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Synthesis of functionalized 5-(3-*R*-1-adamantyl)uracils and related compounds

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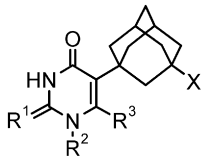
ABSTRACT

Efficient synthetic approaches to functionalized 5-(3-*R*-1-adamantyl)uracils and related compounds (R=OH, COOH, NH_2, etc.) are described. The selective hydroxylation of the adamantane tertiary C–H bonds in 5-(1-adamantyl)uracils with H_2SO_4 in trifluoroacetic anhydride is used as the key step. Subsequent electrophilic reactions of 5-(3-hydroxy-1-adamantyl)uracils with *N*- and *C*-nucleophiles in CF_3COOH, H_2SO_4 or H_2SO_4/AcOH media yielded derivatives with amide, amino, aryl, carboxy and thiourea groups in the adamantane core. The preliminary evaluation of the antiviral activity revealed that some of the synthesized species display moderate antiviral activity against HSV-1 (SI~20) in *Vero* cells.

1. Introduction

Functionalized uracil derivatives are essential units of many biological compounds and active components of many pharmaceuticals. Thus, new and improved synthetic routes to them continue to be important in modern organic chemistry. Among these compounds, the adamantane-containing ones are of special interest due to their known and versatile biological activity provided by adamantane unit itself. The combination of pyrimidine nucleic bases and adamantane units in one molecule has led to compounds with notable antiviral,[1] anticancer[2] and antibacterial[3] activities. In most cases, a ring-closure procedure has been employed allowing to obtain *C*-2-,[4] *C*-4-,[5] *C*-5-[2a–c,6,7] and *C*-6-[1a,2f,8] adamantylated pyrimidines. We have introduced a simple and efficient route to *C*-5-adamantylated hydroxy- and aminopyrimidines by reaction of the corresponding pyrimidines with 1-adamantanol in a trifluoroacetic acid (TFA) medium.[1b,9] Later on, this was extended to *C*-5-adamantylated uridine and 2-thiobarbituric acid.[10] *N*-1-Adamantylation can be performed by the Friedel–Crafts alkylation of, for instance, silylated uracil or thiouracil with 1-chloroadamantane.[11]

At the same time, to the best of our knowledge, no adamantylated pyrimidines bearing any functional group in the adamantane unit have been reported to date. Meanwhile, these compounds have potential for special pharmacological activity. Moreover, they seem to be useful in developing of novel conjugates of adamantanes and biogenic molecules. Here we report the synthesis of a number of 5-(3-*R*-1-adamantyl)uracils and related compounds **I** with functional groups in adamantane core and the preliminary evaluation of their *anti*-HSV activity.



I; R^1 = O, NH; R^2 = H, CH_2COOH, R^3 = H, OH
X = OH, NH_2, $NHC(S)NH_2$, NHC(O)R, Ar, COOH, CH_2COOH

2. Results and discussion

We supposed that the *C*-5-adamantane-functionalized pyrimidines **I** can be obtained either by a direct adamantylation of uracil and its congeners with pre-functionalized adamantanols in TFA, given the efficiency and operational simplicity of this reaction for 1-adamantanol,[1b,9b] or through a direct functionalization of the tertiary adamantane C–H bond in 5-(1-adamantyl)pyrimidines. Both

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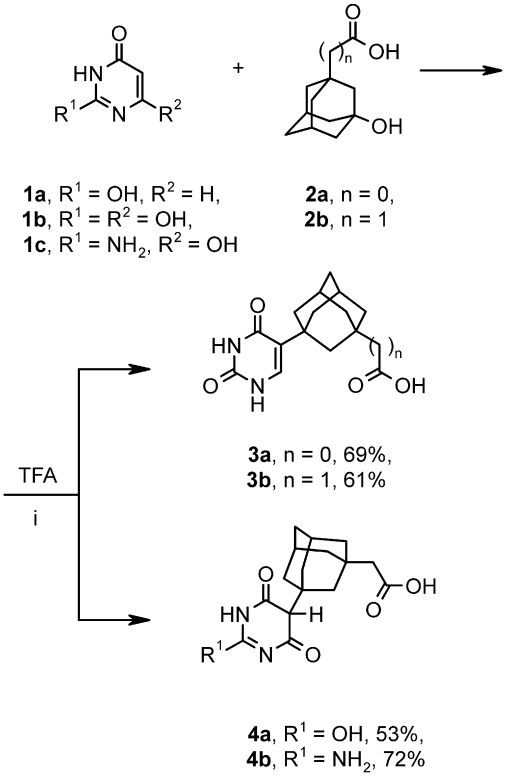
approaches have been explored in the present study. In course of the research we were interested mainly in the introduction of hydroxy, carboxy and amino groups into the tertiary position of the adamantane fragments of these molecules since these groups are well known in adamantane chemistry to possess high synthetic value.[12]

In the first place, we investigated the interaction of hydroxy- and aminopyrimidines **1** with the carboxylated adamantanols **2** in a TFA medium (Scheme 1). It was found that the addition of a catalytic amount of triflic acid into TFA had a dramatic effect on the reaction efficiency. Thus, uracil **1a** was selectively converted into the corresponding carboxy (**3a**) and carboxymethyl (**3b**) derivatives in 69 and 61% yields; whereas in the absence of catalyst, the yield of **3b** fell down to 41%, and the reaction between **1a** and **2a** didn't take place at all. Most probably, the electron withdrawing carboxylic group, when it is directly attached to the adamantane nucleus as in **2a**, suppresses the generation of the required carbocationic intermediate in neat TFA.



Scheme 1. Direct *C*-5-adamantylation of pyrimidines **1a**–**c** with pre-functionalized 1-adamantanols **2a**,**b**: (i) cat.=CF_3SO_3H for **3** and **4a** or $LiClO_4$ for **4b**.

