (C^{Ad}), 34.8 (CH_2^{Ad}), 28.3 (CH^{Ad}) ppm. MS (ESI): m/z=384.9 $[M+H]^+$, for $C_{16}H_{20}N_2O_7S$ H (385.41).

*4.2.18. 5-[3-(α-Butylsulfamoylcarboxymethyl)-1-adamantyl]uracil (**21**).* Obtained from 5-(3-carboxymethyl-1-adamantyl)uracil **19** (0.10 g, 0.33 mmol), H_2SO_4 (98%, 0.06 mL, 1.1 mmol), and TFAA (0.9 mL) as described for **2a** (method A). The residue formed after removal of TFAA was dissolved in dry DMF (1 mL), and *n*-butylamine (0.2 mL, 2.0 mmol) was added. The mixture was stirred for 12 h at room temperature, diluted with water, acidified with HCl to pH 2, and allowed to stay at 0 °C for 48 h. The solid formed was collected, washed with water, and dried. Yield: 68% (0.10 g), white solid, mp >300 °C. Anal. Calcd for $C_{20}H_{29}N_3O_6S$ (439.53): C, 54.65; H, 6.65; N, 9.56. Found: C, 54.89; H, 6.72; N, 9.21. IR (KBr, cm^{-1}): 1710 (CO), 1156 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ=6.84 (br s, 1H, CH^{Pyr}), 3.12 (s, 1H, CHCO), 2.84–1.20 (m, 20H, H^{Ad}+$CH_2CH_2CH_2$), 0.87 (t, J=7.3 Hz, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=169.5 (COOH), 163.4, 150.9 (C^{Pyr}), 136.2 (CH^{Pyr}), 119.7 (C^{Pyr}), 76.5 (*C*HCO), 42.4, 38.9 (CH_2^{Ad}), 38.7 (NCH_2), 35.8, 35.5 (C^{Ad}), 34.8 (CH_2^{Ad}), 29.1 (NCH_2CH_2), 28.3 (CH^{Ad}), 19.1 (CH_2CH_3), 13.5 (CH_3) ppm.

4.3. X-ray crystallographic analysis

Crystals of compounds **6** and **10** suitable for X-ray analysis were grown at room temperature from 2-propanol solutions. The data were collected at room temperature [295(2) K] by using graphite monochromated Cu Kα (1.54179 Å) radiation, ω-scan mode. The WinGX standard procedure was applied for data reduction.[16] Two standard reflections were measured every 120 min as intensity control. No absorption correction was applied. The structure was solved and refined with the SHELX program.[17]

The non-hydrogen atoms were refined by using the anisotropic full matrix least-square procedure. The hydrogen atoms of **6** were located from a difference Fourier map and refined freely. For **10** all hydrogen atoms were placed in the calculated positions and allowed to ride on their parent atoms [C–H 0.93–0.98, NH 0.86 Å; U_{iso}=1.2 U_{eq}(parent atom)]. The isotropic displacement parameters for freely refined hydrogen atoms (**6**) are in the range of 0.05(1)–0.11 Å^2. Refinement was made against all reflections. Molecular geometry calculations were performed with the SHELX program, and the molecular graphics were prepared by using DIAMOND software.[18] The crystallographic data and structure refinement details are presented in Table 2.

Table 2
Crystal data and structure refinement details for **6** and **10**

Compound	**6**	**10**
CCDC #	859912	859911
Empirical formula	$C_{26}H_{32}N_2O_3S$	$C_{12}H_{16}O_5S\cdot C_5H_6N$
Crystal size, mm	0.05×0.07×0.1	0.02×0.03×0.1
T, K	295	295
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/n$	P-1
a, Å	15.468(2)	9.5931(12)
b, Å	9.3764(14)	10.230(4)
c, Å	17.277(3)	13.120(3)
α, β, γ	110.21(3)	109.61, 95.90, 111.57(2)
V, Å^3	2351.5(7)	1089.6(5)
Z	4	2
D_{calcd}, g/cm^{-3}	1.278	1.309
μ, mm	1.461	1.606
Θ range, °	3.31–70.95	3.70–71.91
Range of h, k, l	−18 to 17, 0–11, 0–21	−11 to 11, −12 to 11, 0–16
Reflections collected	4672	4478
Independent reflections	4530	4281
Observed reflections [$I>2\sigma(I)$]	2736	3638
$R(F^2)$	0.063	0.049
$Rw(F^2)$	0.15	0.14
Goodness of fit	1.024	1.026
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.208, −0.353	0.361, −0.270

4.4. Pharmacology

4.4.1. Cells and viruses. Vero cells culture (green monkey kidney cells) was grown in Eagle's medium (Institute of Poliomyelitis and Viral Encephalitides, Moscow, Russia) supplemented with 10% fetal calf serum ('PanEco', Moscow). Herpes simplex virus type 1 (strain KL 1, HSV-1) and type 2 (strain VN, HSV-2) were from the Laboratory of Virus Museum (Ivanovsky Institute of Virology, Moscow, Russia).

4.4.2. Cytotoxicity assays. Vero cells in 96-well microtiter plates were treated with different concentrations of the experimental drugs (1.4×10^5 cells in 185 μL of the medium per well). Cell cultures were incubated for 72 h. At the indicated time, the cells were colored with Trypan Blue, and the cell number was determined. The 50% minimum cytotoxic concentration (MCC_{50}) was defined as the compound concentration required reducing the cell number by 50%.

4.4.3. Antiviral assays. Vero cells were inoculated with HSV-1 or HSV-2 at an input of 0.1 PFU (plaque formation units) per cell and then incubated with a medium containing various concentrations of studied compounds for 48 h (95–100% virus-inducted cytopathicity in the untreated control). Antiviral activity was expressed as the compound concentration required to reduce virus-inducted cytopathicity by 50% (MIC_{50}) compared to untreated control.

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