Synthesis and Anti-HIV Activity of Triazolo-Fused 3′,5′-Cyclic Nucleoside Analogues Derived from an Intramolecular *Huisgen* 1,3-Dipolar Cycloaddition

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Triazolo-fused 3′,5′-cyclic nucleoside analogues were synthesized by an intramolecular 1,3-dipolar cycloaddition of nucleoside-derived azido-alkynes in a regio- and stereospecific manner. The thymine nucleoside base in these target compounds was transformed successfully into the corresponding 5-methylcytosine component. The synthesized compounds were examined in a MAGI assay for exploring the anti-HIV activity and in a H9 T lymphocytes assay for measuring the cell toxicity.

Introduction. – Modification of nucleosides has been demonstrated as one of the most promising pathways in searching for new therapeutic agents for the past decades [1]. Nucleoside reverse transcriptase inhibitors (NRTIs), structurally featured as 2′,3′-dideoxynucleoside analogs, constitute an important class of antiviral drugs that mechanistically act as chain terminators for the production of viral genomic material in its life cycle [2]. It has been revealed that the conformation of the sugar ring has a profound impact on the biological activity of nucleosides, and many cyclic nucleoside analogues with restricted conformation have been designed and synthesized to probe the conformational preference demanded by the specific enzyme, aiming at finding new and better drugs with improved profiles in drug resistance and delayed toxicity after long-term treatment [3][1c].

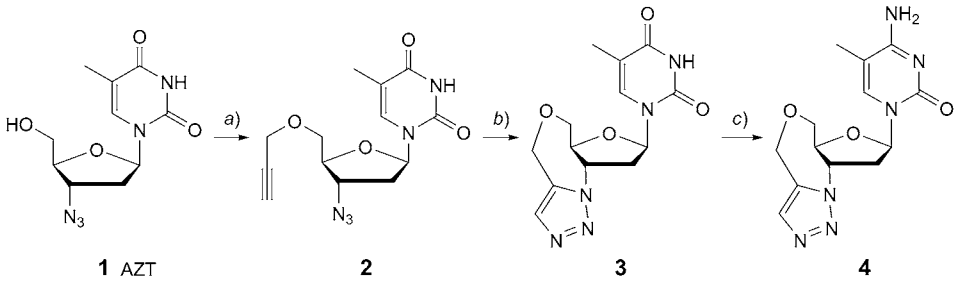
The *Huisgen* 1,3-dipolar cycloaddition between azides and alkynes as one of the most powerful click reactions has gained considerable attention and has found many applications in recent years [4]. Noteworthy, the five-membered 1,2,3-triazole moiety formed in this reaction has been employed as a widespread pharmacophore associated with anti-HIV, anti-allergic, antifungal, antimicrobial, and other biological activities [5]. Thus, the structural features and physiochemical properties of the triazole fragment are of great interest in drug design and discovery [6].

As our efforts in the development of synthetic methods for the construction of cyclic nucleoside analogues, we have previously reported the synthesis of 2′,3′-fused uridines *via* intramolecular *Michael* addition and of 4′-spironucleosides *via* 1,5-hydrogen translocation reactions [7]. We envisioned that enclosing a triazole moiety into cyclic nucleosides would lead to a type of unexplored and unique compounds that will combine a conformational-restriction concept with a triazole-structure feature in the drug design. Herein, we report the synthesis of triazolo-fused tricyclic nucleosides *via* intramolecular 1,3-dipolar cycloaddition between a 3′-α- or 3′-β-azido and a 5′-

alkyne moiety and, alternatively, between a 5′-azido and 3′-α- or 3′-β-alkyne moiety of thymidine and its 3′-epimer, respectively, and the subsequent transformation of the cyclized products into the corresponding 5-methylcytosine nucleosides (thymine = 5-methylpyrimidine-2,4(1*H*,3*H*)-dione; cytosine = 4-aminopyrimidin-2(1*H*)-one). Furthermore, the anti-HIV activities of all the target compounds are also described.

Results and Discussion. – We started our synthesis from azide **1** which was derived from thymidine following a literature procedure [8]. Selective propargylation (= prop-2-ynylation) of the 5′-OH group was conducted with propargyl bromide (= 3-bromoprop-1-yne) employing NaH as a base in THF under ultrasonic irradiation [9] to give the precursor **2** in 85% yield. The azido-alkyne derivative **2** was then heated under reflux in toluene [10] to afford the desired triazolo-fused cyclic compound **3** in 87% yield. The polar addition product was normally precipitated and purified by an easy procedure. Furthermore, the nucleobase thymine in the resulting cyclic nucleoside **3** was successfully transformed into 5-methylcytosine to give compound **4** in a moderate yield by means of a two-step procedure [11], firstly, by treatment with $POCl_3$ and 1*H*-1,2,4-triazole in the presence of Et_3N, and then by treatment with ammonia in dioxane (*Scheme 1*).

