Synthesis and Anti-HIV Activity of Triazolo-Fused 2′,3′-Cyclic Nucleoside Analogs Prepared by an Intramolecular *Huisgen* 1,3-Dipolar Cycloaddition

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Triazolo-fused 2′,3′-cyclic nucleoside analogs were synthesized by an intramolecular 1,3-dipolar cycloaddition of nucleoside-derived azido alkynes in a regio- and stereospecific manner. The uracil base in these target compounds was successfully transformed to the corresponding cytosine. The synthesized compounds were examined in a MAGI assay for their anti-HIV activities, and in a H9 T lymphocytes assay for their cell toxicities.

Introduction. – 2′,3′-Dideoxynucleosides, such as 3′-azido-3′-deoxythymidine (AZT; zidovudine) [1], 2′,3′-dideoxycytidine (ddC, zalcitabine) [2], 2′,3′-dideoxyinosine (ddI, didanosine) [3], and 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T, stavudine) [4], have played an important role in antiviral therapy against human immunodeficiency virus type 1 (HIV-1). The mechanism of action of these nucleosides includes their conversion by host cellular kinases into the corresponding triphosphate forms (dNTP), which then serve as competitive inhibitors for HIV reverse transcriptase and/or as chain terminators due to the lack of a 3′-OH functionality for further chain elongation for viral cDNA synthesis [5]. However, the usefulness of these medicines was disturbed because of emerging drug resistance and long-term toxicity. Although a combination therapy, known as 'cocktail' therapy, by employing two or three antiviral drugs together minimizes the encountered problems to a certain extend, the impasse of clinically new viral strains resistant to marketed drugs remains. In this context, there is an urgent need to investigate and develop new antiviral agents against HIV which could be used alone and/or in combination therapy [6].

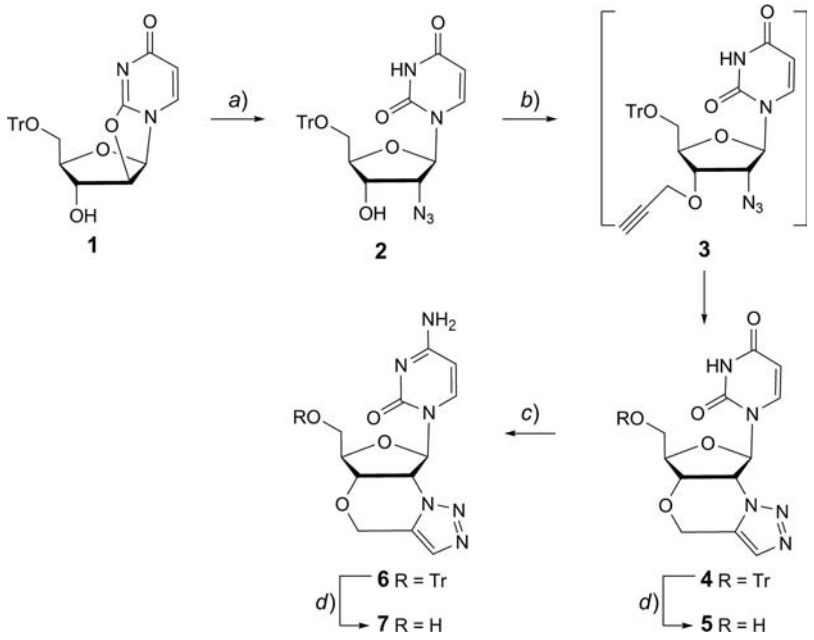
Although the causes of side effects are not exactly clear, structural simplicity of the existing antiviral nucleosides which makes them to lack selectivity between cellulous DNA polymerases and viral reverse transcriptase is one of reasons [5d]. Therefore, it is desirable to find new nucleoside analogs with a certain structural complexity, which would enhance the differentiation between the host and the viral enzymes, resulting in a better therapeutic index. Most nucleosides in solution typically exist in equilibrium between two major sugar pucker forms of N- and S-type, and the preferential conformation of a nucleoside, depending on the pattern and electronic feature of the substituents on the sugar ring, has a significant impact on its biological activity. In particular, the bridged nucleosides, constructed by linking two positions on the sugar *via* a newly-formed cyclic system, can be locked into one of these conformations and may better fulfill the requirements of the target biomolecules, leading to improved bioactivity profiles [7].

The *Huisgen* 1,3-dipolar cycloaddition between azides and alkynes as one of the most powerful 'click' reactions has gained considerable attention and has found many applications in recent years [8]. Adoption of this cycloaddition intramolecularly constitutes a powerful tool to construct triazolo-fused cyclic systems [9]. Several members of the 1,2,3-triazole family have been already shown to possess interesting biological properties [10], and the triazole with its novel structural features and physiochemical properties is regarded as a privileged structure in drug design and discovery [10a][11].

Our research efforts focus on developing synthetic methods for the construction of novel cyclic nucleoside analogs of antiviral and therapeutic relevance. We have previously reported the synthesis of 2′,3′-fused uridines *via* intramolecular *Michael* addition and of 4′-spironucleosides *via* 1,5-H shift reactions [12]. We recently reported a synthesis of triazolo-fused 3′,5′-cyclic nucleoside analogs *via* intramolecular *Huisgen* 1,3-dipolar cycloaddition, on the basis of consideration to combine a conformational-restriction concept with a triazole structure in the drug design [12e]. As a continuation, we report here the synthesis of triazolo-fused tricyclic 2′,3′-dideoxy nucleosides *via* an intramolecular 1,3-dipolar cycloaddition between a 2′-α-azido and a 3′-α- or 3′-β-alkynyl moiety and, alternatively, between a 3′-α-azido and a 2′-α- or 2′-β-alkynyl moiety of the uridine derivatives. The subsequent transformation of the uracil products to the corresponding cytosine nucleosides and the anti-HIV activities of some of the synthesized compounds are also included.

Results and Discussions. – Our first target was the construction of 2′,3′-fused cyclic uridine **4**. In this molecule the newly constructed ring is in *cis* configuration, and the triazole moiety is directly linked to C(2′). Therefore, according to structural features of the products, a retrosynthetic analysis leads to cycloaddition precursor **3**, in which the dipolar azido group at C(2′) and the propargyl group as dipole acceptor at C(3′) are in *cis*-configuration (*Scheme 1*). Thus, we started our synthesis from 2,2′-anhydro-5′-*O*-trityluridine (Tr = triphenylmethyl) **1** [13] by ring opening with NaN_3 at high temperature to introduce an N_3 group at C(2′). Selective propargylation of the OH group at C(3′) was carried out by the treatment of **2** with NaH under ultrasonic irradiation, followed by addition of 3-bromoprop-1-yne [14]. Although the formation of a less polar compound was indicated by TLC, we found that this compound was transformed during the reaction to a more polar product, which became the only one when the starting material **2** was totally consumed. We assume that the formed compound **3** underwent a cycloaddition to afford the cyclic compound **4** due to the proximity of N_3 and propargyl groups in *cis*-configuration (*Scheme 1*). Indeed, a polar compound was isolated by chromatographic purification, and its structure was elucidated as the triazolo-fused cyclic nucleoside **4** based on the ^{1}H-NMR and ^{13}C-NMR spectroscopic data, in which a resonance at 7.56 ppm for a H-atom, and two resonances at 142.1 and 139.5 ppm for two C-atoms characterized the triazole structure. A standard condition was employed for the deprotection of the 5′-*O*-Tr group to give 2′,3′-fused cyclic 5′-hydroxy-uridine **5**. The nucleobase uracil in compound **4** was successfully transformed, by a two-step procedure [15], to cytosine to give compound **6**, which was treated with acid for deprotection to give the corresponding 2′,3′-fused cyclic cytidine **7**.

