Tetrahedron xxx (2014) 1–8

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of acyclic nucleoside analogues based on 1,2,4-triazolo[1,5-*a*]pyrimidin-7-ones by one-step Vorbrüggen glycosylation

Igor A. Khalymbadzha [a], Tatyana S. Shestakova [a], Julia O. Subbotina [a,b], Oleg S. Eltsov [a], Alexandra A. Musikhina [a], Vladimir L. Rusinov [a], Oleg N. Chupakhin [a], Inna L. Karpenko [c], Maxim V. Jasko [c], Marina K. Kukhanova [c], Sergey L. Deev [a,*]

[a] *Ural Federal University, 19 Mira Street, Ekaterinburg 620002, Russia*
[b] *I.Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 22 S. Kovalevskoy Street, Ekaterinburg 620219, Russia*
[c] *Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, 32 Vavilov Street, Moscow 119991, Russia*

ARTICLE INFO

Article history:
Received 14 August 2013
Received in revised form 5 December 2013
Accepted 20 December 2013
Available online xxx

Keywords:
Acyclovir analogues
1,2,4-Triazolo[1,5-*a*]pyrimidine-7-one
TMSOTf
Vorbrüggen glycosylation
Herpes simplex virus
Regioselectivity
Transglycosylation

ABSTRACT

New acyclovir analogues were obtained by reaction of 1,2,4-triazolo[1,5-*a*]pyrimidin-7-ones **4a**–**i** with (2-acetoxyethoxy)methyl acetate **5** in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as catalyst (Vorbrüggen procedure). Coupling between compounds **4a**–**f** and **5** led to a mixture of N3- and N4-isomers **6** and **7**, respectively. On the contrary, the reaction of compounds **4g**–**i** with **5** proceeded selectively with formation of N3-isomers only. It was found that the ratio of **6a**–**f** and **7a**–**f** depends on the presence or the absence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA). Glycosylated products **6a**–**f** and **7a**–**f** underwent reversible isomerization under TMSOTf treatment. The ratio of glycosylated products of the coupling reaction between **4** and **5** was thermodynamically controlled. A similar reaction occurred if $ZnCl_2$ was chosen as a catalyst, although lower yields of the acyclic analogues of nucleosides were observed. The glycosylation of other purines (adenine and guanine) can be achieved via the non-BSA modification of the Vorbrüggen procedure.

1. Introduction

Derivatives of 1,2,4-triazolo[1,5-*a*]pyrimidines represent the core for many biologically active compounds.[1] Inclusion of an *N*-alkyl or ribofuranosyl fragment in the structure of heterocycles of this class can be used to design antiviral and anticancer compounds. For example, *N*3-benzyl-1,2,4-triazolo[1,5-*a*]pyrimidine derivate **1** was described as potent growth inhibitor in a PTEN deficient cancer cell line (Fig. 1).[2] Compound **2**, bearing a butyl moiety, with a terminal hydroxyl group linked to the azine cycle showed an antiherpetic activity. This compound suppressed efficiently the replication of herpes simplex virus (HSV) in cell cultures.[3] Ribosylated 1,2,4-triazolo[1,5-*a*]pyrimidin-7-ones **3** exhibited a moderate activity against the rhinovirus comparable with ribavirin.[4]

Considering the therapeutic potential of nucleoside analogues based on 1,2,4-triazolo[1,5-*a*]pyrimidin-7-ones, the development of new efficient and easy to control synthetic routines to obtain them became our current interest. Continuing our efforts to find new potent inhibitors of HSV replication we have synthesized a series of new acyclic analogues of nucleosides based on 1,2,4-triazolo[1,5-*a*]pyrimidin-7-ones **4a**–**i**.

2. Results and discussion

Nucleoside analogues based on 1,2,4-triazolo[1,5-*a*]pyrimidines are typically prepared via coupling of NH-heterocycles with ribose derivatives. Synthetic method, a so called 'one-pot' protocol of

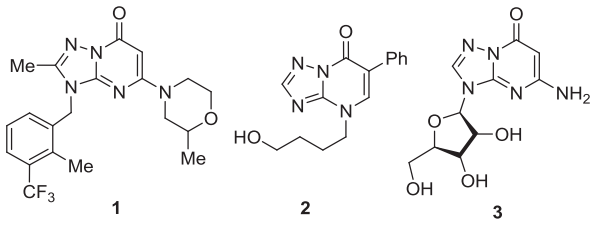


Fig. 1. *N*-Substituted 1,2,4-triazolo[1,5-*a*]pyrimidines with antiviral and anticancer activity.

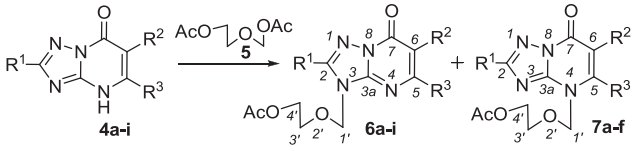
* Corresponding author. Tel.: +7 343 375 4501; fax: +7 343 374 0458; e-mail address: deevsl@yandex.ru (S.L. Deev).

0040-4020/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tet.2013.12.051

Vorbrüggen glycosylation, is one of the most convenient procedures to obtain nucleosides and their analogues.[5]

Previously, we have described an example of successful ribosylation of heterocycles **4d**–**f** via the Vorbrüggen method, although the mechanistic details of the reaction and its dependency on the reaction conditions were not investigated.[6] Herein, we present a study on the mechanism of Vorbrüggen glycosylation of 1,2,4-triazolo[1,5-*a*]pyrimidin-7-ones **4a**–**i** with (2-acetoxyethoxy) methyl acetate **5** under varied reaction conditions (Table 1). The introduction of acetate **5** into a coupling reaction with NH-heterocycles enables the acquisition of the analogues of acyclovir, which is still considered the gold standard for HSV therapy.[7] Altogether, two methods (A and B) were employed. In method A, the reaction mixture in MeCN was treated with BSA, the silylation reagent, and TMSOTf, the catalyst for glycosylation. The coupling between compounds **4a**–**i** and **5** was also observed if a mixture of reagents in MeCN was treated with TMSOTf only (method B).

Table 1
Coupling reaction of **4a**–**i** and **5a**



4,6,7	a	b	c	d	e	f	g	h	i
R^1	H	Me	SMe	H	Me	SMe	H	Me	SMe
R^2	H	H	H	Ph	Ph	Ph	H	H	H
R^3	Me	Me	Me	H	H	H	Ph	Ph	Ph

Entry	Heterocycle	Method[a]	Ratio **6**/**7**[b]	Yield[c] %
1	**4a**	A	62:38	56
		B	100:0	60
2	**4b**	A	51:49	59
		B	75:25	49
3	**4c**	A	52:48	63
		B	94:6	80
4	**4d**	A	5:95	86
		B	75:25	48
5	**4e**	C	4:96	40
		A	40:60	70
		B	70:30	43
		C	8:92	27
6	**4f**	A	4:96	59
		B	60:40	46
		C	0:100	28
7	**4g**	A	100:0	39
		B	100:0	41
8	**4h**	A	100:0	75
		B	100:0	24
9	**4i**	A	100:0	35
		B	100:0	34

[a] Legends for reaction conditions A: MeCN (7 mL), BSA (2 mmol), **4a**–**i** (1.8 mmol), **5** (2 mmol), TMSOTf (2 mmol), 0.5 h; B: MeCN (7 mL), **4a**–**i** (1.8 mmol), **5** (2 mmol), TMSOTf (2 mmol), 0.2 h; C: **4a**–**i** (1.8 mmol), **5** (4 mmol), $ZnCl_2$ (0.1 mmol), 140–160 °C, 0.5 h.
[b] Ratio **6**/**7** was determined by ^{1}H NMR spectroscopy.
[c] Isolated overall yields.