Scheme 1

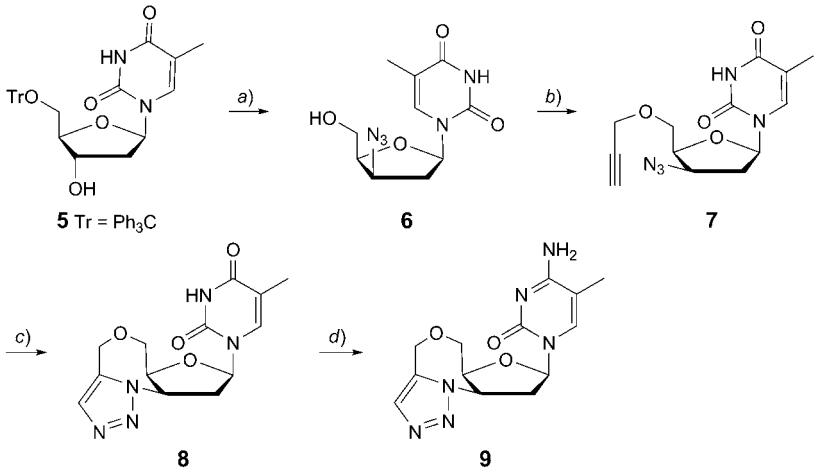


a) NaH, THF, propargyl bromide (= 3-bromoprop-1-yne), ultrasound; 85%. *b*) Toluene, reflux; 87%. *c*) 1. $POCl_3$, 1*H*-1,2,4-triazole, MeCN, Et_3N; 2. dioxane, $NH_3 \cdot H_2O$; 65% (2 steps).

To study the steric effect for the cycloaddition and to produce other novel compounds, we synthesized the 3′-β-azido compound **6** from **5** following a literature method [12] (*Scheme 2*). Selective propargylation of the 5′-hydroxy group was achieved under the same conditions as for the preparation of **2** to give precursor **7**, which was then cyclized to the triazolo-fused compound **8** and transformed to the 5-methylcyctosine compound **9** under the conditions shown in *Scheme 2*. Interestingly, we detected some amount of the cyclization product when compound **7** was placed at room temperature for a period of time. It is reasoned that the steric proximity of the azido and alkynyl groups in *cis* configuration in **7** made the cycloaddition with compound **7** more feasible in comparison to that with compound **2**.

Next, we synthesized compounds **10** [13] and **14** [14] as precursors, in which an azido group was introduced at the 5′ position while the propargyl functionality was attached at the 3′-α- or 3′-β position as ether appendage (*Scheme 3*). The precursors **11** and **15** were heated under reflux in toluene to produce the corresponding cyclic products **12**