Scheme 1

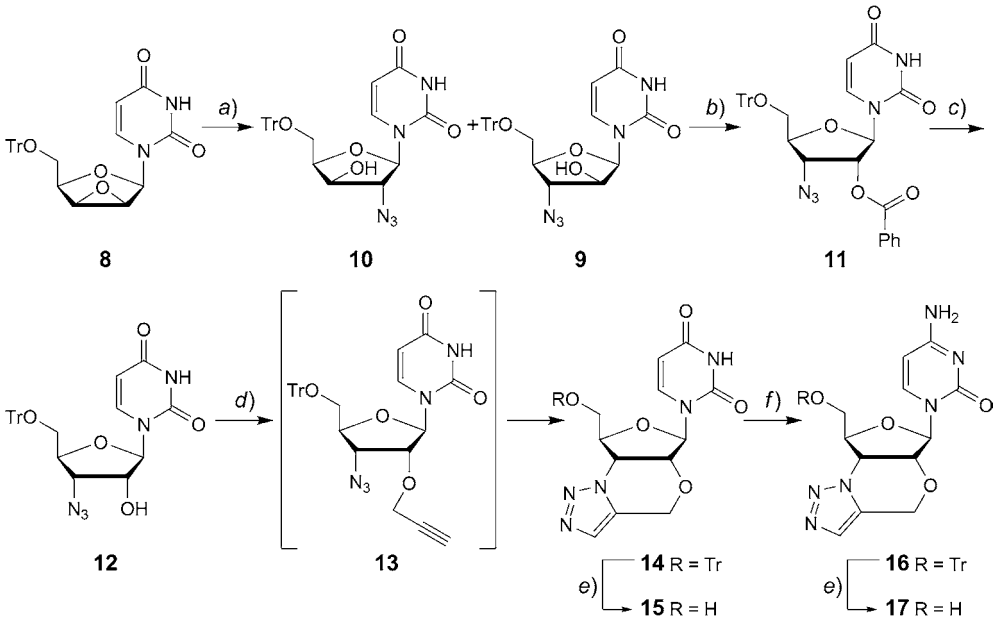


a) NaN_3, DMF, 140°, 65%. *b*) NaH, 3-bromoprop-1-yne, ultrasonic irradiation; 87%. *c*) 1. $POCl_3$, 1*H*-1,2,4-triazole, MeCN, Et_3N; 2. dioxane, NH_4OH; 60% (2 steps). *d*) AcOH, 40°; 80% for **5**, 76% for **7**. Tr = Triphenylmethyl.

We next attempted to synthesize 2′,3′-fused nucleosides **14** in which the newly constructed ring is also in *cis*-configuration, but the triazole moiety is linked to C(3′) (*Scheme 2*). Based on the retrosynthetic analysis, we prepared first the cycloaddition precursor **13**. Thus, ring opening of 2′,3′-epoxide uridine [16] with NaN_3 in DMF at 130° led to a mixture of 3′-azido-arabinofuranose-containing **9** and 2′-azido-xylofuranose-containing **10** in a ratio of 7:3. After separation of these two isomers, the configuration at C(2′) of **9** was inverted by a three-step transformation involving mesylation of the 2′-OH group, replacement of the methylsulfonyl group by the benzoate anion to give compound **11**, and hydrolysis of the PhCO group with NaOH to afford **12**. The same conditions were employed for selective propargylation on 2′-OH of compound **12**, and similarly we obtained product **14** by an intramolecular cycloaddition of **13** during this reaction. Again the uracil compound **14** was converted to the corresponding cytosine derivative **16** by the same procedure for nucleobase transformation as described for compound **4**. Removal of the Tr group of **14** and **16** afforded **15** and **17**, respectively, with free 5′-OH groups.

Next, we attempted at the synthesis of 2′,3′-fused nucleosides **19** and **24**, in which the newly constructed ring is *trans*-configurated, and the triazole moiety is alternatively connected with C(2′) or C(3′). We intended to examine the feasibility of the intramolecular 1,3-dipolar cycloaddition for the synthesis of such *trans*-fused cyclic nucleosides and to probe the stereochemical requirements for the antiviral activity of

Scheme 2

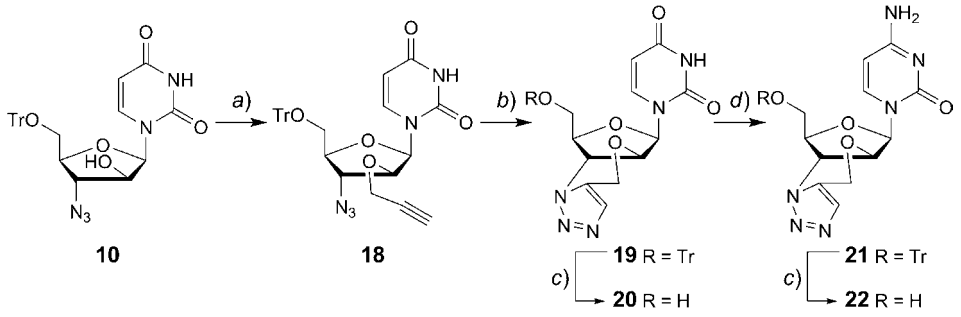


a) NaN_3, DMF, 130°, 65%. *b*) 1. MsCl, CH_2Cl_2, Et_3N; 2. PhCOOK, DMF, 100°; 68% (2 steps). *c*) NaOH, MeOH, r.t.; 75%. *d*) NaH, THF, 3-bromoprop-1-yne, ultrasonic irradiation; 40%. *e*) 80% AcOH, 40°, 70%. *f*) 1. $POCl_3$, 1*H*-1,2,4-triazole, MeCN, Et_3N; 2. dioxane, NH_4OH; 60% (2 steps).

these compounds. Starting from compounds **9** or **10** under similar conditions for selective propargylation of the OH group gave precursor **18** or **23**, respectively (*Schemes 3* and *4*). In contrast to the precursors of **4** and **13** which underwent spontaneous cycloaddition during propargylation, **18** and **23** could be isolated. This can be rationalized by the *trans*-configuration of N_3 and propargyl groups in **18** or **23**, the distances from each other making the cycloaddition less feasible compared to that of **4** and **13**. However, cycloaddition reaction took place, when **18** or **23** was dissolved in toluene and heated at reflux, to give the desired cyclized product **19** or **24**, respectively. By similar procedures for deprotection and nucleobase transformation as for compound **4**, **19** was converted to **20**, **21**, and **22**, respectively, and **24** correspondingly gave **25**, **26**, and **27**.