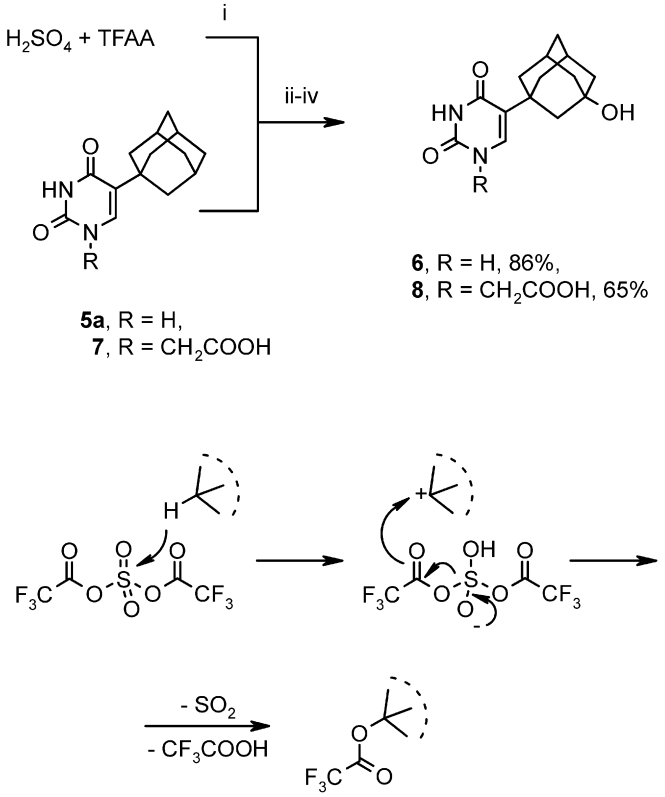
Under the similar conditions, barbituric acid **1b** and 2-amino-4,6-dihydroxypyrimidine **1c** were transformed into carboxymethylated adamantylpyrimidines **4a**,**b**. However, to obtain **4b** we used lithium perchlorate rather than triflic acid as a catalyst in order to avoid a possible pyrimidine base **1c** deactivation in the electrophilic substitution reaction due to protonation of the amino group.

Pyrimidines **1** possess nucleophilic sites of different types and, generally, could be alkylated at *C*-5, *O*- and *N*-atoms, so the substitution pattern in the heterocycles thus formed cannot be easily predicted. In our case, the *C*-5-location of the adamantane unit in **3** and **4** was unambiguously proved by ^1H and ^{13}C NMR experiments. In the ^1H NMR spectra of **3a**,**b** single aromatic and both NH signals appear, while the intensity of singlets at ~2.8 ppm (H-5) in the spectra of **4a**,**b** corresponds to only one proton in both cases. In the ^{13}C NMR spectra of **3** and **4** the chemical shifts of adamantane quaternary carbons (δ C^{1Ad} 34–39 ppm) are typical for C–C bond (compare to 51–53 ppm for C^{1Ad}–N[9b]). The signals of *C*-5-carbons bounded to an odd number of protons (^{13}C NMR with APT) at 61–62 ppm also support the structure suggested for **4a**,**b**.

It should be noted that 2-amino and 2-thiopyrimidines with H, Me or Cl at *C*-4-position as well as cytosine undergo the TFA-mediated adamantylation of the exocyclic NH_2 or SH-groups instead of the pyrimidine ring.[2d,e,10] It is reasonable to assume that the additional OH-groups at *C*-4 and *C*-6-positions of pyrimidines **2** facilitate the *C*-5-adamantylation of the heterocycle.

Adamantanols are widely used as starting compounds in adamantane chemistry, and hence selective hydroxylation of the adamantane tertiary C–H bond in 5-(1-adamantyl)pyrimidines seems rather promising for the synthesis of broad spectrum of novel functionalized adamantylpyrimidines. Previously, we have developed a simple and efficient protocol of *direct* adamantane tertiary C–H bond hydroxylation using 1.2–2 equiv of H_2SO_4 as an oxidant in trifluoroacetic acid anhydride (TFAA).[13] We decided to apply such conditions for selective oxidation of 5-(1-adamantyl)uracil **5a**, supposing also that the uracil unit in **5a** would tolerate them better than those severe conditions, which are commonly used for the functionalization of adamantanes.[12,14]

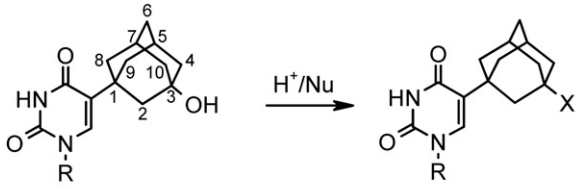
However, we have found that the oxidation of **5a** performed with the simultaneous mixing of components, as described earlier for adamantane,[13] leads to a mixture of compounds, which is hard to analyze. As the case may be, the presence of free sulfuric acid in the reaction mixture allows the formation of multiple side products. It is known that the interaction of sulfuric acid with the excess of TFAA results in formation of bis(trifluoroacetyl) sulfate,[15] which, evidently, could serve as an oxidizer in this process. Following the proposal, the mixture of sulfuric acid and TFAA was heated to reflux until a homogeneous solution was formed (approximately 2 h), then uracil **5a** was added, and the resultant mixture was heated for additional 4 h. After removal of the solvent and basic hydrolysis, the desired 5-(3-hydroxy-1-adamantyl)uracil **6** was isolated in 86% yield. Reaction conditions and possible mechanism are shown in Scheme 2. Under the same



Scheme 2. Direct hydroxylation of adamantyluracils **5a** and **7** in H_2SO_4–TFAA medium: (i) −Δ, 2 h; (ii) −Δ, 4 h; (iii) −1 N NaOH; (iv) −1 N HCl.

conditions, 5-(1-adamantyl)barbituric acid **5b** or 5-(1-adamantyl)-2-amino-4,6-dihydroxypyrimidine **5c** do not undergo the oxidation, probably due to their low solubility in TFAA. At the same time, the direct C–H bond hydroxylation with bis(trifluoroacetyl)sulfate in TFAA was successfully applied to 5-(1-adamantyl)-1-carboxymethyluracil **7**, which can be easily prepared from 1-carboxymethyluracil and 1-adamantanol in TFA. The desired 1-carboxymethyl-5-(3-hydroxy-1-adamantyl)uracil **8** was obtained in 65% yield.

As we stated earlier,[9b,16] TFA represents an excellent medium for the alkylation of *C*-, *N*- and *P*-nucleophiles with 1-adamantanols and other tertiary alcohols. We utilized this method for the adamantylation of different *N*- and *C*-nucleophiles (nitriles, urea, thiourea, arenes) with alcohols **6** and **8** (Scheme 3). Heating of **6** with phenol and **8** with toluene gave arenes **9** and **10** correspondingly; the Ritter reaction of **6** with chloroacetonitrile in TFA under reflux led to chloroacetamide **11** in good yield; while the adamantylated nicotinamide **12** was obtained in just a moderate yield even in the presence of $LiClO_4$ as a catalyst. The interaction of **6** with thiourea yielded the *N*-adamantylated thiourea **13**; the same synthesis performed with urea as a nucleophile gave a complex mixture of compounds. However, carrying out the latter reaction in presence of catalytic amount of CF_3SO_3H led exclusively to amine **14**. For the electrophilic reactions of hydroxylated adamantyluracil **6**, other acidic media were applied as well. Thus, under the Koch reaction conditions (H_2SO_4+HCOOH), alcohol **6** was converted into carboxylic acid **3a**, while conducting the Ritter reaction of **6** with chloroacetonitrile in the mixture of acetic and sulfuric acids gave chloroacetamide **11**. Scheme 3 summarizes the above mentioned derivatizations of adamantyl core in **6** and **8** by the electrophilic reactions in acidic medium.