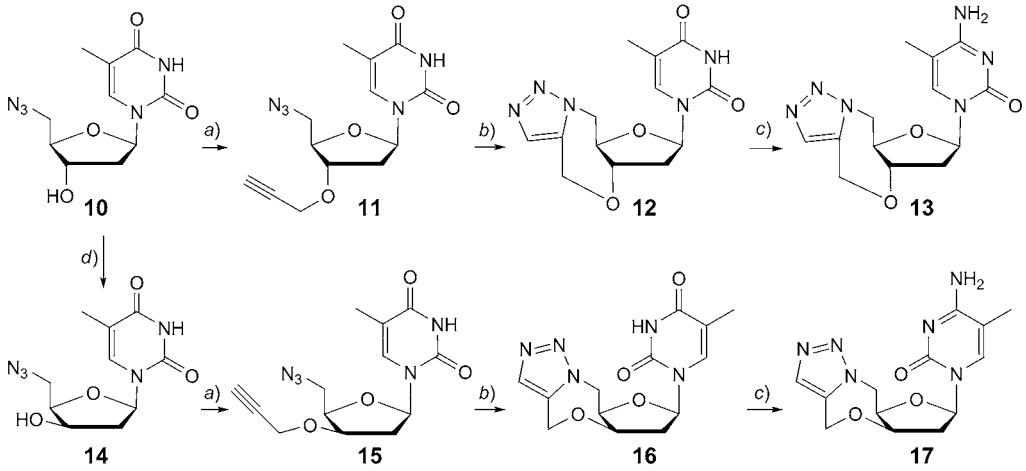
Scheme 2



a) 1. MsCl (= $MeSO_2Cl$), THF, Et_3N; 2. LiN_3, DMF, 100°; 3. 80% AcOH, 50°; 72% (3 steps). *b*) Propargyl bromide, THF, NaH; 75%. *c*) Toluene, reflux; 78%. *d*) 1. $POCl_3$, 1*H*-1,2,4-triazole, MeCN, Et_3N; 2. dioxane, $NH_3 \cdot H_2O$; 64% (2 steps).

and **16** which were transformed into the 5-methylcytosine products **13** and **17**, respectively. Similarly as with compound **7**, we observed that a cycloaddition reaction took place spontaneously when compound **15** was left standing at room temperature.

Scheme 3



a) Propargyl bromide, THF, NaH; 75%. *b*) Toluene, reflux; 78%. *c*) 1. $POCl_3$, 1*H*-1,2,4-triazole, MeCN, Et_3N; 2. dioxane, $NH_3 \cdot H_2O$; 50% (2 steps). *d*) 1. Ph_3P, DIAD (= diisopropyl azodicarboxylate = diisopropyl diazenedicarboxylate), DMF; 2. 1N NaOH (aq.), EtOH; 70% (2 steps).

The structures of the triazolo-fused nucleosides were established on the basis of their spectroscopic data. For example, a *s* at δ(H) 7.71 in the ^{1}H-NMR spectrum of **12** indicated the H-atom of triazole ring. In addition, in the ^{13}C-NMR spectrum, the triazole C(4) and C(5) resonances were observed at δ(C) 136.59 and 133.50 which is in accordance with characteristic ^{13}C-NMR shifts of 1,5-regioisomers [15]. Furthermore, compound **12** was crystallized from MeOH and AcOEt, and was subjected to X-ray crystal-structure analysis. The crystal structure (*Fig.*) unambiguously showed that the triazole moiety of the fused nucleoside was indeed 1,5-disubstited, and additionally, that the sugar ring was locked in the south conformation (C(2′) (= C7) up and C(3′) (= C8) down corresponding to O–C(4′) (= O3)).

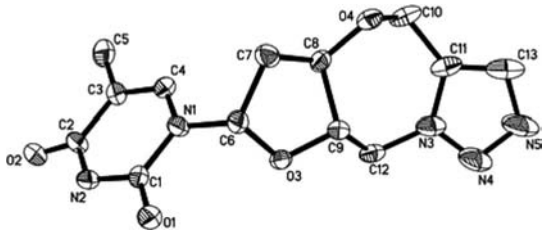


Figure. *Crystal structure of compound* **12**. Arbitrary atom numbering.

The antiviral activity of the newly designed and synthesized triazolo-fused nucleoside analogues were tested in a MAGI assay by the published procedure [16]. The viral infectivity was measured in MAGI-CCR5 cells infected by HIV-1 NL4-3 particles upon treatment with 50 μM of each compound. The cell toxicity of these compounds was evaluated with H9 T lymphocytes. The 3′-azido-3′-deoxythymidine (AZT; **1**) was selected as the reference compound in the tests. Although the biological results indicated that compounds **9** and **16** possessed the most significant antiviral activity with relatively low cell toxicity among the synthesized compounds, all the tested triazolo-fused cyclic compounds offered inferior anti-HIV activity compared with the reference compound **1** under the test conditions.

Conclusions. – We demonstrated that an intramolecular 1,3-dipolar cycloaddition of an azido and an alkyne moiety is a powerful means to synthesize triazolo-fused cyclic nucleosides. The triazole moiety of these analogues tolerated a standard transformation procedure of the 4-carbonyl into a 4-amino group in pyrimidine nucleosides. Some of the novel compounds showed moderate anti-HIV activity in the test assay. Further expansions of the presented methodology to the synthesis of other relevant triazolo-fused cyclic nucleosides in searching for antiviral agents are under investigation in this laboratory and will be disclosed in due course.