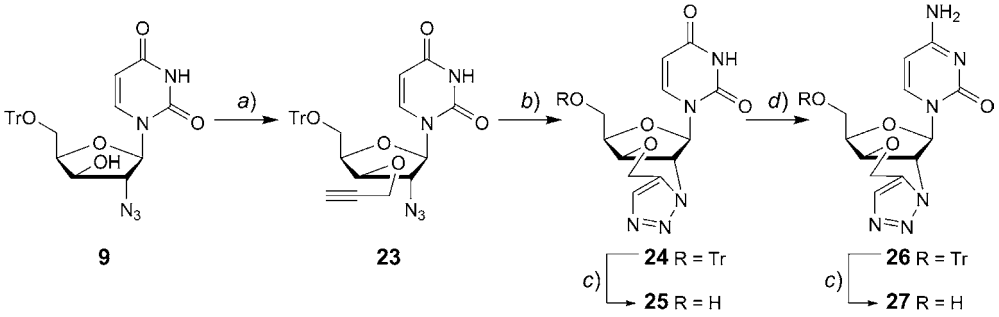
Finally, we selected the synthesized compounds **5**, **7**, **20**, and **22** for the primary evaluation of their anti-HIV activities. These compounds contain free 5′-OH groups and represent some key structural features of target molecules, such as *cis*- and *trans*-fused rings, the triazole moiety, and uracil and cytosine as nucleobases. In the biological tests, MAGI-CCR5 cells were infected by HIV-1 NL4-3 particle with a treatment of 50 μM of each compound. The cell toxicities of these compounds were evaluated with H9 T lymphocytes. 3′-Azidothymidine (AZT) was selected as the reference compound in the tests (viral infectivity as 1, and cell toxicity as 100). The test results indicated that compound **22** possesses the most significant antiviral activity with relatively low cell

Scheme 3



a) NaH, THF, 3-bromoprop-1-yne, ultrasonic irradiation; 40%. *b*) Toluene, reflux; 87%. *c*) 80% AcOH, 40°, 70%. *d*) 1. $POCl_3$, 1*H*-1,2,4-triazole, MeCN, Et_3N; 2. dioxane, NH_4OH; 60% (2 steps).

Scheme 4



a) NaH, THF, 3-bromoprop-1-yne, ultrasonic irradiation; 70%. *b*) Toluene, reflux; 87%. *c*) 80% AcOH, 40°; 70%. *d*) 1. $POCl_3$, 1*H*-1,2,4-triazole, MeCN, Et_3N; 2. dioxane, NH_4OH; 60% (2 steps).

toxicity (viral infectivity 67, cell toxicity 100) among the tested compounds. However, all the tested triazolo-fused cyclic compounds exhibited inferior anti-HIV activities compared with the reference compound AZT.

Conclusions. – We have demonstrated that intramolecular 'click chemistry' involving azido and alkynyl groups is a powerful tool to synthesize triazolo-cyclic 2′,3′-fused nucleosides. The triazole moiety of these analogs has been shown to be tolerated in a standard procedure for transforming 4-carbonyl to 4-amino group in a nucleobase. Some of the novel compounds showed moderate anti-HIV activities. Extension of this methodology to the synthesis of other relevant triazolo-fused cyclic nucleosides in searching for antiviral agents are under investigation in our laboratory, and the results will be disclosed in due course.

Experimental Part

General. All reactions were carried out under N_2. CH_2Cl_2 was dried (anh. $CaCl_2$). All other commercial reagents were used as received without additional purification. Anal. TLC: 2.5 × 5 cm plates coated with a 0.25-mm thickness of silica gel *GF 254*. Column chromatography (CC): silica gel *G* (SiO_2; 200–300 mesh; *Qingdao Haiyang Chemical Company*, P. R. China). ^{1}H- and ^{13}C-NMR Spectra: at 300 (^{1}H) and 75 MHz (^{13}C), resp.; in $CDCl_3$ or (D_6) DMSO; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. HR-MS: *Bruker micrOTOF-Q-II* mass spectrometer equipped with an electrospray-ionization (ESI) source; in *m*/*z*. MS: *Applied-Biosystems-ABI-Q-Trap* mass spectrometer equipped with an atmospheric-pressure chemical-ionization (APCI) source; in *m*/*z*.

3′-Deoxy-3′-azido-5′-O-*(triphenylmethyl)uridine* (=*1-(2-Azido-2-deoxy-5*-O-*(triphenylmethyl)-β*-L-*ribofuranosyl)pyrimidine-2,4(1*H,*3*H*)-dione*; **2**). To a soln. of **1** (0.319 g, 0.68 mmol) in dry DMF (7 ml) was added NaN_3 (0.221 g, 3.4 mmol), and the mixture was heated to 130° for 5 h, until the reactant was consumed (checked by TLC). Then, the mixture was cooled to r.t. 70 ml of H_2O were added, and the mixture was extracted with AcOEt (3 × 30 ml). The combined extract was dried (Na_2SO_4) and concentrated, and the crude product was purified by CC (SiO_2; CH_2Cl_2/MeOH 50 : 1): **2** (0.225 g, 65%). ^{1}H-NMR ($CDCl_3$): 9.83 (*s*, 1 H); 7.93 (*d*, *J* = 8.1, 1 H); 5.97 (*d*, *J* = 2.7, 1 H); 5.37 (*d*, *J* = 8.1, 1 H); 4.54 (*s*, 1 H); 4.20 (*dd*, *J* = 5.1, 2.7, 1 H); 4.06 (*d*, *J* = 6.9, 1 H); 3.60 (*d*, *J* = 9.6, 1 H); 3.56–3.50 (*m*, 1 H); 2.95 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 163.5; 150.2; 143.1; 139.6; 128.6; 128.1; 127.5; 102.4; 87.8; 83.1; 69.7; 67.0; 61.6. HR-ESI-MS: 534.1749 ($[M+Na]^+$, $C_{28}H_{25}N_5NaO_5^+$; calc. 534.1753).

*1-{(5a*R,*6*S,*8*R,*8a*S*)-5a,6,8,8a-Tetrahydro-6-[triphenylmethoxy)methyl]-4*H-*furo[3,4-*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazin-8-yl}pyrimidine-2,4(1*H,*3*H*)-dione* (**4**). To a soln. of **2** (0.225 g, 0.44 mmol) in dry THF (5 ml) was added NaH (60%, 350 mg, 0.88 mmol), and the mixture was stirred in an ice-bath for 30 min. Then, progargyl bromide (1.30 ml, 15.0 mmol) was added, and the mixture was subjected to ultrasound irradiation (50 min) at r.t. After the reactants were consumed, 2 ml of MeOH and 5 ml H_2O were added to the mixture. Then, the mixture was extracted with AcOEt (3 × 2.5 ml). The combined extract was dried (Na_2SO_4) and concentrated, and the crude product was purified by CC (SiO_2, CH_2Cl_2/MeOH 80 : 1): **4** (0.145 g, 60%). ^{1}H-NMR ($CDCl_3$): 8.67 (*s*, 1 H); 7.73 (*d*, *J* = 8.1, 1 H); 7.56 (*s*, 1 H); 7.51–7.24 (*m*, 16 H); 6.24 (*d*, *J* = 8.1, 1 H); 5.54 (*d*, *J* = 8.1, 1 H); 5.12 (*dd*, *J* = 15.0, 8.1, 2 H); 4.76 (*d*, *J* = 14.7, 1 H); 4.48–4.34 (*m*, 2 H); 3.70 (*d*, *J* = 10.8, 1 H); 3.55 (*d*, *J* = 11.0, 1 H). ^{13}C-NMR ($CDCl_3$): 163.0; 150.3; 143.1; 139.5; 130.0; 128.7; 128.3; 127.8; 103.9; 8.3; 86.6; 82.7; 76.9; 63.9; 61.2; 59.1. HR-ESI-MS: 550.2093 ($[M+H]^+$, $C_{31}H_{28}N_5O_5^+$; calc. 550.2090).