6, R = H,
8, R = CH_2COOH

3a, R = H, X = COOH,
9, R = H, X = *p*-$C_6H_4(OH)$,
10, R = CH_2COOH, X = *p*-Tol,
11, R = H, X = $NHC(O)CH_2Cl$,
12, R = H, X = NHC(O)(3-Py),
13, R = H, X = $NHC(S)NH_2$,
14, R = H, X = NH_2

Entry	Alcohol	Conditions	Product (yield, %)
1	**6**	HCOOH, H_2SO_4, 0 °C → rt, 24 h	**3a** (84)
2	**6**	PhOH, TFA, 95 °C, 15 h	**9** (77)
3	**8**	$PhCH_3$, TFA, 95 °C, 15 h	**10** (91)
4	**6**	$ClCH_2CN$, TFA, 105 °C, 15 h	**11** (74)
5	**6**	$ClCH_2CN$, AcOH/H_2SO_4, 0 °C → rt, 24 h	**11** (69)
6	**6**	3-PyCN, TFA, 115 °C, 22 h	**12** (27)
7	**6**	thiourea, TFA, 95 °C, 15 h	**13** (91)
8	**6**	urea, 2% triflic acid/TFA, 115 °C, 10 h	**14** (88)

Scheme 3. Electrophilic reactions of 5-(3-hydroxy-1-adamantyl)uracils **6**, **8**.

All the novel compounds were characterized by their ^1H, ^{13}C NMR- and ESI mass-spectra. The additivity of ^{13}C substituents chemical shifts (SCS) was applied for the unambiguous assignment of signals of adamantane carbons in 1,3-disubstituted adamantanes **3**,**4**,**6**,**8**–**14** and as a verification of the selectivity of *C*-5-adamantylation of uracil and related compounds **1** (the adamantane carbon atoms numeration is showed in Scheme 3). To calculate these ^{13}C chemical shifts we employed adamantylpyrimidines **5a–c** and **7** as model compounds and SCS of HO, COOH, CH_2COOH, NH_2, $NHC(S)NH_2$, $NHC(O)CH_2Cl$, *p*-tolyl and *p*-hydroxyphenyl groups (Table 1). The SCS values reported in Table 1 were calculated by subtracting the chemical shifts of identical carbons in adamantane from that of corresponding monosubstituted adamantane.

Table 1
^{13}C Chemical shifts (δ C^{Ad}) of adamantylpyrimidines **5a–c**, **7** and ^{13}C substituents chemical shifts (SCS) in monosubstituted adamantanes (ppm; DMSO-d_6, 20 °C)

Compound	δ C^{Ad}			
	C^{α}	C^{β}	C^{γ}	C^{δ}
5a	35.3	39. 7	28.3	36.4
5b	37.8	39.9	28.2	35.9
5c	38.7	39.6	29.0	35.8
7	34.7	40.0	28.3	36.7
R	SCS^{Ad}, $\Delta\delta$			
HO	37.3	7.2	1.5	-2.1
NH_2	24.4	3.4	1.8	-1.6
CH_2COOH	3.2	3.8	-0.6	-1.7
$NHC(O)CH_2Cl$	22.6	2.7	0.2	-2.1
COOH	10.9	0.5	-0.7	-2.0
$NHC(S)NH_2$	24.6	5.1	1.1	-3.0
p-$C_6H_4(OH)$	6.3	4.9	-0.2	-1.8
p-Tol[a]	7.1	5.1	0.3	-1.3

[a] in $CDCl_3$.

The structure of **8** has been confirmed by X-ray analysis (Fig. 1). Suitable crystal of this compound was grown at room temperature from a solution of ethanol/H_2O (2:1).

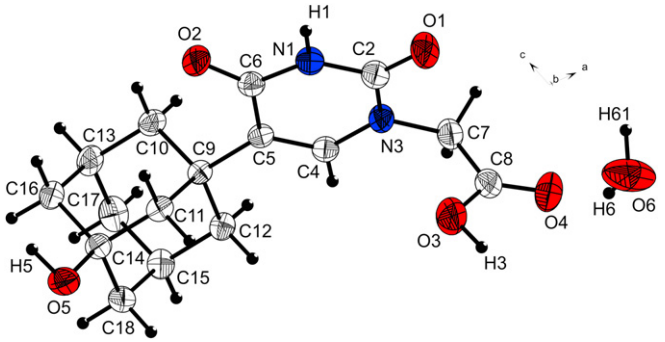


Figure 1. The asymmetric unit of **8**, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

The X-ray study revealed that in the crystal molecules of **8** form complicated system of hydrogen bonds, geometric parameters of which are presented in the Table 2. Each molecule is involved in one centrosymmetric dimer via N1–H1···O1^{iii} hydrogen bond and simultaneously in another dimer via hydrogen bond with participation of hydroxyl group O5–H5···O2^{iv}, extending into infinite ribbons along the axis *a*. Adjacent ribbons are connected by hydrogen bonds of the acids-groups and solvate water molecules O3–H3···O6^{i}, O6–H6···O4 thus generating an undulated sheet almost normally to *b* axis (Fig. 2). There are no significant direction-specific interactions between adjacent sheets.

Table 2
Geometric parameters of the hydrogen bonds of **8**

D-H···A	D-H/Å	H···A/Å	D···A/Å	D-H···A/°	Symmetry codes
O6–H6···O4	0.93(4)	1.98(4)	2.851(3)	155(4)	x, y, z
O3–H3···O6^{i}	0.99(3)	1.59(3)	2.574(2)	170(3)	(i) 1−x, −y, 1−z
O6-H61···O5^{ii}	0.89(4)	1.90(4)	2.763(2)	161(3)	(ii) 1+x, y, z
N1–H1···O1^{iii}	0.85(2)	1.97(2)	2.824(2)	176(2)	(iii) 1−x, −y, 2−z
O5–H5···O2^{iv}	1.01(3)	1.85(3)	2.832(2)	165(3)	(iv) −x, −y, 2−z

5-(3-Carboxy-1-adamantyl)- and 5-(3-amino-1-adamantyl)uracils (compounds **3a** and **14**) displayed the most pronounced antiviral activity towards HSV-1 and had a selectivity index (SI=MCC_{50}/MIC_{50}) of ca. 20. Nicotinamide **12** and thiourea **13** had the highest cytotoxicity while not revealing antiviral activity towards HSV-1, and for the latter, towards HSV-2 at subtoxic concentration in *Vero* cell culture.