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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. Column chromatography

(CC): silica gel *G* (SiO_2; 200–300 mesh; *Qingdao Haiyang Chemical Company*, P. R. China). Anal. TLC: 2.5 × 5 cm plates coated with a 0.25 mm thickness of SiO_2 *GF 254*. ^{1}H- and ^{13}C-NMR Spectra: *Mercury 300BB*; at 300 (^{1}H) and 75 MHz (^{13}C); 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′-Azido-3′-deoxy-5′-O-*(prop-2-yn-1-yl)thymidine* (**2**) [9]. To a soln. of 3′-azido-3′-deoxythymidine (**1**; 2.67 g, 10 mmol) in dry THF (100 ml) was added NaH (60%; 600 mg, 15 mmol), and the mixture was activated at r.t. by ultrasound irradiation (30 min). Propargyl bromide (1.30 ml, 15.0 mmol) was added, and the reaction was continued at r.t. under ultrasound irradiation (50 min). After the reactants were consumed, MeOH (2 ml) and then H_2O (100 ml) were added to the mixture, which was extracted with AcOEt (3 × 50 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): pure **2** (2.58 g, 85%). ^{1}H-NMR ($CDCl_3$, 300 MHz): 10.10 (*s*, 1 H); 7.52 (*s*, 1 H); 6.18 (*t*, *J* = 6.3, 1 H); 4.19–4.25 (*m*, 1 H); 4.17 (*s*, 2 H); 3.98 (*t*, *J* = 1.8, 1 H); 3.82 (*dd*, *J* = 2.4, 2.1, 1 H); 3.66 (*dd*, *J* = 2.4, 2.1, 1 H); 2.49 (*s*, 1 H); 2.23–2.28 (*m*, 2 H); 1.84 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 164.1; 150.4; 135.5; 110.8; 84.6; 82.9; 78.5; 75.5; 68.9; 60.5; 58.4; 37.6; 12.4. APCI-MS: 306.2 ($[M+H]^+$, $C_{13}H_{16}N_5O_4^+$; calc. 306.1).

*5-Methyl-1-[(6a*S*,8*R*,9a*S*)-6a,8,9,9a-tetrahydro-4*H*,6*H*-furo[2,3-*c*][1,2,3]triazolo[1,5-*e*][1,4]oxazepin-8-yl]pyrimidine-2,4(1*H*,3*H*)-dione* (**3**). A soln. of **2** (1 g, 3.3 mmol) in toluene (25 ml) was heated to reflux for 24 h and then cooled to r.t. The mixture was concentrated and the crude product purified by CC (SiO_2 (short column), AcOEt/MeOH 15:1): pure **3** (0.87 g, 87%). ^{1}H-NMR ((D_6)DMSO, 300 MHz): 11.39 (*s*, 1 H); 7.76 (*s*, 1 H); 7.54 (*d*, *J* = 1.2, 1 H); 6.34 (*dd*, *J* = 2.4, 2.1, 1 H); 5.25–5.35 (*m*, 1 H); 5.07 (*d*, *J* = 15, 1 H); 4.65 (*d*, *J* = 15, 1 H); 4.27 (*dd*, *J* = 3.3, 3.6, 1 H); 3.89 (*t*, *J* = 10.2, 1 H); 3.64–3.71 (*m*, 1 H); 3.36–3.47 (*m*, 1 H); 2.86–2.90 (*m*, 1 H); 1.82 (*s*, 3 H). ^{13}C-NMR ((D_6)DMSO, 75 MHz): 163.7; 150.3; 136.9; 136.6; 132.9; 110.2; 83.2; 78.1; 72.4; 61.1; 60.5; 32.7; 12.1. ESI-HR-MS: 306.1197 ($[M+H]^+$, $C_{13}H_{16}N_5O_4^+$; calc. 306.1209).