Glycosylation of **4a**–**f** in the presence of BSA and TMSOTf led to a mixture of N3- and N4-isomers, **6a**–**f** and **7a**–**f**, respectively, in different ratios. While the prevalence of N3-isomers **6a**–**c** was observed in case of glycosylation of **4a**–**c** (see Table 1), the coupling of **4d**–**f** with **5** led to mixtures largely containing the products of N4-glycosylation, **7d**–**f**. It should be also highlighted that the reaction between **4g**–**i** and **5** was selective and yielded only N3-isomers **6g**–**i**. This selectivity was attributed to the bulky phenyl group protecting the N4 position from coupling.

The structure of products **6a**–**i** and **7a**–**f** was studied by ^{1}H–^{13}C HMBC two-dimensional NMR experiments. Compounds **6a**–**i** exhibit a cross peak between 1′ proton and C2 and C3a atoms in their HMBC spectra (see Supplementary data). This observation confirms that the alkyl substituent is linked to the N3 atom of the heterocycle. In the case of triazolopyrimidines **7a**–**f**, the N4 position of acyclic fragment was supported by cross peak between the C5 and H1′ atoms. Additionally, the structure of compounds **6e** and **7e** was determined by X-ray crystallography (Figs. 2 and 3).

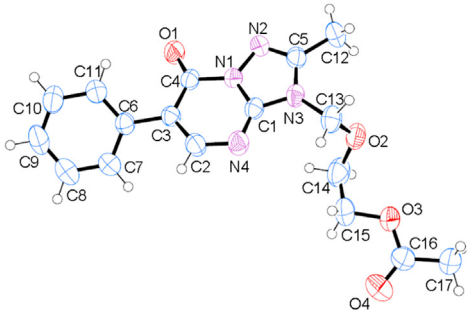


Fig. 2. ORTEP diagram of the X-ray structure of compound **6e**.

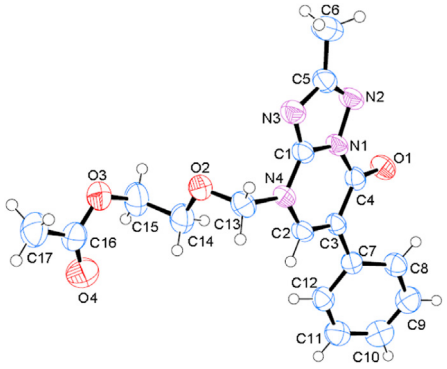


Fig. 3. ORTEP diagram of the X-ray structure of compound **7e**.

The possibility to obtain various regioisomers under Vorbrüggen reaction conditions is well documented.[8] For example, depending on the temperature regimen, Vorbrüggen reaction with alloxazine resulted in two different products of glycosylation.[9] This phenomenon was explained by isomerization of the N-glycosylation products. Isomerization was registered for different nucleoside analogues based on purines, imidazo[1,2-*a*][1,2,4]triazin-7-ones and other non-natural NH-heterocycles.[10] It is usually initiated by addition of TMSOTf in reaction.

Indeed, dissolution of compounds **6a**–**f** in MeCN, containing 2 equiv of trimethylsilyl trifluoromethanesulfonate yielded a mixture of N3- and N4-isomers, **6a**–**f** and **7a**–**f**. The reverse reaction was also observed: the treatment of a solution of N4-isomers **7a**–**f** with 2 equiv of TMSOTf led to a mixture of N4- and N3-isomers as well. This observation allowed us to modify the 'one-pot' Vorbrüggen procedure of coupling **4a**–**f** with **5** in order to achieve a better ratio of N3/N4-isomers. Glycosylation of **4a**–**f** was carried out in the presence of TMSOTf solely (method B) and yielded a mixture of compounds **6a**–**f** containing the acyclic fragment in the azole ring as major products (Table 1).

Based on the observation described above we have assumed that compounds **7a**–**f** were the products of isomerization of **6a**–**f** and the final ratio of isomers in the coupling reaction between **4a**–**f** and **5** directly depends on the contribution of a reversible N3⇄N4 isomerization process in different conditions.

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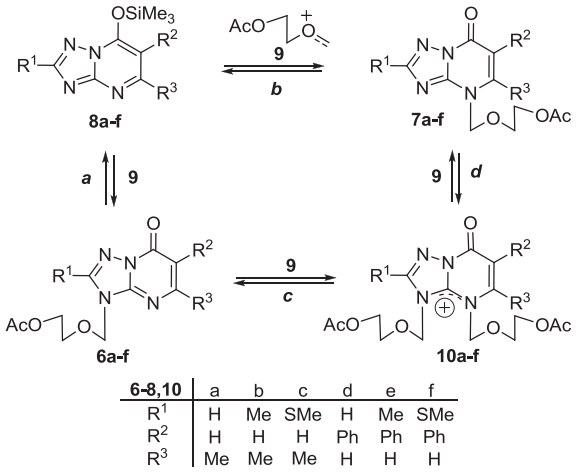
Thus, the general Scheme 1 describing the formation of glycosylation products for triazolopyrimidines **4a**–**f** should include the rearrangement step of compounds **6a**–**f**/**7a**–**f** into **7a**–**f**/**6a**–**f**. This process occurs through the cleavage of the C1′–N3/C1′–N4 bond in **6a**–**f**/**7a**–**f** and may lead to the cation **9** and to *O*-silylated derivatives **8a**–**f** (reactions *a* and *b* in Scheme 1). Compounds **8a**–**f** again react with cation **9** producing isomeric alkyl derivatives **7a**–**f**/**6a**–**f**. There is also an alternative pathway to form diglycosides **10a**–**f** as a result of secondary alkylation of **6a**–**f**/**7a**–**f** by cation **9**. Next, diglycosides **10a**–**f** can be converted back to mono-*N*-alkyl derivatives **7a**–**d**/**6a**–**f** (reactions *c* and *d* in Scheme 1). Similar transglycosylation was previously described for purine nucleosides.[8]

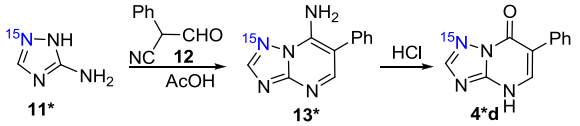


6-8,10	a	b	c	d	e	f
R^1	H	Me	SMe	H	Me	SMe
R^2	H	H	H	Ph	Ph	Ph
R^3	Me	Me	Me	H	H	H

Scheme 1. Possible pathways of formation of **6a**–**f** and **7a**–**f**.