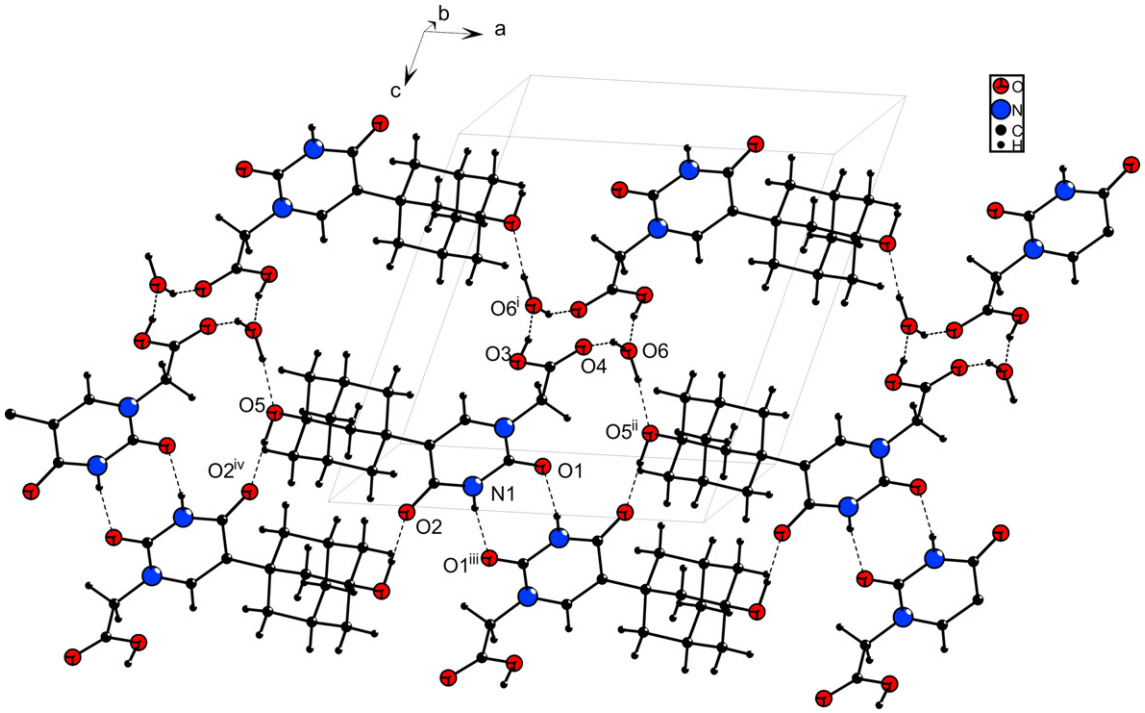


Figure 2. Part of the crystal structure of **8**, showing the formation of undulated sheets almost normal to *b* axis via strong hydrogen bonds N–H···O and O–H···O. Hydrogen bonds are shown as dashed lines.

The cytotoxicity and antiviral activity of the novel adamantylated pyrimidines were examined against herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) in *Vero* cells according to the previously reported method.[17] From the MIC_{50} and MCC_{50} values presented in Table 3, it appears that most of synthesized substances possess low cytotoxicity and display moderate antiviral activity, yet significantly inferior to the reference pharmaceutical Zovirax.

Table 3
Cytotoxicity and *anti*-HSV activity of adamantylpyrimidines **3a**, **6**, **8**, **11**–**14** in *Vero* cells culture (μg/cm^{-3})[a]

Compound	MCC_{50}[b]	HSV-1		HSV-2	
		MIC_{50}[c]	SI	MIC_{50}	SI
3a	1000	50	20	100	10
6	250	125	2	NA	
8	1000	100	10	500	2
11	500	100	5	50	10
12	250	NA		50	5
13	125	NA		NA	
14	1000	50	20	500	5
Zovirax	500	0.4	1250	0.2	2500

[a] The results represent data from three separate experiments, each of which was performed in duplicate. The variation of these results under standard operating procedures is below ±10%.
[b] MCC_{50}—minimum cytotoxic concentration causing 50% growth inhibition of *Vero* cells.
[c] MIC_{50}—minimum inhibitory concentration reducing the cytopatogenic effect of virus by 50%.

3. Conclusions

In conclusion, we have developed the effective approaches to adamantylated uracils and related compounds with various functional groups in the adamantane core. These compounds may be obtained (i) by interaction of hydroxy- and aminopyrimidines with 3-carboxy- or 3-carboxymethyl-1-adamantanols in TFA or (ii) via selective C–H bond hydroxylation of the bridgehead position of adamantane nucleus of 5-(1-adamantyl)uracils **5a** and **7** with bis-trifluoroacetylsulfate in TFAA medium. Electrophilic reactions of 5-(3-hydroxy-1-adamantyl)uracils **6**, **8** with *N*- and *C*-nucleophiles in acidic media (TFA, H_2SO_4, H_2SO_4/AcOH) were conducted to obtain adamantyluracils with amide, amino, aryl, carboxy and thiourea groups in the adamantane core. The examination of the antiviral activity demonstrated that most of synthesized compounds possess only moderate antiviral activity against HSV-1 and HSV-2.

4. Experimental

4.1. Synthesis

^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Avance 400 spectrometer and referenced to DMSO-d_6 (2.50 ppm for ^{1}H and 39.52 ppm for ^{13}C). Signals labelled with an asterisk * are close to one another and could not be attributed more

definitely without additional experiments. To assign the chemical shifts in the ^{1}H and ^{13}C NMR spectra the following symbols were used: H^R and C^R for hydrogen and carbon atoms of the pyrimidine (R=Pyr), adamantane (R=Ad), aryl (R=Ar) and pyridine (R=Py) fragments. ESI-MS analyses were performed using Agilent 1100 LC/MS instrument. Melting points are uncorrected. Analytical thin-layer chromatography was performed on Kieselgel 60 F_{254} precoated aluminium plates (Merck), spots were visualized under UV light (254 nm). Silica gel column chromatography was performed using Merck Kieselgel 60 0.040–0.063 mm. Chemicals were commercial grade and used without further purification. 3-Carboxy-1-adamantanol **2a**,[18] 3-carboxymethyl-1-adamantanol **2b**[19], 5-(1-adamantyl)pyrimidines **5a–c**,[1b,9] and 1-carboxymethyluracil[20] were prepared as described.