*4-Amino-5-methyl-1-[(6a*S*,8*R*,9a*S*)-6a,8,9,9a-tetrahydro-4*H*,6*H*-furo[2,3-*c*][1,2,3]triazolo[1,5-*e*]-[1,4]oxazepin-8-yl]pyrimidin-2(1*H*)-one* (**4**). To a soln. of **3** (0.87 g, 2.84 mmol) in MeCN (30 ml) was added 1*H*-1,2,4-triazole (3.09 g, 44.87 mmol) and Et_3N (7.81 ml, 56.09 mmol) at 0° under N_2. $POCl_3$ (1.04 ml, 11.21 mmol) was then added, and the resulting mixture was stirred at r.t. for 24 h. The mixture was filtrated and the solid washed with Et_3N/MeCN 1:4 (50 ml). The filtrate was concentrated and the residue 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 purified by CC (SiO_2, 10 → 40% MeOH/AcOEt): pure **4** (0.56 g, 65%). White solid. ^{1}H-NMR ((D_6)DMSO, 300 MHz): 7.76 (*s*, 1 H); 7.47 (*s*, 1 H); 7.43 (br. *s*, 1 H); 6.92 (br. *s*, 1 H); 6.32 (*dd*, *J* = 2.4, 2.1, 1 H); 5.26–5.35 (*m*, 1 H); 5.07 (*d*, *J* = 15, 1 H); 4.68 (*d*, *J* = 15, 1 H); 4.28 (*dd*, *J* = 3.6, 3.6, 1 H); 3.92 (*t*, *J* = 9.9, 1 H); 3.64–3.71 (*m*, 1 H); 3.36–3.48 (*m*, 1 H); 2.72–2.80 (*m*, 1 H); 1.89 (*s*, 3 H). ^{13}C-NMR ((D_6)DMSO, 75 MHz): 165.5; 154.9; 138.8; 137.0; 132.9; 102.1; 84.2; 78.2; 72.5; 61.1; 60.6; 33.4; 13.2. ESI-HR-MS: 305.1380 ($[M+H]^+$, $C_{13}H_{17}N_5O_4^+$; calc. 305.1357).

*1-(3′-Azido-2′,3′-dideoxy-β-*D-threo*-pentofuranosyl)thymine* (**6**). To a soln. of **5** (9.68 g, 20 mmol) in anh. THF (200 ml) was added Et_3N (15.4 ml, 100 mmol). The mixture was cooled to 0° (ice bath), and MsCl (3.3 ml, 24 mmol) in anh. THF (20 ml) was added dropwise during 20 min. After the reactants were consumed, the mixture was filtrated, and the filtrate was concentrated. The residue was dissolved in AcOEt (200 ml), the soln. washed with brine (3 × 100 ml), dried (Na_2SO_4), and concentrated, and the crude product dissolved in anh. DMF (200 ml). To this soln., LiN_3 (1.82 g, 37. 2 mmol) was added. The mixture was heated at 100° for 8 h, cooled to r.t. and poured into ice water (400 ml). The mixture was extracted with AcOEt (3 × 150 ml), the combined org. layer washed with brine and concentrated, and the crude product purified by CC (SiO_2, AcOEt/petroleum ether 1:2) to afford a white solid. This solid was subsequently treated with 80% aq. AcOH (300 ml) at r.t. overnight, and the volatile matters were then evaporated. The residue was triturated with AcOEt and $CHCl_3$ to give the crude detritylation product **6** (3.86 g, 72%). ^{1}H-NMR ($CDCl_3$, 300 MHz): 9.20 (*s*, 1 H); 7.60 (*s*, 1 H); 6.20 (*dd*, *J* = 3.6, 7.5); 4.25–4.34 (*m*, 1 H); 4.09–4.18 (*m*, 1 H); 3.98–4.09 (*m*, 2 H); 2,72–2.81 (*m*, 1 H); 2.18–2.24 (*m*, 1 H); 1.87–1.96 (*m*, 3 H). ^{13}C-NMR ($CDCl_3$): 164.50; 152.61; 135.47; 111.36; 83.23; 82.38; 64.78; 62.69; 39.16; 12.56. APCI-MS: 268.2 ($[M+H]^+$, $C_{10}H_{14}N_5O_4^+$; calc. 268.1).

1-[3′-Azido-2′,3′-dideoxy-5′-O-*(prop-2-yn-1-yl)-β*-D-threo-*pentofuranosyl]thymine* (**7**). As described for **2**, with crude **6** (3.86 g, 14 mmol), THF (140 ml), NaH (60%; 894 mg, 22.4 mmol), and propargyl bromide (1.9 ml, 22.4 mmol): pure **7** (3.31 g, 75%). ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.83 (*s*, 1 H); 7.51 (*s*, 1 H); 6.21 (*dd*, *J* = 3.9, 7.8, 1 H); 4.27 (*s*, 3 H); 4.16–4.27 (*m*, 1 H); 3.87–3.89 (*m*, 2 H); 2.69–2.78 (*m*, 1 H); 2.51 (*s*, 1 H); 2.12–2.18 (*m*, 1 H); 1.95 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 164.00; 150.61; 135.40; 110.95; 83.65; 80.38; 78.67; 75.31; 67.58; 60.84; 58.57; 38.06; 12.62. ESI-HR-MS: 306.1210 ($[M+H]^+$, $C_{13}H_{16}N_5O_4^+$; calc. 306.1197).