To prove the mechanism of transglycosylation in N4- and N3-isomers, **6a**–**f** and **7a**–**f**, we have performed experiments with ^{15}N-labeled compounds. The formation of cation **9** was confirmed by experiments with [1-^{15}*N*]-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one **4*****d** (86%, ^{15}N), which was obtained from ^{15}*N*-amino-1,2,4-triazine **11*** (Scheme 2). Reaction of **11*** with formyl derivative **12** led to azoloazine **13***. Refluxing of **13*** with HCl gave **4*****d**. Isotope enrichment of heterocycle **4*****d** was verified by analysis of the integrated intensity of the H2 signal (Fig. 4A). Incorporation of ^{15}N-labeled 1,2,4-triazolo[1,5-*a*]pyrimidin-7-one **4*****d** in isomerization of **6d**/**7d** led to the mixture of compounds **4**$^{\#}$**d**, **6**$^{\#}$**d**, and **7**$^{\#}$**d** in 100:45:55 ratio (Scheme 3). The ^{15}N enrichment for **4**$^{\#}$**d**, **6**$^{\#}$**d**, and **7**$^{\#}$**d** was ~43%. Isotope enrichment was determined by integrated intensity in the ^{1}H NMR spectra (Fig. 4B–D). Inclusion of ^{15}N in the products of isomerization undoubtedly confirms the formation of cation intermediate **9** during the rearrangement **6d**⇄**7d**. It should be noted that isotopic enrichment in **4**$^{\#}$**d**, **6**$^{\#}$**d**, and **7**$^{\#}$**d** showed that the equilibrium **6d**⇄**7d** was reached in the isomerization process. The state of equilibrium was achieved in 30 days. This fact can be taken as proof that compounds **6d** and **7d** have equal thermodynamic stability.

To evaluate the relative thermodynamic stability of isomers **6d**–**f** and **7d**–**f** we have performed DFT calculations (B3LYP/6-31G*



Scheme 2. Synthesis of [1-^{15}*N*]-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one **4*****d**.

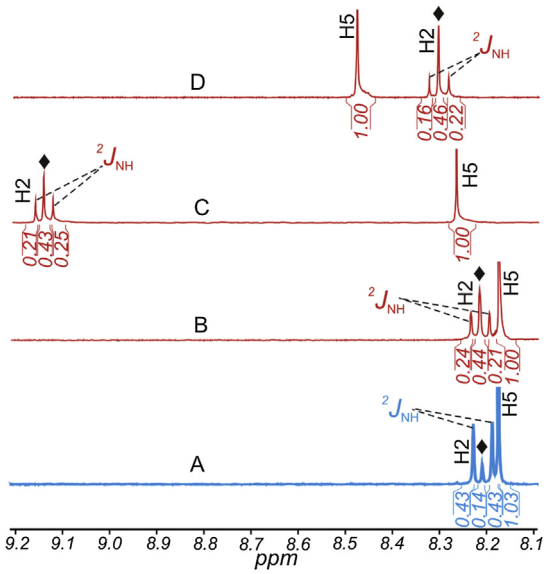
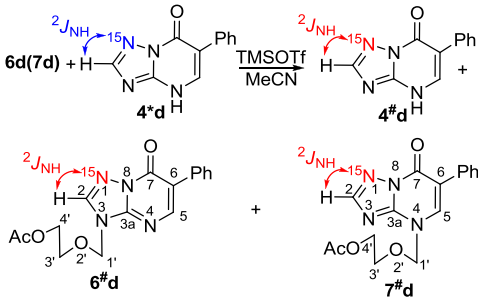


Fig. 4. Fragment of 1D ^{1}H NMR spectra for **4*****d** (A), **4**$^{\#}$**d** (B), **6**$^{\#}$**d** (C), **7**$^{\#}$**d** (D). Unlabeled components of signals H2 are marked by black diamond (◆).



Scheme 3. Isomerization of **6d**/**7d** in presence of [1-^{15}*N*]-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one **1*****d**. Observed ^{1}H–^{15}N coupling constants in 1D ^{1}H NMR spectra are shown by blue (~86%, ^{15}N) and red (~43%, ^{15}N) arrows.

approximation) using Gaussian 09 package.[11] All compounds were initially optimized and the character of local minima was confirmed by Hessian calculations. Obtained data and calculated heats of formation for **6d**–**f** and **7d**–**f** confirmed that the N4-isomers as glycosylation products of the coupling reaction of heterocycles **4d**–**f** are slightly more stable when compared to the N3-isomers (Fig. 5). The energy difference between the values of relative enthalpy of formation for N3- and N4-isomers was 0.3–2.4 kcal/mol. Thus, the glycosylation is thermodynamically controlled. Obtained values of H_f were in good agreement with N3/N4 isomeric ratio observed in the reaction of glycosylation **4d**–**f** (method A, Table 1). Furthermore, the calculated relative stability of other possible products of glycosylation **14d**–**f** suggested that they were not formed due to their low stability comparing to products **6d**–**f**, **7a**–**d**.

An alternative route to acyclovir analogues includes the coupling between **5** and NH-heterocycles catalyzed via Lewis acids.[12] We found that heterocycles **4d**–**f** react with **5** in the presence of $ZnCl_2$ at high temperatures. The glycosylation of **4d**,**e** yielded **6d**,**e** and **7d**,**e** in the mixture, and N4-isomer was a major product (Table 1). Regarding compound **4f**, only N4-isomer **7f** was isolated. It should be mentioned that the total yields of glycosylated products obtained through this procedure were lower than those observed for the 'one-pot' Vorbrüggen glycosylation. Additionally, the $ZnCl_2$ catalyst did not enable reaction direction control. As a result, this catalyst it can be suitable for the synthesis of isomers with a high

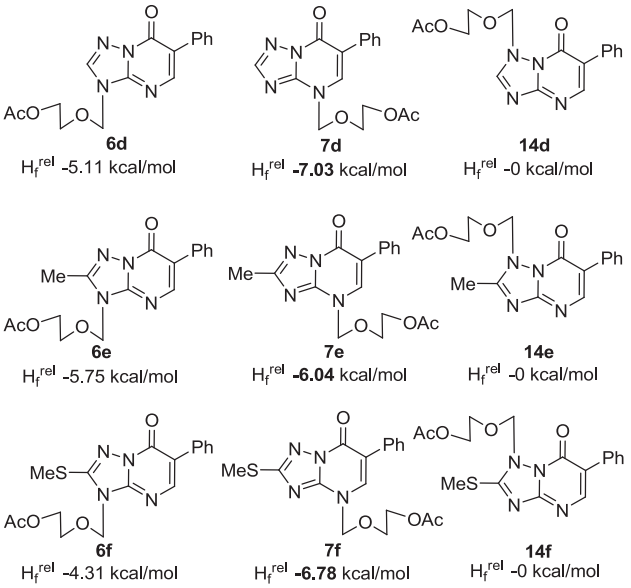
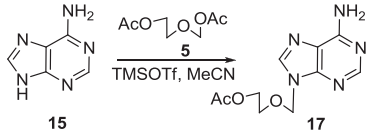


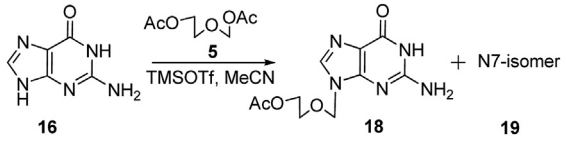
Fig. 5. Values of relative enthalpy of formation for **6d**–**f**, **7a**–**d** and possible products of N1-glycosylation **14d**–**f**.

thermodynamic stability. Additionally, we found that the heating of alkyl derivative **6d** at 160 °C in an excess of (2-acetoxyethoxy) methyl acetate **5** with $ZnCl_2$ gives **7d**. This result confirms that $ZnCl_2$-catalyzed coupling between **4d**–**f** and **5** includes the isomerization **6**→**7**. This rearrangement is irreversible.