*4.1.1. General procedure for the synthesis of **3a**,**b**, **4a**.* A mixture of the corresponding pyrimidine **1a**,**b** (1.2 mmol) and the alcohol **2a**,**b** (1 mmol) in TFA (2 mL) in presence of a catalytic amount of CF_3SO_3H (0.02 mL) was kept for 12 h at 105±5 °C in the case of **2a** or at 95±5 °C in the case of **2b**. On completion of the reaction, the solvents were removed under reduced pressure. The resulting dark oil was treated with water (5 mL) and left overnight. The solid formed was filtered, washed with water (2×5 mL) and acetone (2×5 mL), dissolved in 1 N NaOH (5 mL) and filtered. The precipitate formed upon addition of concd HCl was collected, washed with water, Et_2O and dried.

*4.1.1.1. 5-(3-Carboxy-1-adamantyl)uracil (**3a**).* Compound **3a** was prepared from uracil **1a** and 3-carboxy-1-adamantanol **2a**, yield 0.20 g (69%); white solid. R_f 0.28 (33% EtOH in $CHCl_3$ (v/v)), mp >300 °C. ^{1}H NMR δ_H (DMSO-d_6): 10.83 (1H, s, NH^{Pyr}), 10.55 (1H, m, NH^{Pyr}), 6.95 (1H, d, J=5.89 Hz, H^{6Pyr}), 2.01 (2H, br s, CH^{Ad}), 1.95–1.40 (12H, m, CH_2^{Ad}). ^{13}C NMR δ_C (DMSO-d_6): 178.4 (COOH), 163.6 (CO^{Pyr}), 151.1 (CO^{Pyr}), 136.8 (C^{6Pyr}), 119.0 (C^{5Pyr}), 40.8 (C^{2Ad}), 40.4 (C^{3Ad}), 38.8 ($C^{8,9Ad}$), 38.0 ($C^{4,10Ad}$), 35.6 (C^{1Ad}), 34.5 (C^{6Ad}), 27.9 ($C^{5,7Ad}$). ESI-MS: m/z=290.9 $[M+H]^+$ for $C_{15}H_{18}N_2O_4$+H (290.32). Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 62.11; H, 6.22; N, 9.83.

*4.1.1.2. 5-(3-Carboxymethyl-1-adamantyl)uracil (**3b**).* Compound **3b** was prepared from uracil **1a** and 3-carboxymethyl-1-adamantanol **2b**, yield 0.19 g (61%); white solid. R_f 0.30 (33% EtOH in $CHCl_3$ (v/v)), mp >300 °C. ^{1}H NMR δ_H (DMSO-d_6): 10.80 (1H, br s, NH^{Pyr}), 10.55 (1H, m, NH^{Pyr}), 6.86 (1H, d, J=5.80 Hz, H^{6Pyr}), 2.02 (2H, br s, CH^{Ad}), 1.97 (2H, s, CH_2COOH), 1.85–1.40 (12H, m, CH_2^{Ad}). ^{13}C NMR δ_C (DMSO-d_6): 172.4 (COOH), 163.4 (CO^{Pyr}), 150.9 (CO^{Pyr}), 136.3 (C^{6Pyr}), 119.3 (C^{5Pyr}), 48.2 (CH_2COOH), 44.2 (C^{2Ad}), 41.1 ($C^{4,10Ad}$), 38.8 ($C^{8,9Ad}$), 35.7 (C^{6Ad}), 34.8 (C^{1Ad}), 32.5 (C^{3Ad}), 28.3 ($C^{5,7Ad}$). ESI-MS: m/z=327.0 $[M+Na]^+$ for $C_{16}H_{20}N_2O_4$+Na (327.35). Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.23; H, 6.55; N, 9.38.

*4.1.1.3. 5-(3-Carboxymethyl-1-adamantyl)barbituric acid (**4a**).* Compound **4a** was prepared from barbituric acid **1b** and 3-carboxymethyl-1-adamantanol **2b**, yield 0.17 g (53%); white solid. R_f 0.28 (10% EtOH in $CHCl_3$ (v/v)), mp=257–259 °C. ^{1}H NMR δ_H (DMSO-d_6): 11.11 (2H, s, NH^{Pyr}), 2.72 (1H, s, H^{5Pyr}), 2.02 (2H, br s, CH^{Ad}), 1.97 (2H, s, CH_2COOH), 1.70–1.35 (12H, m, CH_2^{Ad}). ^{13}C NMR δ_C (DMSO-d_6): 172.3 (COOH), 168.7 ($CO^{4,6Pyr}$), 151.5 (CO^{2Pyr}), 61.1 (C^{5Pyr}), 47.9 (CH_2COOH), 44.5 (C^{2Ad}), 40.7 ($C^{4,10Ad}$), 39.2 ($C^{8,9Ad}$), 38.5 (C^{1Ad}), 35.2 (C^{6Ad}), 33.1 (C^{3Ad}), 28.5 ($C^{5,7Ad}$). ESI-MS m/z=358.9 $[M+K]^+$ for $C_{16}H_{20}N_2O_5$+K (359.44). Anal. Calcd for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.74. Found: C, 59.87; H, 6.23; N, 8.46.

*4.1.2. 2-Amino-5-(3-carboxymethyl-1-adamantyl)-4,6-dihydroxypyrimidine (**4b**).* A mixture of 2-amino-4,6-dihydroxypyrimidine (0.38 g, 3 mmol) **1c** and 3-carboxymethyl-1-adamantanol **2b** (0.42 g, 2 mmol) in TFA (4 mL) in presence of a catalytic amount of lithium perchlorate was heated for 18 h at 95±5 °C. On completion of the reaction, solvents were removed at reduced pressure, residue was treated with water (10 mL) and filtrate left cooled overnight. The precipitate formed was collected and dried. Yield: 0.40 g (62%); colourless needle-shaped crystals. R_f 0.21 (10% EtOH in $CHCl_3$ (v/v)), mp >300 °C. ^{1}H NMR δ_H (DMSO-d_6): 2.89 (s, 1H, H^{5Pyr}), 2.03 (br s, 2H, CH^{Ad}), 1.98 (s, 2H, CH_2COOH), 1.75–1.40 (m, 12H, CH_2^{Ad}). ^{13}C NMR δ_C (DMSO-d_6): 172.2 (COOH), 168.4 ($CO^{4,6Pyr}$), 155.3 (CO^{2Pyr}), 61.8 (C^{5Pyr}), 47.7 (CH_2COOH), 44.4 (C^{2Ad}), 40.5 ($C^{4,10Ad}$), 39.1 (C^{1Ad}), 38.9 ($C^{8,9Ad}$), 35.0 (C^{6Ad}), 33.0 (C^{3Ad}), 28.4 ($C^{5,7Ad}$). ESI-MS: m/z=341.9 $[M+Na]^+$ for $C_{16}H_{21}N_3O_4$+Na (342.36). Anal. Calcd for $C_{16}H_{21}N_3O_4$: C, 60.18; H, 6.63; N, 13.16. Found: C, 60.27; H, 6.51; N, 13.47.