*5-Methyl-1-[(6a*S,*8*R,*9a*R*)-6a,8,9,9a-tetrahydro-4*H,*6*H-*furo[2,3-*c*][1,2,3]triazolo[1,5-*e*][1,4]-oxazepin-8-yl]pyrimidine-2,4(1*H,*3*H*)-dione* (**8**). As described for **3**: **8** (78%). ^{1}H-NMR ((D_6)DMSO, 300 MHz): 11.28 (*s*, 1 H); 7.63 (*s*, 1 H); 6.92(*d*, *J* = 0.9, 1 H); 6.10 (*dd*, *J* = 4.2, 6.6, 1 H); 5.50 (*dd*, *J* = 4.8, 10.8, 1 H); 5.15 (*d*, *J* = 15, 1 H); 4.77 (*d*, *J* = 15, 1 H); 4.38–4.40 (*m*, 1 H); 4.26–4.32 (*m*, 1 H); 3.95 (*dd*, *J* = 7.2, 14.8, 1 H); 3.18–3.26 (*m*, 1 H); 2.89–2.96 (*m*, 1 H); 1.54 (*s*, 3 H). ^{13}C-NMR ((D_6)DMSO, 75 MHz): 163.49; 150.13; 136.48; 134.41; 132.13; 108.38; 82.83; 79.42; 70.40; 62.70; 59.69; 37.09; 12.56. ESI-HR-MS: 306.1205 ($[M+H]^+$, $C_{13}H_{16}N_5O_4^+$; calc. 306.1197).

*4-Amino-5-methyl-1-[(6a*S,*8*R,*9a*R*)-6a,8,9,9a-tetrahydro-4*H,*6*H-*furo[2,3-*c*][1,2,3]triazolo[1,5-*e*]-[1,4]oxazepin-8-yl]pyrimidin-2(1*H*)-one* (**9**). As described for **4**: **9** (64%). ^{1}H-NMR ((D_6)DMSO, 300 MHz): 7.61 (*s*, 1 H); 7.17 (*s*, 1 H); 6.80 (*s*, 1 H); 6.71 (*s*, 1 H); 6.09–6.12 (*m*, 1 H); 5.46–5.49 (*m*, 1 H); 5.13 (*d*, *J* = 14.1, 1 H); 4.79 (*d*, *J* = 6.9,1 H); 4.28–4.37 (*m*, 2 H); 4.00 (*d*, *J* = 14.1, 1 H); 3.15–19 (*m*, 1 H); 2.87–2.92 (*m*, 1 H); 1.61 (*s*, 3 H). ^{13}C-NMR ((D_6)DMSO, 75 MHz): 164.84; 154.43; 137.85; 137.60; 132.97; 101.53; 84.55; 80.63; 71.38; 63.49; 60.80; 38.34; 14.12. ESI-HR-MS: 305.1365 ($[M+H]^+$, $C_{13}H_{17}N_5O_4^+$; calc. 305.1357).

5′-Azido-5′-deoxy-3′-O-*(prop-2-yn-1-yl)thymidine* (**11**). As described for **2**: **11** (75%). ^{1}H-NMR ($CDCl_3$, 300 MHz): 9.80 (*s*, 1 H); 7.30 (*s*, 1 H); 6.21 (*t*, *J* = 6.9, 1 H); 4.28 (*t*, *J* = 3, 1 H); 4.15–4.19 (*m*, 2 H); 4.09–4.11 (*m*, 1 H); 3.71 (*dd*, *J* = 2.4, 13.2, 1 H); 3.58(*dd*, *J* = 3.3, 13.2, 1 H); 2.40–2.50 (*m*, 2 H); 2.16–2.18 (*m*, 1 H); 1.91 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 164.00; 150.46; 135.27; 111.37; 84.91; 82.21; 78.80; 78.13; 75.35; 56.89; 52.17; 36.88; 12.56. APCI-MS: 306.1 ($[M+H]^+$, $C_{13}H_{16}N_5O_4^+$; calc. 306.1).