The scope of the 'one-pot' Vorbrüggen procedure presented in this paper was not limited by the type of NH-heterocycles **4a**–**i**. The BSA free 'one-pot' coupling of adenine **15** and guanine **16** with compound **5** (Schemes 4 and 5) was also successful. In the former case, the product **17** with 30% yield was separated, while the latter led to the products **18** and **19** in a 96:4 ratio. Compounds **17** and **18** were isolated and characterized by ^1H NMR spectra. The structures of **17** and **18** were confirmed via the analysis of the chemical shifts of purine protons.[13,14] Although compound **19** was not separated, its structure was resolved via ^1H NMR spectra.[15] Despite the low yields for the products of interest, this example reflects the potential for the BSA free 'one-pot' Vorbrüggen procedure to be transferred to other types of NH-heterocycles. However, a careful examination and the optimization of the reaction conditions (temperature, solvents, etc.) are further required.

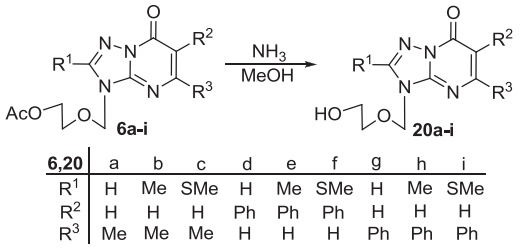


Scheme 4. Coupling reaction of adenine **15** with **5**.

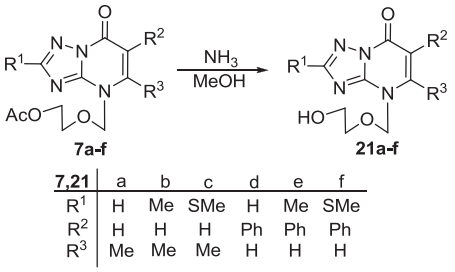


Scheme 5. Coupling reaction of guanine **16** with **5**.

Deprotection of **6a**–**i** and **7a**–**f** yielded new acyclovir analogues **20a**–**i** and **21a**–**f** (Schemes 6 and 7). The cytotoxicity and antiviral activity of **20a**–**i** and **21a**–**f** were examined against HSV-1 in Vero



Scheme 6. Deacetylation of compounds **6a**–**i**.



Scheme 7. Deacetylation of compounds **7a**–**f**.

cells according to the previously reported procedure.[3] Among these acyclic analogues, compound **20f** has exhibited weak anti-HSV activity compared to acyclovir (Table 2). Its toxicity was comparable with the toxicity of acyclovir and the selectivity index was significantly lower than that of acyclovir.[16]

Table 2
Cytotoxicity and anti-HSV activity of new acyclovir analogues

Compound	CD_{50} (mM)	Multiplicity of infection			
		0.1 PFU/cell		0.01 PFU/cell	
		ID_{50}[a] (mM)	SI	ID_{50}[a] (mM)	SI
20a	4.62	NA		NA	
20b	4.20	NA		NA	
20c	3.70	NA		>3.70	>1
20d	>3.49	3.49	>1	1.74	>2
20e	>3.33	2.50	>1.33	0.83	>4
20f	>3.01	0.75	4	0.37	>8
20g	>3.49	3.49	>1	1.74	>2
20h	>3.33	2.50	>1.33	0.83	>4
20i	>3.01	3.01	>1	0.75	>4
21a	>4.62	NA		NA	
21b	>4.20	NA		NA	
21c	>3.70	3.70	>1	1.35	>2
21d	>3.49	3.49	>1	1.74	>2
21e	>3.33	3.33	>1	1.66	>2
21f	>3.01	3.01	>1	1.50	>2
Acyclovir	2.2	0.00282	780		

CD_{50}—cytotoxic dose, i.e., the agent concentration, at which 50% of uninfected cells die; ID_{50}—inhibitory dose, i.e., the agent concentration, at which the cytopathic effect is decreased by 50%; SI—selectivity index, CD_{50}/ID_{50}; PFU—plaque forming unit.

[a] Mean values of three independent experiments are given.

3. Conclusions

We have studied the reaction of 1,2,4-triazolo[1,5-*a*]pyrimidin-7-ones **4a**–**i** with (2-acetoxyethoxy)methyl acetate **5**. This reaction was susceptible to the nature of the substituents in **4a**–**i** and to the reaction conditions. The appearance of a bulky group at position 5 of the pyrimidine ring of compounds **4g**–**i** leads to an exclusive selectivity of glycosylation. In other cases a mixture of N3- and N4-

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isomers, **6a**–**f** and **7a**–**f**, was observed. The formation of products **7a**–**f** occurs through the isomerization of **6a**–**f** by a reaction similar to the process of transglycosylation, previously described in purine nucleosides. The final ratio of products **6**/**7** depends on their relative thermodynamic stability. Studied coupling reaction between 1,2,4-triazolo[1,5-*a*]pyrimidin-7-ones **4a**–**i** and (2-acetoxyethoxy) methyl acetate **5** was found to be useful to obtain new acyclic analogues of nucleosides.

4. Experimental section

4.1. General experimental methods

Commercially available reagents and catalysts were used as obtained, unless otherwise stated, from freshly opened containers without further purification. MeCN was distilled over P_2O_5. NMR spectra were recorded on a Bruker Avance II 400 MHz spectrometer using DMSO-d_6 as solvent. ^{1}H NMR spectra were recorded at 400 MHz; multiplicities are designated as s (singlet), d (doublet), t (triplet), br (broad), and m (multiplet). ^{1}H chemical shifts were referenced relative to the residual CD_2H signal of DMSO-d_6 at 2.50 ppm. ^{13}C and ^{15}N NMR spectra were registered at 100.6 and 40.5 MHz, respectively. ^{13}C and ^{15}N chemical shifts were referenced relative to TMS and liquid NH_3, respectively. The line positions of signals in ^{1}H, ^{13}C, and ^{15}N NMR spectra are given in ppm (δ). ^{1}H and ^{13}C resonance assignment was done using gradient enhanced versions of 2D ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC spectra. Column chromatography was carried out on silica gel 60 (230–400 mesh). Analytical TLC was performed using silica gel aluminum sheets. HMRS for ^{15}N-labeled compounds were acquired on a 7-Tesla Finnigan LTQ FT spectrometer equipped with an Ion Max electrospray ion source. Mass spectra (MS) for unlabeled compounds were recorded on a Bruker Daltonics micrOTOF-Q II mass spectrometer equipped with an orthogonal electrospray ionization (ESI) source, a six-port divert valve, and syringe pump kd Scientific with a flow rate of 180 μL/h. Melting points are uncorrected. IR spectra were recorded using a Bruker Alpha (NPVO, ZnSe) IR-Fur spectrometer; absorbance frequencies are given at maximum intensity in cm^{-1}. Elemental analyses were carried out using a CHNS/O analyzer Perkin–Elmer 2400 Series II instrument. Obtained compounds **6e** and **7e** were recrystallized from *i*-propanol and gave single crystals suitable for X-ray crystallographic analysis. The diffraction data were collected on X-ray diffractometer Xcalibur S CCD with Mo Kα radiation (λ=0.71073 Å, graphite monochromator, $\omega/2\theta$-scanning technique). All structures were solved by direct methods implemented in the SHELXS-97 program.[17] The refinement was carried out by full matrix anisotropic least-squares methods on F^2 for all reflections for non-H atoms by using the SHELXL-97 program.[18] The X-ray CIF files have been deposited at the Cambridge Crystallographic Data Centre and allocated with the deposition numbers CCDC 928809 (compound **6e**) and CCDC 930137 (compound **7e**). Copies of the data can be obtained, free of charge, from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk; Internet: www.ccdc.cam.ac.uk). Experimental data for compounds **6b**,**c**,**e**,**f**,**h**,**i**, **7b**,**c**,**e**,**f**, **20b**,**c**,**e**,**f**,**h**,**i**, and **21b**,**c**,**e**,**f** are available in Supplementary data.