*4.1.3. 5-(1-Adamantyl)-1-carboxymethyluracil (**7**).* A mixture of 1-carboxymethyluracil (0.26 g, 1.5 mmol) and 1-adamantanol (0.29 g, 1.9 mmol) in TFA (2 mL) was heated for 12 h at 95±5 °C. On completion of the reaction, solvents were removed at reduced pressure, the residue was dissolved in 1 N NaOH (10 mL) and filtered. The precipitate formed upon addition of concd HCl to the filtrate was collected, washed with water and dried. Yield 0.25 g (55%); white solid. R_f 0.20 (10% EtOH in $CHCl_3$ (v/v)), mp >300 °C. ^{1}H NMR δ_H (DMSO-d_6): 11.12 (1H, s, NH^{Pyr}), 7.22 (1H, s, H^{6Pyr}), 4.40 (2H, s, CH_2COOH), 1.93 (3H, br s, CH^{Ad}), 1.88–1.54 (12H, m, CH_2^{Ad}). ^{13}C NMR δ_C (DMSO-d_6): 170.0 (COOH), 163.4 (CO^{Pyr}), 151.0 (CO^{Pyr}), 141.5 (C^{6Pyr}), 120.9 (C^{5Pyr}), 49.1 (CH_2COOH), 40.0 ($C^{2,8,9Ad}$), 36.7 ($C^{4,6,10Ad}$), 34.7 (C^{1Ad}), 28.3 ($C^{3,5,7Ad}$). ESI-MS: m/z=342.8 $[M+K]^+$ for $C_{16}H_{20}N_2O_4$+K (343.44). Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20. Found: C, 62.18; H, 6.52; N, 9.55.

*4.1.4. General procedure for the synthesis of **6**, **8**.* A mixture of TFAA (3.4 mL, 24 mmol) and 98% sulfuric acid (0.24 mL, 4.4 mmol) was heated to reflux for 2 h at 60–65 °C. The adamantyluracil (**5a** or **7**, 2 mmol) was added to the formed homogeneous solution and the resulting mixture was heated for 4 h at 70–75 °C. On completion of the reaction, solvents were removed at reduced pressure, the residue was dissolved in 1 N NaOH (10 mL), heated for 2 h at 45–50 °C, the basic solution was cooled to rt and filtered. The precipitate formed upon addition of concd HCl to the filtrate was collected, washed with water and dried.

*4.1.4.1. 5-(3-Hydroxy-1-adamantyl)uracil (**6**).* Compound **6** was prepared from **5a**, yield 0.45 g (86%); white solid. R_f 0.70 (33% EtOH in $CHCl_3$ (v/v)), mp >300 °C. ^{1}H NMR δ_H (DMSO-d_6): 10.87 (1H, s, NH^{Pyr}), 10.59 (1H, m, NH^{Pyr}), 6.87 (1H, d, J=5.89 Hz, H^{6Pyr}), 4.41 (1H, br s, OH), 2.11 (2H, br s, CH^{Ad}), 1.90–1.40 (12H, m, CH_2^{Ad}). ^{13}C NMR δ_C (DMSO-d_6): 163.5 (CO^{Pyr}), 150.9 (CO^{Pyr}), 136.3 (C^{6Pyr}), 118.8 (C^{5Pyr}), 66.7 (C^{3Ad}), 47.5 (C^{2Ad}), 44.6 ($C^{4,10Ad}$), 38.5 ($C^{8,9Ad}$), 37.3 (C^{1Ad}), 35.3 (C^{6Ad}), 30.0 ($C^{5,7Ad}$). ESI-MS: m/z=284.6 $[M+Na]^+$ for $C_{14}H_{18}N_2O_3$+Na (285.31). Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68. Found: C, 64.25; H, 6.98; N, 10.31.

*4.1.4.2. 5-(3-Hydroxy-1-adamantyl)-1-carboxymethyuracil (**8**).* Compound **8** was prepared from **7**, yield 0.42 g (65%); colourless crystals. R_f 0.26 (33% EtOH in $CHCl_3$ (v/v)), mp >300 °C. ^{1}H NMR δ_H (DMSO-d_6): 11.16 (1H, s, NH^{Pyr}), 7.27 (1H, s, H^{6Pyr}), 4.42 (3H, br s, CH_2COOH+OH), 2.13 (2H, br s, CH^{Ad}), 2.10–1.40 (12H, m, CH_2^{Ad}). ^{13}C NMR δ_C (DMSO-d_6): 169.7 (COOH), 163.0 (CO^{Pyr}), 150.5 (CO^{Pyr}), 141.1 (C^{6Pyr}), 119.5 (C^{5Pyr}), 66.7 (C^{3Ad}), 48.7 (CH_2COOH), 47.7 (C^{2Ad}), 44.6 ($C^{4,10Ad}$), 38.7 ($C^{8,9Ad}$), 37.6 (C^{1Ad}), 35.2 (C^{6Ad}), 30.0 ($C^{5,7Ad}$). ESI-MS: m/z=343.0 $[M+Na]^+$ for $C_{16}H_{20}N_2O_5$+Na (343.35). Anal. Calcd for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.74. Found: C, 60.08; H, 6.36; N, 8.68.

Crystal data. $C_{16}H_{20}N_2O_5 \cdot H_2O$, M=320.35×18.02, monoclinic, a=11.7625(11), b=11.4654(18), c=12.320(2), β=108.009(11)°,

V=1580.1(4) Å^3, space group $P2_1/c$, Z=4, D_c=1.422 g cm^{-3}, μ(Mo Kα)=0.917.

Data collection. X-ray diffraction data were collected from a colourless crystal (size 0.1×0.1×0.4 mm) on an Enraf Nonius CAD4 diffractometer using graphite monochromated Cu Kα (1.54179 Å) radiation at room temperature [293(2) K], ω-scan mode at 295 K. R=0.038 for 2442 independent observed reflections with [$I>2\sigma(I)$]. The WinGX standard procedure was applied for data reduction.[21] Two standard reflections were measured every 120 min as intensity control. No absorption correction was applied.

Structure analysis and refinement. The structure was solved and refined with SHELX program.[22] The non-hydrogen atoms were refined using the anisotropic full matrix least squares procedure. The molecular graphics were prepared using DIAMOND.[23] The H atoms attached to carbons were placed in the calculated positions and allowed to ride on their parent atoms (C–H 0.97–0.98; U_{iso}=1.2U_{eq}(parent atom)). H atoms attached to nitrogen and oxygen were determined from a difference Fourier synthesis and refined freely. The isotropic displacement parameters for freely refined hydrogen atoms are 0.05–0.14(1) Å^2. Refinement was made against all reflection. The threshold expression of $F^2>2\sigma(F^2)$ is used for calculation R-factor, the final value of which is 0.038.