*5-Methyl-1-[(5a*S,*7*R,*8a*R*)-5a,6,8a,9-tetrahydro-4*H,*7*H-*furo[3,2-*b*][1,2,3]triazolo[1,5-*e*][1,4]-oxazepin-7-yl]pyrimidine-2,4(1*H,*3*H*)-dione* (**12**). As described for **3**: **12** (78%). ^{1}H-NMR ((D_6)DMSO, 300 MHz): 11.35 (*s*, 1 H); 7.71 (*s*, 1 H); 7.47 (*d*, *J* = 1.2, 1 H); 6.17–6.21 (*m*, 1 H); 5.09 (*d*, *J* = 14.4, 2 H); 4.62–4.70 (*m*, 2 H); 4.42–4.51 (*m*, 1 H); 3.49–3.56 (*m*, 1 H); 2.37–2.44 (*m*, 2 H); 1.83 (*s*, 3 H). ^{13}C-NMR ((D_6)DMSO, 75 MHz): 163.45; 150.28; 136.59;136.28; 133.50; 110.25; 83.87; 81.92; 76.68; 61.47; 50.86; 35.86; 12.09. ESI-HR-MS: 306.1209 ($[M+H]^+$, $C_{13}H_{16}N_5O_4^+$; calc. 306.1197).

*4-Amino-5-methyl-1-[(5a*S,*7*R,*8a*R*)-5a,6,8a,9-tetrahydro-4*H,*7*H-*furo[3,2-*b*][1,2,3]triazolo[1,5-*e*]-[1,4]oxazepin-7-yl]pyrimidin-2(1*H*)-one* (**13**). As described **4**: **13** (50%). ^{1}H-NMR ((D_6)DMSO, 300 MHz): 7.71 (*s*, 1 H); 7.41 (*s*, 1 H); 7.37 (br. *s*, 1 H); 6.89 (br. *s*, 1 H); 6.19–6.22 (*m*, 1 H); 5.07–5.13 (*m*, 2 H); 4.64–4.74 (*m*, 2 H); 4.42 (*dd*, *J* = 4.8, 5.1, 1 H); 3.50–3.57 (*m*, 1 H); 2.32–2.40 (*m*, 2 H); 1.89 (*s*, 3 H). ^{13}C-NMR ((D_6)DMSO, 75 MHz): 165.45; 154.97; 138.44; 136.71; 133.55; 102.31; 83.80; 82.73; 76.81; 61.49; 51.00; 36.40; 13.21. ESI-HR-MS: 305.1348 ($[M+H]^+$, $C_{13}H_{17}N_5O_4^+$; calc. 305.1357).

1-(5′-Azido-2′,5′-dideoxy-β-D-threo-*pentofuranosyl)thymine* (**14**) [17]. DIAD (3.8 ml, 18.8 mmol) was added dropwise to a soln. of Ph_3P (4.98 g, 18.8 mmol) in DMF (100 ml) at 0°, and the mixture was stirred for 30 min at 0°. After addition of **10** (5 g, 18.8 mmol), the reaction was continued for 2 h at r.t. The mixture was poured into cold Et_2O to produce a white precipitate which was collected by filtration to give 1-(2,3′-anhydro-5′-azido-2′,5′-dideoxy-*β*-D-*threo*-pentofuranosyl)thymine. This compound was dissolved in EtOH (50 ml) and was treated with aq. 1N NaOH (25 ml) for 3 h. The mixture was neutralized with 1N HCl and all volatile matters were evaporated. The crude product was purified by CC (SiO_2 AcOEt/CH_2Cl_2 1:1): **14** (3.49 g, 86%). ^{1}H-NMR ($CDCl_3$, 300 MHz): 9.91 (*s*, 1 H); 7.52 (*s*, 1 H); 6.03 (*dd*, *J* = 2.1, 2.1, 1 H); 4.45 (*d*, *J* = 2.7, 1 H); 3.98–4.08 (*m*, 2 H); 3.73 (*d*, *J* = 6.3, 1 H); 2.42–2.51 (*m*, 2 H); 1.86 (*s*, 3 H). APCI-MS: 268.3 ($[M+H]^+$, $C_{10}H_{14}N_5O_4^+$; calc. 268.1).