4.2. Synthesis

Compounds **4a**–**i**[6,19–24] and **5**[25] were prepared as previously described.

*4.2.1. General procedures for coupling reactions of NH-heterocycles **4a**–**i** with compound **5**. Method A*. A solution of 1,2,4-triazolo[1,5-*a*]pyrimidine **4** (1.80 mmol), (2-acetoxyethoxy)methyl acetate **5** (475 mg; 2.69 mmol) and TMSOTf (600 mg; 2.70 mmol) in MeCN (10 mL) including BSA (549 mg; 2.70 mmol) was stirred at ambient temperature for 3 h and then neutralized with $NaHCO_3$, extracted with CH_2Cl_2 (2×20 mL), dried (Na_2SO_4), and concentrated in vacuo. The products were separated by column chromatography (hexane/EtOAc 10:1 →0:100).

Method B. A solution of 1,2,4-triazolo[1,5-*a*]pyrimidine **4** (1.80 mmol), (2-acetoxyethoxy)methyl acetate **5** (475 mg; 2.69 mmol), and TMSOTf (600 mg; 2.70 mmol) in MeCN (10 mL) was stirred at ambient temperature for 0.2 h and then neutralized with $NaHCO_3$, extracted with CH_2Cl_2 (2×20 mL), dried (Na_2SO_4), and concentrated in vacuo. The products were isolated by column chromatography (hexane/EtOAc 10:1 →0:100).

Method C. A mixture of 1,2,4-triazolo[1,5-*a*]pyrimidines **4d**–**f** (1.80 mmol), (2-acetoxyethoxy)methyl acetate **5** (700 mg; 3.97 mmol), and $ZnCl_2$ (14 mg; 0.10 mmol) was heated at 140–160 °C for 0.5 h in an oil bath. The reaction mixture was then cooled, and product **6d**,**e** or **7d**–**f** was isolated via column chromatography on silica gel (hexane/EtOAc 10:1 →0:100).

*4.2.1.1. 3-[(2-Acetoxyethoxy)methyl]-5-methyl-1,2,4-triazolo[1,5-a]pyrimidin-7-one (**6a**).* White solid; yield 34% (162 mg, procedure A)/60% (287 mg, procedure B); mp 140 °C; ^{1}H NMR δ: 1.94 (3H, s, CO–C*H*$_3$), 2.29 (3H, s, Me), 3.80–3.82 (2H, m, OC3′H$_2$), 4.09–4.11 (2H, m, OC4′H$_2$), 5.49 (2H, s, NC1′H$_2$), 6.00 (1H, s, H6), 9.01 (1H, s, H2); ^{13}C NMR δ: 20.23 (CO–*C*H$_3$), 23.7 (Me), 62.7 (C4′), 67.5 (C3′), 73.0 (C1′), 102.0 (C6), 142.6 (C2), 148.3 (C3a), 155.4(C7), 163.9 (C5), 170.1 (*C*O–CH$_3$); MS (ESI) *m*/*z*: 267.11 [M+H]$^+$; IR: 1535, 1585, 1682, 1733, 2943, 3099. Found: C, 49.58; H, 5.27; N, 20.96. $C_{11}H_{14}N_4O_4$ requires C, 49.62; H, 5.30; N, 21.04.

*4.2.1.2. 3-[(2-Acetoxyethoxy)methyl]-6-phenyl-1,2,4-triazolo[1,5-a]pyrimidin-7-one (**6d**).* White solid; yield 4% (23 mg, procedure A)/36% (213 mg, procedure B)/2% (9 mg, procedure C); mp 152 °C; ^{1}H NMR δ: 1.96 (3H, s, CO–C*H*$_3$), 3.83–3.85 (2H, m, OC3′H$_2$), 4.10–4.13 (2H, m, OC4′H$_2$), 5.56 (2H, s, NC1′H$_2$), 7.30–7.34 (1H, m, H*p*(Ph)), 7.40–7.44 (2H, m, H*m*(Ph)), 7.68–7.70 (2H, m, H*o*(Ph)), 8.28 (1H, s, H5), 9.13 (1H, s, H2); ^{13}C NMR δ: 20.5 (CO–*C*H$_3$), 62.7 (C4′), 67.6 (C3′), 73.2 (C1′), 116.2 (C6), 127.0 (C*p*), 128.2 (C*m*), 128.3 (C*o*), 134.3 (C*i*), 143.4 (C2), 148.3 (C3a), 151.8 (C5), 154.8 (C7), 170.2 (*C*O–CH$_3$); MS (ESI) *m*/*z*: 329.12 [M+H]$^+$; IR: 1549, 1605, 1674, 1688, 1737, 2954, 3134. Found: C, 58.28; H, 4.77; N, 17.12. $C_{16}H_{16}N_4O_4$ requires C, 58.53; H, 4.91; N, 17.06.

*4.2.1.3. 3-[(2-Acetoxyethoxy)methyl]-5-phenyl-1,2,4-triazolo[1,5-a]pyrimidin-7-one (**6g**).* White solid; 39% (218 mg, procedure A)/41% (242 mg, procedure B); mp 145 °C; ^{1}H NMR δ: 1.94 (3H, s, CO–C*H*$_3$), 3.88–3.90 (2H, m, OC3′H$_2$), 4.12–4.14 (2H, m, OC4′H$_2$), 5.61 (2H, s, NC1′H$_2$), 6.74 (1H, s, H6), 7.50–7.51 (3H, m, H*p*(Ph)+H*m*(Ph)), 8.11–8.14 (2H, m, H*o*(Ph)), 9.11 (1H, s, H2); ^{13}C NMR δ: 20.5 (COCH$_3$), 62.8 (C4′), 67.7 (C3′), 73.1 (C1′), 99.1 (C6), 127.1 (C*o*), 128.7 (C*m*), 130.5 (C*p*), 136.5 (C*i*), 143.2 (C2), 148.9 (C3a), 156.1 (C7), 160.2 (C5), 170.2 (*C*O–CH$_3$); MS (ESI) *m*/*z*: 329.13 [M+H]$^+$; IR: 1544, 1674, 1733, 3046, 3109. Found: C, 58.45; H, 4.97; N, 16.93. $C_{16}H_{16}N_4O_4$ requires C, 58.53; H, 4.91; N, 17.06.