*1-[(5a*R,*6*S,*8*R,*8a*S*)-5a,6,8,8a-Tetrahydro-6-(hydroxymethyl)-4*H-*furo[3,4-*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazin-8-yl]pyrimidine-2,4(1*H,*3*H*)-dione* (**5**). A soln. of **4** (0.2 g, 0.36 mmol) in 80% AcOH aq. (3.6 ml) was heated to 40° for 5 h. Then, the mixture was concentrated to dryness under reduced pressure and was purified by CC (SiO_2, CH_2Cl_2/MeOH 20 : 1): **5** (0.3 g, 60%). ^{1}H-NMR ((D_6)DMSO): 7.98 (*d*, *J* = 8.1, 1 H); 7.62 (*s*, 1 H); 5.98 (*d*, *J* = 8.1, 1 H); 5.75 (*d*, *J* = 8.1, 1 H); 5.26 (*dd*, *J* = 8.1, 5.1, 1 H); 5.18 (*d*, *J* = 15.2, 1 H); 4.85 (*d*, *J* = 15.2, 1 H); 4.68 (*d*, *J* = 4.8, 1 H); 4.24 (*t*, *J* = 3.6, 1 H); 3.73 (*d*, *J* = 3.7, 2 H). ^{13}C-NMR ((D_6)DMSO): 163.5; 150.8; 140.8; 131.2; 128.6; 103.5; 86.1; 84.1; 76.8; 61.6; 61.0; 58.4; 40.1; 39.8; 39.5; 39.2; 38.9. HR-ESI-MS: 330.0816 ($[M+Na]^+$, $C_{12}H_{13}N_5NaO_5^+$; calc. 330.0814).

*4-Amino-1-{(5a*R,*6*S,*8*R,*8a*S*)-5a,6,8,8a-tetrahydro-6-[triphenylmethoxy)methyl]-4*H-*furo[3,4-*b*][1,2,3]-triazolo[1,5-*d*][1,4]oxazin-8-yl}pyrimidin-2(1*H*)-one* (**6**). To a soln. of **5** (0.508 g, 0.925 mmol) in MeCN (10 ml), was added 1*H*-1,2,4-triazole (1.023 g, 14.8 mmol) and Et_3N (2.53 ml, 18.22 mmol), and the resulting mixture was stirred at 0° for 0.5 h under N_2. $POCl_3$ (0.3 ml, 3.37 mmol) was then added, and the mixture was filtered, and the solid was washed with a soln. of Et_3N/MeCN 1 : 4 (50 ml). The filtrate was evaporated to dryness, and the residue was dissolved in dioxane (5 ml) and treated with sat. $NH_3 \cdot H_2O$ (2 ml). After stirring for 12 h, the mixture was concentrated, and the crude product was purified by CC (SiO_2, CH_2Cl_2/MeOH 50 : 1): **6** (0.3 g, 60%). ^{1}H-NMR ((D_6)DMSO): 7.73 (*d*, *J* = 7.4, 1 H); 7.61 (*s*, 1 H); 7.47–7.17 (*m*, 22 H); 6.06 (*d*, *J* = 8.1, 1 H); 5.75 (*d*, *J* = 7.3, 1 H); 5.33 (*dd*, *J* = 8.1, 5.1, 1 H); 5.16 (*d*, *J* = 15.1, 1 H); 4.86 (*d*, *J* = 15.2, 1 H); 4.68 (*d*, *J* = 5.1, 1 H); 4.26 (*s*, 1 H); 3.49 (*dd*, *J* = 10.3, 4.5, 1 H); 3.38 (*dd*, *J* = 10.1, 4.2, 1 H). ^{13}C-NMR ((D_6)DMSO): 165.5; 155.0; 143.3; 140.9; 131.5; 131.4; 130.6; 128.3; 127.9; 127.8; 127.2; 95.4; 86.8; 86.5; 81.2; 79.1; 76.0; 63.8; 60.5; 57.5. HR-ESI-MS: 549.2251 ($[M+H]^+$, $C_{31}H_{29}N_6O_4^+$; calc. 549.2250).

*4-Amino-1-[(5a*R*,6*S*,8*R*,8a*S*)-5a,6,8,8a-tetrahydro-6-(hydroxymethyl)-4*H*-furo[3,4-*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazin-8-yl]pyrimidin-2(1*H*)-one* (**7**). As described for **5**. ^{1}H-NMR ((D$_6$)DMSO): 7.93 (*d*, *J* = 7.5, 1 H); 7.63 (*s*, 1 H); 7.42 (*d*, *J* = 25.2, 2 H); 6.03 (*d*, *J* = 8.4, 1 H); 5.88 (*d*, *J* = 7.5, 1 H); 5.25 (*dd*, *J* = 8.4, 4.8, 1 H); 5.18 (*d*, *J* = 15.2, 1 H); 4.84 (*d*, *J* = 15.2, 1 H); 4.64 (*d*, *J* = 4.8, 1 H); 4.19 (*t*, *J* = 3.6, 1 H); 3.68 (*d*, *J* = 3.6, 2 H). ^{13}C-NMR ((D$_6$)DMSO): 165.9; 155.7; 142.2; 131.0; 128.3; 96.1; 87.4; 83.6; 76.9; 61.7; 60.9; 58.1. HR-ESI-MS: 307.1154 ([*M* + H]$^+$, $C_{12}H_{15}N_6O_4^+$; calc. 307.1155).

*1-(3-Azido-3-deoxy-5-*O*-(triphenylmethyl)-β-*D*-arabinofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione* (**9**) *and 1-(2-Azido-2-deoxy-5-*O*-(triphenylmethyl)-β-*D*-xylofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione* (**10**). To a soln. of **8** (5.0 g, 10.68 mmol) in dry DMF (100 ml) was added NaN_3 (3.47 g, 53.42 mmol), and the mixture was heated to 130° for 5 h. After the reactants were consumed, 500 ml of H_2O were added, and the mixture was extracted with AcOEt (3 × 100 ml). The combined extract was dried (Na_2SO_4) and concentrated, and the crude product was purified by CC (SiO_2; CH_2Cl_2/MeOH 60 :1): pure **9** (3.55 g, 65%) and **10** (1.64 g, 30%).

Data of **9**. ^{1}H-NMR ($CDCl_3$): 10.47 (*s*, 1 H); 7.48 (*dd*, *J* = 7.6, 3.4, 8 H); 7.37 – 7.01 (*m*, 14 H); 5.80 (*s*, 1 H); 5.24 (*d*, *J* = 8.4, 1 H); 4.58 (*s*, 1 H); 4.47 (*s*, 1 H); 4.26 (*s*, 1 H); 4.14 (*s*, 1 H); 3.59 (*ddd*, *J* = 14.4, 10.5, 5.0, 2 H). ^{13}C-NMR ($CDCl_3$): 165.6; 150.5; 143.4; 141.1; 128.7; 128.7; 127.9; 127.8; 127.7; 127.1; 127.0; 100.1; 90.8; 87.0; 84.6; 73.3; 70.0; 61.8. HR-ESI-MS: 534.1746 ([*M* + H]$^+$, $C_{28}H_{25}N_5NaO_5^+$; calc. 534.1753).