1-[5′-Azido-2′,5′-dideoxy-3′-O-*(prop-2-yn-1-yl)-β*-D-threo-*pentofuranosyl]thymine* (**15**). As described for **2**: **15** (75%). ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.89 (*s*, 1 H); 7.52 (*d*, *J* = 1.2, 1 H); 6.31 (*dd*, *J* = 3.0, 8.1, 1 H); 4.27 (*m*, 1 H); 4.20 (*d*, *J* = 2.4, 2 H); 4.04–4.11 (*m*, 1 H); 3.69 (*d*, *J* = 6.3, 2 H); 2.53–

2.61 (*m*, 1 H); 2.49 (*t*, *J* = 2.4, 1 H); 2.25–2.31 (*m*, 1 H); 1.94 (*d*, *J* = 1.2, 3 H). ^{13}C-NMR ((D$_6$)DMSO, 75 MHz): 163.96; 150.65; 136.00; 110.93; 83.91; 81.55; 78.47; 76.76; 75.44; 56.74; 49.44; 37.41; 13.60. APCI-MS: 306.2 ($[M+H]^+$, $C_{13}H_{16}N_5O_4^+$; calc. 306.1).

*5-Methyl-1-[(5a*R*,7*R*,8a*R*)-5a,6,8a,9-tetrahydro-4*H*,7*H*-furo[3,2-*b*][1,2,3]triazolo[1,5-*e*][1,4]oxazepin-7-yl]pyrimidine-2,4(1*H*,3*H*)-dione* (**16**). As described for **3**: **16** (78%). ^{1}H-NMR ((D$_6$)DMSO, 300 MHz): 11.25 (*s*, 1 H); 7.76 (*s*, 1 H); 6.43 (*d*, *J* = 1.2,1 H); 5.96 (*dd*, *J* = 1.8, 8.1, 1 H); 5.17 (*dd*, *J* = 4.5, 15.3, 1 H); 5.02 (*dd*, *J* = 1.8, 15.3, 1 H); 4.93 (*d*, *J* = 14.4, 1 H); 4.75 (*d*, *J* = 14.4, 1 H); 4.51 (*dd*, *J* = 2.1, 4.5, 1 H); 4.49–4.52 (*m*, 1 H); 2.65–2.74 (*m*, 1 H); 1.91 (*dd*, *J* = 1.5, 15.3, 1 H); 1.49 (*d*, *J* = 1.2, 3 H). ^{13}C-NMR ((D$_6$)DMSO, 75 MHz): 163.64; 150.23; 136.77; 135.30; 132.11; 108.07; 83.23; 79.33; 76.58; 58.38; 47.37; 39.81; 12.27. ESI-HR-MS: 306.1210 ($[M+H]^+$, $C_{13}H_{16}N_5O_4^+$; calc. 306.1197).

*4-Amino-5-methyl-1-[(5a*S*,7*R*,8a*R*)-5a,6,8a,9-tetrahydro-4*H*,7*H*-furo[3,2-*b*][1,2,3]triazolo[1,5-e][1,4]oxazepin-7-yl]pyrimidin-2(1*H*)-one* (**17**). As described for **4**: **17** (50%). ^{1}H-NMR ((D$_6$)DMSO, 300 MHz): 7.75 (*s*, 1 H); 7.17 (br. *s*, 1 H); 6.66 (br. *s*, 1 H); 6.17 (*s*, 1 H); 5.88 (*d*, *J* = 7.8, 1 H); 5.15–5.21 (*m*, 1 H); 5.04 (*d*, *J* = 15.3, 1 H); 4.87 (*d*, *J* = 14.1, 1 H); 4.72 (*d*, *J* = 14.4, 1 H); 4.48 (*s*, 1 H); 4.17 (*s*, 1 H); 2.50–2.69 (*m*, 1 H); 1.84 (*d*, *J* = 14.1, 1 H); 1.53 (*s*, 3 H). ^{13}C-NMR ((D$_6$)DMSO, 75 MHz): 165.11; 154.83; 137.18; 136.81; 132.01; 99.68; 83.94; 79.49; 76.55; 58.21; 47.42; 40.23; 13.18. ESI-HR-MS: 305.1369 ($[M+H]^+$, $C_{13}H_{17}N_6O_3^+$; calc. 305.1357).

Crystallographic Data of **12**. $C_{13}H_{15}N_5O_5$, M_r 321.30, orthorhombic, space group $P3(2)$, a = 12.1795(8), b = 12.1795(8), c = 8.9404(12) Å, V = 1148.54(19) Å^3, Z = 3, D_{calc} = 1.394 g cm^{-3}, T 293(2) K, μ = 0.110 mm^{-1}, $F(000)$ = 504, λ = MoK_α, α = 0.71073 Å, 6533 reflections measured, 2694 unique, observed with $I > 2\sigma(I)$; final R_1 = 0.0412, wR_2 = 0.0978. CCDC-817212 contains the supplementary crystallographic data for compound **12**. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request.cif.

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