*4.2.1.4. 4-[(2-Acetoxyethoxy)methyl]-5-methyl-1,2,4-triazolo[1,5-a]pyrimidin-7-one (**7a**).* White solid; yield 22% (105 mg, procedure A); mp 116°C; ^{1}H NMR δ: 1.95 (3H, s, CO–C*H*$_3$), 2.50 (3H, s, Me), 3.76–3.79 (2H, m, C3′H$_2$), 4.09–4.11 (2H, m, C4′H$_2$), 5.72 (2H, s, NC1′H$_2$), 6.05 (1H, s, H6), 8.23 (1H, s, H2); ^{13}C NMR δ: 17.6 (CO–*C*H$_3$), 20.5 (Me), 62.7 (C3′), 67.1 (C4′), 76.5 (C1′), 100.9 (C6), 151.6 (C2), 152.4 (C3a), 152.5 (C5), 154.9 (C7), 170.1 (*C*O–CH$_3$); MS (ESI) *m*/*z*: 265.12 [M+H]$^+$; IR: 1314, 1563, 1689, 1732, 2949, 3099. Found: C, 49.71; H, 5.38; N, 21.07. $C_{11}H_{14}N_4O_4$ requires C, 49.62; H, 5.30; N, 21.04.

*4.2.1.5. 4-[(2-Acetoxyethoxy)methyl]-6-phenyl-1,2,4-triazolo[1,5-a]pyrimidin-7-one (**7d**).* Colorless crystals; yield 82% (484 mg, procedure A)/12% (71 mg, procedure B)/38% (227 mg, procedure C); mp 161 °C; ^{1}H NMR δ: 1.92 (3H, s, CO–C*H*$_3$), 3.85–3.87 (2H, m, OC3′H$_2$), 4.10–4.12 (2H, m, OC4′H$_2$), 5.66 (2H, s, NC1′H$_2$), 7.37–7.40 (1H, m, H*p*(Ph)), 7.45–7.48 (2H, m, H*m*(Ph)), 7.65–7.67 (2H, m, H*o*(Ph)), 8.33 (1H, s, H2), 8.50 (1H, s, H5); ^{13}C NMR δ: 20.5 (CO–*C*H$_3$), 62.8 (C4′), 67.5 (C3′), 80.1 (C1′), 112.8 (C6), 127.8 (C*p*), 128.3 (C*m*), 128.7 (C*o*), 132.7 (C*i*), 140.8 (C5), 150.5 (C3a), 152.3 (C2), 155.1 (C7), 170.2 (*C*O–CH$_3$); MS (ESI) *m*/*z*: 329.13 [M+H]$^+$; IR: 1574, 1668, 1727, 3062. Found: C, 58.31; H, 4.73; N, 17.04. $C_{16}H_{16}N_4O_4$ requires C, 58.53; H, 4.91; N, 17.06.

*4.2.2. Synthesis of ^{15}N-labeled compounds and isomerization of **6d**/**7d** in presence of **4***d.* Compounds **11*** (^{15}N, ~86%) and **12** were obtained by described procedures.[26,27]

*4.2.2.1. [1-^{15}N]-3-Amino-1,2,4-triazole (**11***) (^{15}N, ~86%).* IR: 1045, 1352, 1615, 2776, 2814, 3151, 3324.

*4.2.2.2. [1-^{15}N]-7-Amino-6-phenyl-1,2,4-triazolo[1,5-a]pyrimidine (**13***) (^{15}N, ~86%).* A solution of ^{15}*N*-3-amino-1,2,4-triazole **11*** (900 mg; 10.59 mmol) and phenyl(formyl)acetonitrile **12** (1536 mg; 10.59 mmol) in acetic acid (6 mL) was refluxed for 3 h. The precipitate formed was filtered off and dried to give compound **13***, which was used without further purification. Pale yellow crystals; yield 45% (1021 mg). ^{1}H NMR δ: 7.41–7.44 (1H, m, H*p*(Ph)), 7.49–7.51 (4H, m, H*o*+H*m*(Ph)), 7.89 (2H, br s, NH$_2$) 8.28 (1H, s, H5), 8.49 (1H, d, $^2J_{NH}$ 16.0 Hz, H2). ^{13}C NMR δ: 104.9 (C6), 127.7 (C*p*), 129.0 (C*m*), 129.3 (C*o*), 133.1 (C*i*), 146.5 (C7, $^2J_{CN}$ 3.2 Hz), 153.8 (C5), 154.6 (C2, $^1J_{CN}$ 3.3 Hz), 154.7 (C3a); ^{15}N NMR δ: 262.5; HRMS (ESI) *m*/*z*: [M+H]$^+$ found 213.0902. $C_{11}H_{10}N_4^{15}N$ requires 213.0906; IR: 705, 1201, 1240, 1461, 1562, 1589, 1632, 3118, 3413.

*4.2.2.3. [1-^{15}N]-6-Phenyl-1,2,4-triazolo[1,5-a]pyrimidin-7-one (**4*****d**) (^{15}N, ~86%).* A mixture of ^{15}*N*-1,2,4-triazolo[1,5-*a*]pyrimidine **13*** (700 mg; 3.30 mmol) and 11 M HCl (8 mL) was refluxed for 7 h. After cooling, a precipitate formed was filtered off and recrystallized from DMF. Colorless crystals; yield 44% (312 mg). ^{1}H NMR δ: 7.32–7.36 (1H, m, H*p*(Ph)), 7.40–7.42 (2H, m, H*m*(Ph)), 7.64–7.66 (2H, m, H*o*(Ph)) 8.22 (1H, s, H5), 8.29 (1H, d, $^2J_{NH}$ 16.0 Hz, H2); ^{13}C NMR δ: 111.9 (C6, $^3J_{CN}$ 1.0 Hz), 127.5 (C*p*), 128.3 (C*m*), 128.7 (C*o*), 133.4 (C*i*), 138.8 (C5), 150.1 (C3a), 152.3 (C2, $^1J_{CN}$ 2.8 Hz), 155.8 (C7, $^2J_{CN}$ 3.5 Hz); ^{15}N NMR δ: 271.7; HRMS (ESI) found 214.0743. $C_{11}H_9ON_4^{15}N$ [M+H]$^+$ requires 214.0746; IR: 684, 765, 1276, 1179, 1633, 2869, 3094.

*4.2.3. Isomerization of compounds **6d**/**7d** in the presence of **4***d.* A solution of **4*****d** (198 mg; 0.93 mmol)/(40 mg; 0.19 mmol), TMSOTf (413 mg; 1.86 mmol)/(84 mg; 0.38 mmol) in anhydrous MeCN (10 mL)/(3 mL) was stirred at ambient temperature for 0.5 h, and compound **6d** (305 mg; 0.93 mmol)/**7d** (61 mg, 0.19 mmol) was added. The resulting solution was allowed to stand at room temperature for 30 days and then 10% aqueous solution of Na_2CO_3 (10 mL/5 mL) was added. The resulting suspension was extracted with CH_2Cl_2 (3×10 mL) and organic layers were separated and concentrated in vacuo. Compounds **6**#**d** and **7**#**d** were isolated by column chromatography (hexane/EtOAc 10:1→1:10). The aqueous layer was acidified to pH 1–2 with 11 M HCl. The precipitate formed was filtered off and dried to give compound **4**#**d**.