Data of **10**. ^{1}H-NMR ($CDCl_3$): 10.35 (*s*, 1 H); 8.02 (*d*, *J* = 8.1, 1 H); 7.48 – 7.25 (*m*, 17 H); 6.12 (*d*, *J* = 5.4, 1 H); 5.37 (*d*, *J* = 8.1, 1 H); 5.11 (*d*, *J* = 5.4, 1 H); 4.61 – 4.55 (*m*, 1 H); 4.23 (*t*, *J* = 7.8, 1 H); 3.77 (*d*, *J* = 8.1, 1 H); 3.60 – 3.38 (*m*, 2 H); 1.73 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 164.6; 151.1; 143.1; 141.8; 128.6; 128.0; 127.4; 101.5; 87.7; 85.0; 79.6; 75.6; 63.8; 61.4. HR-ESI-MS: 534.1740 ([*M* + Na]$^+$, $C_{28}H_{25}N_5NaO_5^+$; calc. 534.1753).

*3′-Azido-2′-*O*-benzoyl-3′-deoxy-5′-*O*-(triphenylmethyl)uridine* (**11**). To a soln. of **9** (2.78 g, 5.5 mmol) in dry CH_2Cl_2 (50 ml) was added Et_3N (8.2 ml, 8.2 mmol), and then MsCl (0.63 ml, 8.2 mmol) was added into the reaction system in ice-bath. After the consumption of the reactant, 30 ml of H_2O were added, and the mixture wase extracted with CH_2Cl_2 (3 × 50 ml), The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to obtain a crude product that was dissolved in dry DMF, and PhCOOK (1.31 g, 8.2 mmol) was added, and the mixture was heated to 100° for 4 h. Then, 500 ml of H_2O were added, and the mixture was extracted with AcOEt (3 × 200 ml). The combined extract was dried (Na_2SO_4) and concentrated, and the crude product was purified by CC (SiO_2; CH_2Cl_2/MeOH 70 :1): **11** (1.85 g, 56%; two steps). ^{1}H-NMR ($CDCl_3$): 8.79 (*s*, 1 H); 7.76 (*d*, *J* = 8.1, 1 H); 7.66 – 7.57 (*m*, 1 H); 7.51 – 7.47 (*m*, 2 H); 7.46 – 7.29 (*m*, 19 H); 7.26 (*s*, 1 H); 6.21 (*d*, *J* = 4.5, 1 H); 5.78 (*dd*, *J* = 5.7, 4.5, 1 H); 5.44 (*dd*, *J* = 8.1, 1.8, 1 H); 4.53 (*t*, *J* = 5.7, 1 H); 4.20 – 4.13 (*m*, 1 H); 3.63 (*dd*, *J* = 11.1, 2.7, 1 H); 3.49 (*dd*, *J* = 11.1, 2.7, 1 H). ^{13}C-NMR ($CDCl_3$): 157.9; 137.7; 134.8; 128.7; 124.9; 123.5; 123.4; 123.1; 123.0; 122.4; 121.9; 97.7; 82.4; 76.6; 70.4; 57.3; 55.2. HR-ESI-MS: 638.2009 ([*M* + Na]$^+$, $C_{35}H_{29}N_5NaO_6^+$; calc. 638.2016).

*3′-Azido-3′-deoxy-5′-*O*-(triphenylmethyl)uridine* (**12**). To a soln. of **11** (1.85 g, 3.1 mmol) in 160 ml of MeOH was added NaOH (0.4 g, 10 mmol), and the resulting mixture was stirred for 2 h at r.t. After consumption of the reactants, the mixture was evaporated to dryness *in vacuo* to obtain a crude product that was purified by CC (SiO_2; CH_2Cl_2/MeOH 50 :1): **12** (1.09 g, 70%). White solid. ^{1}H-NMR ($CDCl_3$): 10.27 (*s*, 1 H); 7.98 (*d*, *J* = 7.8, 1 H); 7.44 – 7.28 (*m*, 16 H); 5.87 (*s*, 1 H); 5.35 (*d*, *J* = 8.1, 1 H); 4.58 (*s*, 1 H); 4.30 (*d*, *J* = 7.2, 1 H); 4.10 (*d*, *J* = 5.7, 1 H); 3.62 (*d*, *J* = 10.5, 1 H); 3.47 (*d*, *J* = 7.8, 2 H). ^{13}C-NMR ($CDCl_3$): 163.5; 151.3; 143.0; 139.9; 128.6; 128.1; 127.5; 102.5; 90.5; 87.7; 81.0; 76.1; 61.7; 59.3. HR-ESI-MS: 534.1748 ([*M* + Na]$^+$,$C_{28}H_{25}N_5NaO_5^+$; calc. 534.1753).

*1-{(5a*R*,6*R*,8*S*,8a*R*)-5a,6,8,8a-Tetrahydro-8-[(triphenylmethoxy)methyl]-4*H*-furo[3,4-*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazin-6-yl}pyrimidine-2,4(1*H*,3*H*)-dione* (**14**). As described for **4**: pure **14** (0.19 g, 60%) ^{1}HNMR ($CDCl_3$): 8.86 (*s*, 1 H); 8.06 (*d*, *J* = 8.4, 1 H); 7.56 (*s*, 1 H); 7.53 – 7.27 (*m*, 18 H); 6.04 (*s*, 1 H); 5.48 (*dd*, *J* = 9.0, 4.5, 1 H); 5.25 (*d*, *J* = 8.4, 1 H); 5.17 (*d*, *J* = 15.3, 1 H); 4.84 (*d*, *J* = 15.6, 1 H); 4.60 (*d*, *J* = 4.8, 1 H); 4.20 (*d*, *J* = 9.0, 1 H); 3.98 (*dd*, *J* = 11.7, 3.0, 1 H); 3.70 (*dd*, *J* = 11.1, 1.5, 1 H). ^{13}C-NMR ($CDCl_3$): 163.5; 150.1; 143.0; 140.3; 129.5; 128.6; 128.5; 128.1; 128.0; 127.6; 127.4; 102.3; 89.3; 87.9; 82.7; 80.1; 61.2; 60.8; 53.9. HR-ESI-MS: 550.2096 ([*M* + H]$^+$, $C_{31}H_{28}N_5O_5^+$; calc. 550.2090).

*1-[(5a*R*,6*R*,8*S*,8a*R*)-5a,6,8,8a-Tetrahydro-8-(hydroxymethyl)-4*H*-furo[3,4-*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazin-6-yl]pyrimidine-2,4(1*H*,3*H*)-dione* (**15**). As described for **5**. ^{1}H-NMR ((D$_6$)DMSO): 11.48

(*s*, 1 H); 8.01 (*d*, *J* = 8.1, 1 H); 7.66 (*s*, 1 H); 5.94 (*s*, 1 H); 5.68 (*d*, *J* = 8.1, 1 H); 5.40 (*s*, 1 H); 5.19 (*d*, *J* = 15.3, 2 H); 4.84 (*s*, 1 H); 4.79 (*s*, 1 H); 4.01 (*s*, 2 H); 3.92–3.81 (*m*, 1 H). ^{13}C-NMR ((D$_6$)DMSO): 163.2; 150.2; 141.3; 141.2; 130.6; 130.5; 128.0; 127.9; 101.8; 101.7; 89.2; 89.2; 83.4; 83.4; 79.1; 79.0; 60.6; 59.4; 53.5. HR-ESI-MS: 308.0998 ([*M* + H]$^+$, $C_{12}H_{14}N_5O_5^+$; calc. 308.0995).