Crystallographic data (excluding structure factors) for the structure **8** have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication nos. CCDC 732269. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

*4.1.5. General procedure for the synthesis of **9**–**14** in TFA medium.* The corresponding adamantanol (**6** or **8**, 1 mmol) and a nucleophilic reagent were heated in TFA (2 mL) (in the case of adamantylation of nicotinic acid nitrile and urea $LiClO_4$ or CF_3SO_3H were added as a catalyst, correspondingly). On completion of the reaction, solvents were removed at reduced pressure, the residue was treated with water (5 mL) and left overnight. Further workup procedure for individual uracils was as follows.

*4.1.5.1. 5-(3-p-Hydroxyphenyl-1-adamantyl)uracil (**9**).* Compound **9** was prepared from **6** and phenol (0.12 g, 1.2 mmol) for 15 h at 95±5 °C. The precipitate formed on completion of the reaction was filtered off, washed with warm water and dried. Yield 0.26 g (77%); white solid. R_f 0.21 (10% EtOH in $CHCl_3$ (v/v)), mp >300 °C. ^{1}H NMR δ_H (DMSO-d_6): 10.88 (1H, s, NH^{Pyr}), 10.61 (1H, m, NH^{Pyr}), 7.12 (2H, d, J=8.71 Hz, H^{Ar}), 6.94 (1H, d, J=5.89 Hz, H^{6Pyr}), 6.67 (2H, d, J=8.70 Hz, H^{Ar}), 2.13 (2H, br s, CH^{Ad}), 2.00–1.60 (12H, m, CH$_2^{Ad}$). ^{13}C NMR δ_C (DMSO-d_6): 163.5 (CO^{Pyr}), 155.1 (C^{Ar}), 151.0 (CO^{Pyr}), 140.9 (C^{Ar}), 136.5 (C^{6Pyr}), 125.6 (CH^{Ar}), 119.4 (C^{5Pyr}), 114.8 (CH^{Ar}), 45.3 (C^{2Ad}), 42.2 (C^{4,10Ad}), 38.8 (C^{8,9Ad}), 35.7* (C^{3Ad}), 35.6* (C^{1Ad}), 35.2 (C^{6Ad}), 28.7 (C^{5,7Ad}). ESI-MS: m/z=339.3 [M+H]$^+$ for $C_{20}H_{22}N_2O_3$+H (339.41). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 71.15; H, 6.51; N, 8.44.

*4.1.5.2. 5-(3-p-Tolyl-1-adamantyl)-1-carboxymethyluracil (**10**).* Compound **10** was prepared from **8** and toluene (0.14 mL, 1.2 mmol) for 15 h at 95±5 °C. The precipitate formed on completion of the reaction was filtered off, washed with water and dried. Yield 0.18 g (91%); white solid. R_f 0.23 (33% EtOH in $CHCl_3$ (v/v)), mp=290 °C. ^{1}H NMR δ_H (DMSO-d_6): 11.19 (1H, s, NH^{Pyr}), 7.32 (1H, s, H^{6Pyr}), 7.23 (2H, d, J=8.11 Hz, H^{Ar}), 7.09 (2H, d, J=8.02 Hz, H^{Ar}), 4.42 (2H, br s, C*H*$_2$COOH), 2.30–1.60 (17H, m, CH^{Ad}+CH$_2^{Ad}$+CH$_3$). ^{13}C NMR δ_C (DMSO-d_6): 169.9 (COOH), 163.3 (CO^{Pyr}), 150.7 (CO^{Pyr}), 147.6 (AdC^{Ar}), 141.4 (C^{6Pyr}), 134.7 (CH$_3$C^{Ar}), 128.9 (CH$_3$CCH^{Ar}), 124.8 (AdCCH^{Ar}), 120.2 (C^{5Ar}), 49.0 (*C*H$_2$COOH), 45.5 (C^{2Ad}), 42.2 (C^{4,10Ad}), 39.0 (C^{8,9Ad}), 36.3* (C^{1Ad}), 35.6 (C^{6Ad}), 35.6* (C^{3Ad}), 28.8 (C^{5,7Ad}), 20.7 (CH$_3$). ESI-MS: m/z=395.2 [M+H]$^+$ for $C_{23}H_{26}N_2O_4$+H (395.47). Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 70.20; H, 6.69; N, 7.29.

*4.1.5.3. 5-(3-Chloromethylcarbamoyl-1-adamantyl)uracil (**11**).* Compound **11** was prepared from **6** and chloroacetonitrile (0.21 g, 2 mmol) for 15 h at 105±5 °C. The solid formed on completion of the reaction was collected, dissolved in 1 N NaOH (5 mL) at rt and filtered off immediately. The basic water solution was made acidic with concd HCl, the resulting precipitate was collected, washed with water and dried. Yield 0.25 g (74%); white solid. R_f 0.38 (10% EtOH in $CHCl_3$ (v/v)), mp >300 °C. ^{1}H NMR δ_H (DMSO-d_6): 10.89 (1H, s, NH^{Pyr}), 10.61 (1H, m, NH^{Pyr}), 7.70 (1H, s, AdNH), 6.88 (1H, d, J=5.89 Hz, H^{6Pyr}), 3.94 (2H, s, CH$_2$Cl), 2.11 (2H, br s, CH^{Ad}), 2.08–1.50 (12H, m, CH$_2^{Ad}$). ^{13}C NMR δ_C (DMSO-d_6): 164.9 (CONH), 163.4 (CO^{Pyr}), 150.9 (CO^{Pyr}), 136.5 (C^{6Pyr}), 118.6 (C^{5Pyr}), 51.9 (C^{3Ad}), 43.5 (CH$_2$Cl), 43.0 (C^{2Ad}), 40.0 (C^{4,10Ad}), 38.5 (C^{8,9Ad}), 35.9 (C^{6Ad}), 35.3 (C^{1Ad}), 28.8 (C^{5,7Ad}). ESI-MS: m/z=338.2 [M+H]$^+$ for $C_{16}H_{20}ClN_3O_3$+H (338.81). Anal. Calcd for $C_{16}H_{20}ClN_3O_3$: C, 56.89; H, 5.97; N, 12.44. Found: C, 56.97; H, 6.08; N, 12.13.