*4.2.3.1. [1-^{15}N]-3-[(2-Acetoxyethoxy)methyl]-6-phenyl-1,2,4-triazolo[1,5-a]pyrimidin-7-one (**6**#**d**) (^{15}N, ~43%).* Yield 99 mg (32%)/14 mg (22%). ^{1}H NMR δ: 1.96 (3H, s, CO–C*H*$_3$), 3.83–3.85 (2H, m, OC3′H$_2$), 4.10–4.13 (2H, m, OC4′H$_2$), 5.56 (2H, s, NC1′H$_2$), 7.30–7.34 (1H, m, H*p*(Ph)), 7.40–7.44 (2H, m, H*m*(Ph)), 7.68–7.71 (2H, m, H*o*(Ph)), 8.28 (1H, s, H5), 9.13 (1H, d, $^2J_{NH}$ 14.3 Hz, H2); ^{13}C NMR δ: 20.5 (CO–*C*H$_3$), 62.8 (C4′), 67.6 (C3′), 73.2 (C1′), 116.3 (C6), 127.0 (C*p*), 128.2 (C*m*), 128.3 (C*o*), 134.3 (C*i*), 143.4 (C2, $^1J_{CN}$ 1.1 Hz), 148.3 (C3a, $^2J_{CN}$ 1.7 Hz), 151.9 (C5), 154.8 (C7, $^2J_{CN}$ 3.0 Hz), 170.2 (*C*O–CH$_3$); ^{15}N NMR δ: 262.8; HRMS (ESI) *m*/*z*: [M+H]$^+$ found 330.1220. $C_{16}H_{17}N_3^{15}NO_4$ requires 330.1216.

*4.2.3.2. [1-^{15}N]-4-[(2-Acetoxyethoxy)methyl]-6-phenyl-1,2,4-triazolo[1,5-a]pyrimidin-7-one (**7**#**d**) (^{15}N, 43%).* Yield 119 mg (35%)/20 mg (32%). ^{1}H NMR δ: 1.92 (3H, s, CO–C*H*$_3$), 3.85–3.87 (2H, m, OC3′H$_2$), 4.10–4.12 (2H, m, OC4′H$_2$), 5.66 (2H, s, NC1′H$_2$), 7.37–7.40 (1H, m, H*p*(Ph)), 7.45–7.48 (2H, m, H*m*(Ph)), 7.65–7.67 (2H, m, H*o*(Ph)), 8.33 (1H, d, $^2J_{NH}$ 16.0 Hz, H2), 8.50 (1H, s, H5); ^{13}C NMR δ: 20.6 (CO–*C*H$_3$), 62.9 (C4′), 67.5 (C3′), 80.2 (C1′), 112.8 (C6), 127.8 (C*p*), 128.4 (C*m*), 128.7 (C*o*), 132.7 (C*i*), 140.8 (C5), 150.6 (C3a), 152.3 (C2), 155.2 (C7), 170.3 (*C*O–CH$_3$); ^{15}N NMR δ: 274.5; HRMS (ESI) *m*/*z*: [M+H]$^+$ found 330.1220. $C_{16}H_{17}N_3^{15}NO_4$ requires 330.1216.

*4.2.3.3. [1-^{15}N]-6-Phenyl-1,2,4-triazolo[1,5-a]pyrimidin-7-one (**4**#**d**) (^{15}N, 43%).* Yield 50 mg (24%)/12 mg (30%). ^{1}H NMR δ: 7.32–7.26 (1H, m, H*p*(Ph)), 7.40–7.42 (2H, m, H*m*(Ph)), 7.42–7.44 (2H, m, H*o*(Ph)), 8.22 (1H, s, H5), 8.29 (1H, d, $^2J_{NH}$ 16.0 Hz, H2); ^{13}C NMR δ: 111.9 (C6), 127.4 (C*p*), 128.2 (C*m*), 128.7 (C*o*), 133.4 (C*i*), 138.8 (C5), 150.1 (C3a), 152.3 (C2, br s), 155.8 (C7).

*4.2.4. Synthesis of compounds **17** and **18** by use of BSA free 'one-pot' Vorbrüggen procedure.* A solution of adenine **15** or guanine **16** (1.48 mmol), (2-acetoxyethoxy)methyl acetate **5** (405 mg; 2.30 mmol), and TMSOTf (511 mg; 2.30 mmol) in anhydrous MeCN (7 mL) was stirred at ambient temperature for 2 h and then diluted with 10 mL acetonitrile with a few drops of water and neutralized with $NaHCO_3$. The resulting suspension was filtered. The filtrate was concentrated in vacuo. The product was isolated by column chromatography (EtOAc/EtOH 20:1 for **17** or $CHCl_3$/EtOH 10:1 for **18**).

*4.2.4.1. 9-[(2-Acetoxyethoxy)methyl]adenine (**17**).* White solid; yield 39% (145 mg). ^{1}H NMR δ: 1.95 (s, 3H, CO–CH$_3$), 3.71–3.73 (m, 2H, OCH$_2$), 4.07–4.09 (m, 2H, OCH$_2$), 5.57 (s, 2H, NCH$_2$), 7.05 (s, 2H, NH$_2$), 8.11 (s, 1H, CH), 8.16 (s, 1H, CH).

*4.2.4.2. 9-[(2-Acetoxyethoxy)methyl]guanine (**18**).* White solid; yield 29% (115 mg). ^{1}H NMR δ: 1.96 (s, 3H, CO–CH$_3$), 3.65–3.67 (m, 2H, OCH$_2$), 4.06–4.08 (m, 2H, OCH$_2$), 5.35 (s, 2H, NCH$_2$), 6.52 (s, 2H, NH$_2$), 7.82 (s, 1H, C8H), 10.65 (s, 1H, NH).

*4.2.5. Deprotection of N-(acetoxyethoxy)methyl-1,2,4-triazolo[1,5-a]pyrimidin-7-ones **6a**–**i** and **7a**–**f**.* A solution of **6** or **7** (1 mmol) in NH$_3$/MeOH (20 mL; saturated at −10 °C) was stirred at ambient temperature for 24 h in a sealed flask. After evaporation of solvent under vacuum, the residue was purified by column chromatography using ethyl acetate (100%) as an eluant to give **20** or **21**.

*4.2.5.1. 3-[(2-Hydroxyethoxy)methyl]-5-methyl-1,2,4-triazolo[1,5-a]pyrimidin-7-one (**20a**).* Colorless crystals; yield 80% (179 mg); mp 186 °C; ^{1}H NMR δ: 2.29 (3H, s, Me), 3.48–3.51 (2H, m, C4′H$_2$), 3.61–3.63 (2H, m, C3′H$_2$), 4.64 (1H, t, *J* 5.4 Hz, OH), 5.49 (2H, s, NC1′H$_2$), 6.00 (1H, s, H6), 8.99 (1H, s, H2); ^{13}C NMR δ: 23.7 (Me), 59.8 (C4′), 71.4 (C3′), 73.3 (C1′), 101.9 (C6), 142.6 (C2), 148.2 (C3a), 155.3 (C7), 163.9 (C5); MS (ESI) *m*/*z*: 225.10 [M+H]$^+$; IR: 1220, 1547, 1592, 1697, 3124, 3344. Found: C, 48.21; H, 5.20; N, 25.15. $C_9H_{12}N_4O_3$ requires C, 48.21; H, 5.39; N, 24.99.