*4-Amino-1-[(5a*R,*6*R,*8*S,*8a*R*)-5a,6,8,8a-tetrahydro-8-[(triphenylmethox)methyl]-4*H-*furo[3,4-*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazin-6-yl]pyrimidin-2(1*H*)-one* (**16**). As described for **6**. ^{1}H-NMR (CDCl$_3$): 8.15 (*d*, *J* = 7.5, 1 H); 7.57–7.24 (*m*, 21 H); 6.04 (*s*, 1 H); 5.39 (*dd*, *J* = 9.3, 4.5, 1 H); 5.32 (*d*, *J* = 7.5, 1 H); 5.09 (*d*, *J* = 15.3, 1 H); 4.77 (*d*, *J* = 15.6, 1 H); 4.58 (*d*, *J* = 4.5, 1 H); 4.20 (*d*, *J* = 9.0, 1 H); 3.90 (*dd*, *J* = 11.4, 2.7, 1 H); 3.71 (*d*, *J* = 10.2, 1 H). ^{13}C-NMR (CDCl$_3$): 166.1; 155.5; 143.3; 140.9; 129.8; 128.6; 127.9; 127.2; 95.1; 90.0; 87.6; 82.3; 80.0; 77.4; 77.0; 76.6; 61.2; 61.0; 53.9. HR-ESI-MS: 549.2245 ([*M* + H]$^+$, $C_{31}H_{29}N_6O_4^+$; calc. 549.2250).

*4-Amino-1-[(5a*R,*6*R,*8*S,*8a*R*)-5a,6,8,8a-tetrahydro-8-(hydroxymethyl)-4*H-*furo[3,4-*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazin-6-yl]pyrimidin-2(1*H*)-one* (**17**). As described for **5**. ^{1}H-NMR ((D$_6$)DMSO): 7.98 (*d*, *J* = 7.5, 1 H); 7.65 (*s*, 1 H); 7.30 (*d*, *J* = 17.1, 2 H); 5.92 (*s*, 1 H); 5.76 (*d*, *J* = 7.5, 1 H); 5.43 (*s*, 1 H); 5.17 (*d*, *J* = 15.0, 1 H); 5.13–5.10 (*m*, 1 H); 4.81 (*d*, *J* = 15.0, 1 H); 4.68 (*d*, *J* = 4.9, 1 H); 4.03 (*d*, *J* = 12.6, 1 H); 3.97 (*d*, *J* = 9.3, 1 H); 3.88–3.82 (*m*, 1 H). ^{13}C-NMR ((D$_6$)DMSO): 166.0; 154.9; 142.1; 130.8; 128.0; 94.3; 90.1; 83.5; 79.5; 60.6; 59.7; 53.8. HR-ESI-MS: 307.1146 ([*M* + H]$^+$, $C_{12}H_{15}N_6O_4^+$; calc. 307.1155).

*1-[3-Azido-3-deoxy-2-*O*-(prop-2-yn-1-yl)-5-*O*-(triphenylmethyl)-β-*D*-arabinofuranosyl]pyrimidine-2,4(1*H,*3*H*)-dione* (**18**). To a soln. of **18** (0.47 g, 0.91 mmol) in dry THF (9 ml) was added NaH (60% in oil; 0.073 g, 1.82 mmol), and the mixture was stirred in an ice-bath for 30 min. Then, allyl bromide (0.08 ml, 0.96 mmol) was added, and the mixture was subjected ultrasound irradiation (50 min) at r.t. After consumption of the reactants, MeOH (3 ml) and 9 ml of H_2O were added separatedly, and the mixture was extracted with AcOEt (3 × 4.5 ml). The combined extracts were dried (Na_2SO_4) to give a crude product that was purified by CC (SiO_2; CH_2Cl_2/MeOH 80 : 1): **18** (0.32 g, 66%). ^{1}H-NMR (CDCl$_3$): 7.81 (*d*, *J* = 8.1, 1 H); 7.63–7.09 (*m*, 26 H); 6.24 (*d*, *J* = 6.0, 1 H); 5.44 (*d*, *J* = 8.1, 1 H); 4.36 (*t*, *J* = 6.6, 1 H); 4.30–4.16 (*m*, 3 H); 3.83–3.74 (*m*, 1 H); 3.55 (*dd*, *J* = 11.1, 3.2, 1 H); 3.41 (*dd*, *J* = 11.1, 3.2, 1 H); 2.54 (*t*, *J* = 2.4, 1 H). HR-ESI-MS: 550.2097 ([*M* + H]$^+$, $C_{31}H_{28}N_5O_5^+$; calc. 550.2090).

*1-[(5a*S,*6*R,*8*S,*8a*R*)-5a,6,8,8a-Tetrahydro-8-[(triphenylmethoxy)methyl]-4*H-*furo[3,4-*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazin-6-yl]pyrimidine-2,4(1*H,*3*H*)-dione* (**19**). A soln. of **18** (0.284 g, 0.52 mmol) in 10 ml of toluene was heated to reflux for 24 h, and then it was cooled to r.t. The mixture was concentrated *in vacuo* to obtain a crude product that was purified by a short CC (SiO_2, CH_2Cl_2/MeOH 40 : 1): pure **3** (0.23 g, 80%). ^{1}H-NMR (CDCl$_3$): 9.16 (*s*, 1 H); 8.39 (*d*, *J* = 8.1, 1 H); 7.63 (*s*, 1 H); 7.52–7.28 (*m*, 17 H); 6.39 (*d*, *J* = 6.0, 1 H); 5.32 (*dd*, *J* = 15.3, 7.9, 2 H); 5.19 (*s*, 1 H); 5.17–5.11 (*m*, 1 H); 4.86 (*t*, *J* = 10.2, 1 H); 4.40 (*d*, *J* = 9.9, 1 H); 4.36–4.24 (*m*, 2 H); 3.75 (*d*, *J* = 10.7, 1 H). ^{13}C-NMR (CDCl$_3$): 163.2; 150.7; 143.4; 140.6; 132.1; 129.0; 129.0; 128.8; 128.4; 127.6; 101.4; 87.4; 79.7; 79.4; 76.9; 64.5; 62.4; 54.2. HR-ESI-MS: 550.2100 ([*M* + H]$^+$, $C_{31}H_{28}N_5O_5^+$; calc. 550.2090).

*1-[(5a*S,*6*R,*8*S,*8a*R*)-5a,6,8,8a-Tetrahydro-8-(hydroxymethyl)-4*H-*furo[3,4-*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazin-6-yl]pyrimidine-2,4(1*H,*3*H*)-dione* (**20**). As described for **5**. ^{1}H-NMR ((D$_6$)DMSO): 8.26 (*d*, *J* = 8.1, 1 H); 7.69 (*s*, 1 H); 6.29 (*d*, *J* = 6.0, 1 H); 5.60 (*d*, *J* = 8.1, 1 H); 5.31 (*d*, *J* = 15.3, 1 H); 5.08 (*d*, *J* = 15.6, 1 H); 4.65 (*dd*, *J* = 10.2, 6.3, 1 H); 4.54 (*t*, *J* = 9.9, 1 H); 4.40 (*d*, *J* = 9.6, 1 H); 4.10 (*s*, 2 H). ^{13}C-NMR ((D$_6$)DMSO): 163.2; 150.4; 140.1; 131.6; 128.7; 101.2; 79.4; 79.2; 78.3; 64.0; 59.5; 53.4. HR-ESI-MS: 308.0999 ([*M* + H]$^+$, $C_{12}H_{14}N_5O_5^+$; calc. 308.0995).