*4.1.5.4. 5-(3-Nicotinamido-1-adamantyl)uracil (**12**).* Compound **12** was prepared from **6** and nicotinic acid nitrile (0.21 g, 2 mmol) for 22 h at 115±5 °C. The solid formed on completion of the reaction was filtered off and dissolved in 1 N NaOH (5 mL) at rt. The basic water solution was neutralized to pH 7–8 with diluted HCl, the resulting precipitate was collected, washed with water and dried. Yield 0.10 g (27%); white solid. Mp decomposes >210 °C. ^{1}H NMR δ_H (DMSO-d_6): 10.84 (1H, br s, NH^{Pyr}), 8.91 (1H, br s, H^{Py}), 8.67 (1H, m, H^{Py}), 8.12 (1H, m, H^{Py}), 7.95 (1H, br s, AdNH), 7.44 (1H, m, H^{Py}), 6.92 (1H, s, H^{6Pyr}), 2.30–1.40 (14H, m, CH^{Ad}+CH$_2^{Ad}$). ^{13}C NMR δ_C (DMSO-d_6): 164.6 (CO^{Pyr}), 163.5 (NHCO), 151.4 (CO^{Pyr}), 150.9 (CH^{Py}), 148.5 (CH^{Py}), 136.6 (C^{6Pyr}), 135.1 (CH^{Py}), 131.2 (CH^{Py}), 123.2 (C^{Py}), 118.7 (C^{5Pyr}), 52.5 (C^{3Ad}), 43.3 (C^{2Ad}), 40.1 (C^{4,10Ad}), 38.6 (C^{8,9Ad}), 36.0 (C^{6Ad}), 35.3 (C^{1Ad}), 29.0 (C^{5,7Ad}). ESI-MS: m/z=366.7 [M+H]$^+$ for $C_{20}H_{22}N_4O_3$+H (367.42). Anal. Calcd for $C_{20}H_{22}N_4O_3$: C, 65.56; H, 6.05; N, 15.29. Found: C, 65.43; H, 6.11; N, 15.41.

*4.1.5.5. 5-(3-Thioureido-1-adamantyl)uracil (**13**).* Compound **13** was prepared from **6** and thiourea (0.19 g, 2.5 mmol) for 15 h at 95±5 °C. The solid formed on completion of the reaction was filtered off, washed with water, dried. Yield 0.29 g (91%); white solid. R_f 0.55 (33% EtOH in $CHCl_3$ (v/v)), mp >300 °C. ^{1}H NMR δ_H (DMSO-d_6): 10.91 (1H, s, NH^{Pyr}), 10.75 (1H, m, NH^{Pyr}), 9.66 (1H, s, NH), 9.20 (2H, s, NH$_2$), 6.99 (1H, d, J=5.97 Hz, H^{6Pyr}), 2.27–1.52 (14H, m, CH^{Ad}+CH$_2^{Ad}$). ^{13}C NMR δ_C (DMSO-d_6): 163.9 (CS), 163.3 (CO^{Pyr}), 150.8 (CO^{Pyr}), 137.0 (C^{6Pyr}), 117.9 (C^{5Pyr}), 53.5 (C^{3Ad}), 45.4 (C^{2Ad}), 42.4 (C^{4,10Ad}), 37.7 (C^{9,10Ad}), 36.8 (C^{1Ad}), 34.4 (C^{6Ad}), 29.7 (C^{5,7Ad}). ESI-MS: m/z=321.1 [M+H]$^+$ for $C_{15}H_{20}N_4O_2S$+H (321.42). Anal. Calcd for $C_{15}H_{20}N_4O_2S$: C, 56.23; H, 6.29; N, 17.49. Found: C, 56.09; H, 6.33; N, 17.27.

*4.1.5.6. 5-(3-Amino-1-adamantyl)uracil (**14**).* Compound **14** was prepared from **6** and urea (0.12 g, 2 mmol) for 10 h at 115±5 °C. The solid formed on completion of the reaction was neutralized to pH 7–8 with 20% aq NaOH solution. The resulting precipitate was collected on a filter, washed with water (2 mL) and dried. Yield 0.23 g (88%); white solid. R_f 0.22 (33% EtOH in $CHCl_3$ (v/v)), mp >300 °C. ^{1}H NMR δ_H (DMSO-d_6): 10.97 (1H, s, NH^{Pyr}), 10.78 (1H, br s, NH^{Pyr}), 7.95 (2H, br s, NH$_2$), 6.96 (1H, d, J=5.97 Hz, H^{6Pyr}), 2.19 (2H, br s, CH^{Ad}), 2.10–1.50 (12H, m, CH$_2^{Ad}$). ^{13}C NMR δ_C (DMSO-d_6): 163.5 (CO^{Pyr}), 150.8 (CO^{Pyr}), 136.9 (C^{6Pyr}), 117.6 (C^{5Pyr}), 51.6 (C^{3Ad}), 42.1 (C^{2Ad}), 39.9 (C^{4,10Ad}), 38.0 (C^{8,9Ad}), 35.8 (C^{1Ad}), 34.6 (C^{6Ad}), 28.5 (C^{5,7Ad}). ESI-MS: m/z=261.6 [M+H]$^+$ for $C_{14}H_{19}N_3O_2$+H (262.33).

Anal. Calcd for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.25; H, 7.18; N, 16.22.

*4.1.6. Synthesis of **3a** and **11** under Koch and Ritter reaction conditions.*

*4.1.6.1. 5-(3-Carboxy-1-adamantyl)uracil (**3a**).* A suspension of **6** (1.05 g, 4 mmol) in 98% sulfuric acid (10 mL) was cooled to 0 °C. Formic acid (98%, 1 mL, 26.5 mmol) was added dropwise over 1 h and reaction mixture was stirred for 24 h at rt. On completion of the reaction the solution was poured on ice, formed precipitate was filtered off, washed with water and dried. Yield 0.97 g (84%).

*4.1.6.2. 5-(3-Chloromethylcarbamoyl-1-adamantyl)uracil (**11**).* To the mixture of **6** (0.93 g, 3.55 mmol) and $ClCH_2CN$ (0.9 ml, 14.2 mmol) glacial acetic acid (1.15 mL) was added, and the resulting mixture was cooled to 0–3 °C. H_2SO_4 (1.15 mL, 22 mmol) was added dropwise keeping the temperature below 10 °C. The resulting solution was stirred for 24 h at rt and poured into ice water (15 mL), the formed precipitate was filtered off, washed with water and dried. Yield 0.83 g (69%).

4.2. Pharmacology

Cells. *Vero* cells culture (green monkey kidney cells) was grown in Eagle's medium (Institute of Poliomyelitis and Viral Encephalitides, Moscow, Russia) supplemented with 10% foetal calf serum ('PanEco', Moscow).

Viruses. 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).

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 coloured 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%.

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 adamantylated pyrimidines 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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References and notes

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