*4.2.5.2. 3-[(2-Hydroxyethoxy)methyl]-6-phenyl-1,2,4-triazolo[1,5-a]pyrimidin-7-one (**20d**).* Colorless crystals; yield 84% (241 mg); mp 164 °C; ^{1}H NMR δ: 3.48–3.52 (2H, m, OC4′H$_2$),

3.64–3.67 (2H, m, OC3′H_2), 4.68 (1H, t, *J* 4.8 Hz, OH), 5.55 (2H, s, C1′H_2), 7.32–7.34 (1H, m, H*p*(Ph)), 7.40–7.44 (2H, m, H*m*(Ph)), 7.69–7.71 (2H, m, H*o*(Ph)), 8.28 (1H, s, H5), 9.12 (1H, s, H2); ^{13}C NMR *δ*: 59.9 (C4′), 71.6 (C3′), 73.5 (C1′), 116.1 (C6), 127.0 (C*p*), 128.2 (C*m*), 128.3 (C*o*), 134.3 (C*i*), 143.4 (C2), 148.2 (C3a), 151.8 (C5), 154.8 (C7); MS (ESI) *m*/*z*: 287.12 $[M+H]^+$; IR: 1545, 1596, 1667, 2908, 3021, 3117, 3354. Found: C, 58.90; H, 4.81; N, 19.46. $C_{14}H_{14}N_4O_3$ requires C, 58.73; H, 4.93; N, 19.57.

*4.2.5.3. 3-[(2-Hydroxyethoxy)methyl]-5-phenyl-1,2,4-triazolo [1,5-a]pyrimidin-7-one (**20g**).* Colorless crystals; yield 84% (240 mg); mp 187 °C; ^{1}H NMR *δ*: 3.52 (2H, br s, C4′H_2), 3.68–3.71 (2H, m, C3′H_2), 4.71 (1H, br s, OH), 5.61 (2H, s, C1′H_2), 6.74 (1H, s, H6), 7.50–7.51 (3H, m, H*m*(Ph)+H*p*(Ph)), 8.12–8.13 (2H, m, H*o*(Ph)), 9.10 (1H, s, H2); ^{13}C NMR *δ*: 59.9 (C4′), 71.7 (C3′), 73.5 (C1′), 99.0 (C6), 127.1 (C*o*), 128.7 (C*m*), 130.5 (C*p*), 136.5 (C*i*), 143.2 (C2), 148.8 (C3a), 156.1 (C7), 160.2 (C5); MS (ESI) *m*/*z*: 287.11 $[M+H]^+$; IR: 1545, 1599, 1673, 2915, 3039, 3108, 3316. Found: C, 58.61; H, 5.08; N, 19.57. $C_{14}H_{14}N_4O_3$ requires C, 58.73; H, 4.93; N, 19.57.

*4.2.5.4. 4-[(2-Hydroxyethoxy)methyl]-5-methyl-1,2,4-triazolo [1,5-a]pyrimidin-7-one (**21a**).* Colorless crystals; yield 62% (139 mg); mp 153 °C; ^{1}H NMR *δ*: 2.52 (3H, s, Me), 3.46–3.50 (2H, m, C4′H_2), 3.58–3.60 (2H, m, C3′H_2), 4.59 (1H, t, *J* 5.4 Hz, OH), 5.71 (2H, s, NC1′H_2), 6.03 (1H, s, H6), 8.22 (1H, s, H2); ^{13}C NMR *δ*: 17.6 (Me), 59.9 (C4′), 71.0 (C3′), 76.7 (C1′), 100.7 (C6), 151.5 (C2), 152.3 (C3a), 152.6 (C5), 154.8 (C7); MS (ESI) *m*/*z*: 225.10 $[M+H]^+$; IR: 1113, 1472, 1564, 1702, 3096, 3404. Found: C, 48.39; H, 5.24; N, 25.21. $C_9H_{12}N_4O_3$ requires C, 48.21; H, 5.39; N, 24.99.

*4.2.5.5. 4-[(2-Hydroxyethoxy)methyl]-6-phenyl-1,2,4-triazolo [1,5-a]pyrimidin-7-one (**21d**).* Colorless crystals; yield 84% (240 mg); mp 138 °C; ^{1}H NMR *δ*: 3.48–3.52 (2H, m, OC4′H_2), 3.65–3.68 (2H, m, OC3′H_2), 4.69 (1H, t, *J* 5.6 Hz, OH), 5.66 (2H, s, C1′H_2), 7.37–7.40 (1H, m, H*p*(Ph)), 7.44–7.46 (2H, m, H*m*(Ph)), 7.66–7.67 (2H, m, H*o*(Ph)), 8.33 (1H, s, H2), 8.48 (1H, s, H5); ^{13}C NMR *δ*: 59.9 (C4′), 71.5 (C3′), 80.3 (C1′), 112.6 (C6), 127.7 (C*p*), 128.3 (C*m*), 128.7 (C*o*), 132.7 (C*i*), 140.8 (C5), 150.5 (C3a), 152.3 (C2), 155.1 (C7); MS (ESI) *m*/*z*: 287.12 $[M+H]^+$; IR: 1574, 1682, 2938, 3080, 3382. Found: C, 58.61; H, 4.74; N, 19.24. $C_{14}H_{14}N_4O_3$ requires C, 58.73; H, 4.93; N, 19.57.

4.3. Computational details

Quantum chemical calculations were performed by employing G09 suit[11] at West Grid supercomputing center (Canada). Compounds were fully optimized at B3LYP/6-31G(d,p) level. The minima were confirmed by frequency calculations.

4.4. Antiviral activity and cytotoxicity

Vero cell culture (green monkey kidney epithelial cells, ATCC No CRL-1586) was obtained from Laboratory of tissues, Ivanovskii Institute of Virology, Russian Academy of Medical Sciences (Moscow). The acyclovir-sensitive HSV-1/L_2 strain was obtained from the State collection of viruses of Ivanovskii Institute of Virology, Russian Academy of Medical Sciences (Moscow). The Vero cell culture was grown in Dulbecco's modified medium (D-MEM) with 5% fetal calf serum (PanEco, Russia) at 37 °C in a 96-well plate in the atmosphere of 5% CO_2.

The antiviral effects of the compounds were estimated from their ability to prevent the development of the virus-induced cytopathic effect (CPE) similar to the procedure described earlier.[3,28,29] Quantitatively the antiviral effect was expressed as ID_{50} (the concentration at which CPE was reduced by 50%). *Vero* cells placed in 96-well plates (0.8×10^6 cell/mL) were infected with the virus with varied multiplicity of infection (0.01 or 0.1 PFU/cell) and incubated in the Eagle's medium supplied with the 199 medium (1:1) and 2% fetal calf serum. The tested compounds at concentrations up to 1000 μM were added directly before infecting. After 72 h incubation the number of living cells was measured using the trypan blue exclusion method. Cytotoxicity (CD_{50}) was estimated in the presence of tested compounds at the concentrations of 0–1000 μM after 72 h incubation with uninfected cells and calculated as compound concentration, at which 50% cells died.[24]

Acknowledgements

This work was supported by the Federal Target Program 'Scientific and Science-Educational Personnel of Innovative Russia' (State contract 14.A18.21.0806) and Russian Foundation for Basic Research (projects 13-04-02059, 12-03-33144, 12-03-31476, and 12-04-00581). J.O.S thanks Compute Canada–Calcul Canada and West Grid for computing resources and Prof. Arvi Rauk (University of Calgary, Canada) for his personal assistance.

Supplementary data

Copies of ^{1}H NMR, and ^{13}C NMR spectra for all new compounds, experimental data for compounds **6b**,**c**,**e**,**f**,**h**,**i**, **7b**,**c**,**e**,**f**, **20b**,**c**,**e**,**f**,**h**,**i**, and **21b**,**c**,**e**,**f**, X-ray crystallography data for compounds **6e** and **7e**, and computational details are available. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.12.051

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Please cite this article in press as: Khalymbadzha, I. A.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2013.12.051