*4-Amino-1-[(5a*S,*6*R,*8*S,*8a*R*)-5a,6,8,8a-tetrahydro-8-[(triphenylmethoxy)methyl]-4*H-*furo[3,4-*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazin-6-yl]pyrimidin-2(1*H*)-one* (**21**). As described for **6**. ^{1}H-NMR ((D$_6$)DMSO): 8.08 (*s*, 1 H); 7.70 (*s*, 1 H); 7.41 (*d*, *J* = 22.1, 23 H); 6.40 (*s*, 1 H); 5.42 (*s*, 1 H); 5.27 (*s*, 1 H); 5.11 (*s*, 1 H); 4.91 (*s*, 1 H); 4.62 (*s*, 1 H); 4.51 (*s*, 1 H); 3.87 (*s*, 1 H); 3.63 (*s*, 1 H). ^{13}C-NMR ((D$_6$)DMSO): 165.5; 155.0; 143.2; 140.7; 131.7; 128.6; 128.3; 128.0; 127.2; 93.8; 86.8; 79.4; 79.3; 76.0; 63.9; 62.2; 54.0. HR-ESI-MS: 549.2247 ([*M* + H]$^+$, $C_{31}H_{29}N_6O_4^+$; calc. 549.2250).

*4-Amino-1-[(5a*S,*6*R,*8*S,*8a*R*)-5a,6,8,8a-tetrahydro-8-(hydroxymethyl)-4*H-*furo[3,4-*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazin-6-yl]pyrimidin-2(1*H*)-one* (**22**). As described for **5**. ^{1}H-NMR ((D$_6$)DMSO): 8.19 (*d*, *J* = 7.5, 1 H); 7.68 (*s*, 1 H); 7.23 (*d*, *J* = 32.1, 2 H); 6.36 (*d*, *J* = 5.7, 1 H); 5.71 (*d*, *J* = 7.5, 1 H); 5.26 (*d*, *J* = 15.0, 1 H); 5.04 (*d*, *J* = 15.6, 1 H); 4.63–4.57 (*m*, 1 H); 4.49 (*t*, *J* = 10.2, 1 H); 4.36 (*d*, *J* = 9.3, 1 H); 4.10 (*s*,

2 H). ^{13}C-NMR ((D$_6$)DMSO): 165.6; 155.3; 140.8; 131.6; 128.7; 93.9; 79.5; 79.4; 77.9; 63.9; 59.7; 53.5. HR-ESI-MS: 329.0978 ([M + Na]$^+$, $C_{12}H_{14}N_6NaO_4^+$; calc. 329.0974).

1-[2-Azido-2-deoxy-3-O-*(prop-2-yn-1-yl)-5*-O-*(triphenylmethyl)-β*-D-*xylofuranosyl]pyrimidine-2,4(1*H,*3*H*)-dione* (**23**). As described for **18**. ^{1}H-NMR (CDCl$_3$): 10.47 (*s*, 1 H); 7.48 (*dd*, *J* = 7.6, 3.4, 8 H); 7.37 – 7.01 (*m*, 14 H); 5.80 (*s*, 1 H); 5.24 (*d*, *J* = 8.4, 1 H); 4.58 (*s*, 1 H); 4.47 (*s*, 1 H); 4.26 (*s*, 1 H); 4.14 (*s*, 1 H); 3.59 (*ddd*, *J* = 14.4, 10.5, 5.0, 2 H). ^{13}C-NMR (CDCl$_3$): 165.6; 150.5; 143.4; 141.1; 128.7; 128.7; 127.9; 127.8; 127.7; 127.1; 127.0; 100.1; 90.8; 87.0; 84.6; 77.4; 77.0; 76.6; 73.3; 70.0; 61.8. HR-ESI-MS: 550.2097 ([M + H]$^+$, $C_{31}H_{28}N_5O_5^+$; calc. 550.2090).

*1-{(5a*R,*6*R,*8*R,*8a*R*)-5a,6,8,8a-Tetrahydro-6-[(triphenylmethoxy)methyl]-4*H-*furo[3,4-*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazin-8-yl}pyrimidine-2,4(1*H,*3*H*)-dione* (**24**). As described for **19**. ^{1}H-NMR (CDCl$_3$): 8.50 (*s*, 1 H); 7.74 (*d*, *J* = 8.1, 1 H); 7.64 (*s*, 1 H); 6.57 (*d*, *J* = 8.1, 1 H); 5.46 (*d*, *J* = 15.3, 1 H); 5.24 (*dd*, *J* = 5.7, 3.4, 1 H); 5.22 – 5.20 (*m*, 1 H); 5.15 (*s*, 1 H); 4.51 – 4.45 (*m*, 1 H); 4.41 (*d*, *J* = 8.1, 1 H); 3.67 (*dd*, *J* = 11.4, 2.1, 1 H); 3.40 (*dd*, *J* = 11.4, 2.7, 1 H). ^{13}C-NMR (CDCl$_3$): 162.4; 150.0; 142.8; 139.4; 130.8; 128.8; 128.7; 128.0; 127.4; 103.4; 88.7; 80.5; 77.8; 75.1; 64.7; 62.2; 58.8. HR-ESI-MS: 550.2096 ([M + H]$^+$, $C_{31}H_{28}N_5O_5^+$; calc. 550.2090).

*1-[(5a*R,*6*R,*8*R,*8a*R*)-5a,6,8,8a-Tetrahydro-6-(hydroxymethyl)-4*H-*furo[3,4-*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazin-8-yl]pyrimidine-2,4(1*H,*3*H*)-dione* (**25**). As described for **5**. ^{1}H-NMR ((D$_6$)DMSO): 8.09 (*d*, *J* = 8.1, 1 H); 7.68 (*s*, 1 H); 6.48 (*d*, *J* = 9.0, 1 H); 5.79 (*d*, *J* = 8.1, 1 H); 5.32 (*d*, *J* = 15.3, 1 H); 5.17 (*d*, *J* = 9.3, 1 H); 5.03 (*d*, *J* = 15.3, 1 H); 4.76 – 4.63 (*m*, 1 H); 4.34 (*d*, *J* = 7.8, 1 H); 3.73 (*s*, 2 H). ^{13}C-NMR ((D$_6$)DMSO): 163.7; 150.9; 140.2; 131.9; 128.8; 103.1; 79.9; 76.5; 76.0; 64.0; 62.8; 59.8; 57.6. HR-ESI-MS: 330.0813 ([M + Na]$^+$, $C_{12}H_{13}N_5NaO_5^+$; calc. 330.0814).

*4-Amino-1-{(5a*R,*6*R,*8*R,*8a*R*)-5a,6,8,8a-tetrahydro-6-[(triphenylmethoxy)methyl]-4*H-*furo[3,4-*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazin-8-yl}pyrimidin-2(1*H*)-one* (**26**). As described for **21**. ^{1}H-NMR (CDCl$_3$): 7.62 (*d*, *J* = 7.5, 1 H); 6.71 (*d*, *J* = 8.7, 1 H); 5.52 (*d*, *J* = 7.5, 1 H); 5.31 (*d*, *J* = 15.3, 1 H); 5.12 (*d*, *J* = 7.2, 1 H); 5.05 (*d*, *J* = 16.7, 1 H); 4.48 (*d*, *J* = 7.2, 2 H); 3.58 (*d*, *J* = 8.7, 1 H); 3.45 (*d*, *J* = 9.0, 1 H). ^{13}C-NMR (CDCl$_3$): 165.6; 150.5; 143.4; 141.1; 128.7; 127.9; 127.8; 127.7; 127.1; 127.0; 100.1; 90.8; 87.0; 84.6; 77.0; 76.6; 73.3; 70.0; 61.8. HR-ESI-MS: 549.2266 ([M + H]$^+$, $C_{31}H_{29}N_6O_4^+$; calc. 549.2250).

*4-Amino-1-[(5a*R,*6*R,*8*R,*8a*R*)-5a,6,8,8a-tetrahydro-6-(hydroxymethyl)-4*H-*furo[3,4-*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazin-8-yl]pyrimidin-2(1*H*)-one* (**27**). As described for **5**. ^{1}H-NMR ((D$_6$)DMSO): 8.00 (*d*, *J* = 7.5, 1 H); 7.66 (*s*, 1 H); 7.40 (*d*, *J* = 11.7, 2 H); 6.51 (*d*, *J* = 9.3, 1 H); 5.86 (*d*, *J* = 7.5, 1 H); 5.30 (*d*, *J* = 15.3, 1 H); 5.23 (*s*, 1 H); 5.15 (*t*, *J* = 9.3, 1 H); 5.03 (*d*, *J* = 15.3, 1 H); 4.69 – 4.61 (*m*, 1 H); 4.49 (*s*, 3 H); 4.36 – 4.26 (*m*, 1 H); 3.71 (*s*, 2 H). ^{13}C-NMR ((D$_6$)DMSO): 165.5; 154.9; 141.3; 131.7; 128.5; 95.3; 80.8; 76.8; 75.6; 63.8; 62.7; 57.5. HR-ESI-MS: 307.1153 ([M + H]$^+$, $C_{12}H_{15}N_6O_4^+$; calc. 307.1155).

REFERENCES

[1] H. Mitsuya, K. J. Weinhold, P. A. Furman, M. H. S. Clair, S. Nusinoff-Lehrman, R. C. Gallo, D. Bolognesi, D. W. Barry, S. Broder, *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096; P. Herdewijn, J. Balzarini, E. De Clercq, R. Pauwels, M. Baba, M. Broder, H. Vanderhaeghe, *J. Med. Chem.* **1987**, *30*, 1270; S. M. Daluge, D. J. Purifoy, P. M. Savina, M. H. S. Clair, N. R. Parry, I. K. Dev, P. Novak, K. M. Ayers, J. E. Reardon, G. B. Roverts, *Antimicrob. Agents Chemother.* **1994**, *38*, 1590.

[2] H. Mitsuya, S. Broder, *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911; C. K. Chu, R. F. Schinazi, B. H. Arnold, D. L. Cannon, B. Doboszewski, V. B. Bhadti, Z. Gu, *Biochem. Pharmacol.* **1988**, *37*, 3543.

[3] E. De Clercq, A. Van Aerschot, P. Herdewijn, M. Baba, R. Pauwels, J. Balzarini, *Nucleosides Nucleotides* **1989**, *8*, 659; R. F. Schinazi, J. P. Sommadossi, V. Saalmann, D. L. Cannon, M. Y. Xie, G. C. Hart, G. A. Smith, E. F. Hahn, *Antimicrob. Agents Chemother.* **1990**, *34*, 1061.

[4] T.-S. Lin, R. F. Schinazi, W. H. Prusoff, *Biochem. Pharmacol.* **1987**, *36*, 2713; J. Balzarini, A. Van Aerschot, P. Herdewijn, E. De Clercq, *Biochem. Pharmacol.* **1989**, *38*, 869.

[5] a) D. M. Huryn, M. Okabe, *Chem. Rev.* **1992**, *92*, 1745; b) P. Herdewijn, *Drug Discovery Today* **1997**, *2*, 235; c) C. Len, G. Mackenzie, *Tetrahedron* **2006**, *62*, 9085; d) E. De Clercq, *Biochim. Biophys. Acta* **2002**, *1587*, 258.

[6] T. Cihlar, A. S. Ray, *Antiviral Res.* **2010**, *85*, 39.

[7] C. Zhou, J. Chattopadhyaya, *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 876.
[8] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem., Int. Ed.* **2001**, *40*, 2004; V. D. Bock, H. Hiemstra, J. H. van Maarseveen, *Eur. J. Org. Chem.* **2006**, 51; W. H. Binder, C. Kluger, *Curr. Org. Chem.* **2006**, *10*, 1791; W. H. Binder, R. Sachsenhofer, *Macromol. Rapid Commun.* **2007**, *28*, 15; W. H. Binder, R. Sachsenhofer, *Macromol. Rapid Commun.* **2008**, *29*, 952.
[9] V. Nair, T. D. Suja, *Tetrahedron* **2007**, *63*, 12247
[10] a) R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E. De Clercq, C.-F. Perno, A. Karlsson, J. Balzarini, M. J. Camarasa, *J. Med. Chem.* **1994**, *37*, 4185; b) M. J. Genin, D. A. Allwine, D. J. Anderson, M. R. Barbachyn, D. E. Emmert, S. A. Garmon, D. R. Graber, K. C. Grega, J. B. Hester, D. K. Hutchinson, J. Morris, R. J. Reischer, C. W. Ford, G. E. Zurenko, J. C. Hamel, R. D. Schaadt, D. Satpert, B. H. Yagi, *J. Med. Chem.* **2000**, *43*, 953; c) W. G. Lewis, L. G. Green, F. Grynszpan, Z. Radić, P. R. Carlier, P. Taylor, M. G. Finn, K. B. Sharpless, *Angew. Chem., Int. Ed.* **2002**, *41*, 1053; d) H. C. Kolb, K. B. Sharpless, *Drug Discovery Today* **2003**, *8*, 1128; e) G. C. Tron, T. Pirali, R. A. Billington, P. L. Canonico, G. Sorba, A. A. Genazzani, *Med. Res. Rev.* **2008**, *28*, 278.
[11] J.-F. Lutz, Z. Zarafshani, *Adv. Drug. Delivery Rev.* **2008**, *60*, 958; A. D. Moorhouse, J. E. Moses, *ChemMedChem* **2008**, *3*, 715; E. De Clercq, *Clin. Microbiol. Rev.* **1997**, *10*, 674; E. De Clercq, *Nat. Rev. Drug Discovery* **2002**, *1*, 13.
[12] a) J. Sun, J. Wu, H. Yang, *Helv. Chim. Acta* **2007**, *90*, 1917; b) J.-B. Sun, H. Yang, J.-C. Wu, *Acta Crystallogr., Sect. E* **2007**, *63*, o724; c) J.-B. Sun, H. Yang, J.-C. Wu, *Acta Crystallogr., Sect. E* **2007**, *63*, o978; d) S.-F. Dang, J.-B. Sun, X.-X. Xu, P. Wang, J.-C. Wu, *Chem. Res. Chin. Univ.* **2008**, *24*, 473; e) J. Sun, X. Liu, H. Li, R. Duan, J. Wu, *Helv. Chim. Acta* **2012**, *95*, 772.
[13] D. P. C. McGee, A. Vaughn-Settle, C. Vargeese, Y. Zhai, *J. Org. Chem.* **1996**, *61*, 781.
[14] K. Teste, L. Colombeau, A. Hadj-Bouazza, R. Lucas, R. Zerrouki, P. Krausz, Y. Champavier, *Carbohydr. Res.* **2008**, *343*, 1490.
[15] A. Matsuda, J. Yasuoka, T. Ueda, *Chem. Pharm. Bull.* **1989**, *37*, 1659.
[16] M. M. Faul, B. E. Huff, S. E. Dunlap, S. A. Frank, J. E. Fritz, S. W. Kaldor, M. E. LeToureau, M. A. Staszak, J. A. Ward, J. A. Werner, L. L. Winneroski, *Tetrahedron* **1997**, *53*, 8085.

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