Microwave-assisted click chemistry: synthesis of mono and bis-1,2,3-triazole acyclonucleoside analogues of Acyclovir *via* copper(I)-catalyzed cycloaddition.

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Abstract

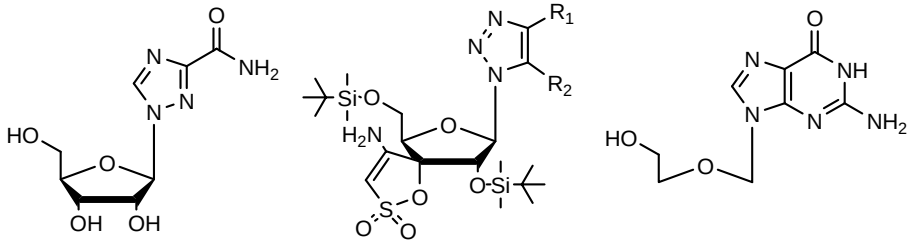
We report a short and efficient synthesis of 1,2,3-triazole and bis-1,2,3-triazoles acyclonucleoside analogues of Acycolovir. A series of novel 1,2,3-triazole acyclonucleosides linked to nucleobases were prepared *via* copper(I)-catalyzed 1,3-dipolar cycloaddition of N-9 propargylpurine , N-1-propargylpyrimidines or N-1-propargylindazoles with the azido-pseudo-sugar under Microwave-assisted synthesis followed by treatment with K_2CO_3/MeOH.

Keywords: 1,3-Dipolar cycloaddition, 1,2,3 triazole, 1,2,3-bis-triazoles, acyclovir, microwave

Introduction

Triazole heterocycles are found to be potent antimicrobial[1], antiviral[2], and anti-proliferative agents[3]. The pharmaceutical importance of triazoles has prompted the design and synthesis of various triazolonucleosides (Figure 1). Ribavirin **1** was the first synthetic triazole nucleoside analogue found to show antiviral activity against many viruses[4] and is still the only small-molecular-weight drug available for treating viral infections caused by hepatitis C virus (HCV). In addition, 1,2,3 triazole TSAO [2',5'-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole-2'', 2-dioxide) **2** analogues exhibited an anti-HIV activity[5]. Moreover, recent studies have disclosed a series of 1,2,3-bis-triazoles as potent HIV-1 protease inhibitors for the inhibition of viral replication[6]**.** Since the discovery of acyclovir [9-((2-hydroxyethoxy) methyl)guanine ACV (Zovirax)] **3** as the highly selective antiviral drug for the

treatment of herpes simplex (HSV)[5] virus infections and Varicella-Zoster l, several acyclonucleosides were synthesized and tested.



1 Ribavirin **2** TSAO analogue **3** Acyclovir

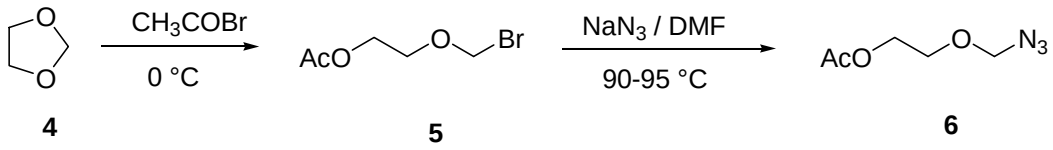
Figure 1. Structure of Ribavirin **1,** TSAO analogue **2** and Acyclovir **3**.

In view of the biological importance of 1,2,3-triazoles and acyclovir, it was of considerable interest to develop a rapid, facile and practical protocol for the formation of compounds incorporating ring systems. In connection to our previous studies on the synthesis of acyclonucleosides, we report here a regioselective synthesis of 1,2,3-triazoles and bis-1,2,3-triazole acyclonucleosides analogues of ACV in which the heterocyclic base is linked to a (2-hydroxyethoxy)methyl *via* a methylene-1,2,3-triazole group. In this paper, we report an efficient approach for the one-pot synthesis of 1,4-disubstituted-1,2,3-triazoles analogues of ACV from propargylated bases and azido-pseudosugar under CuI catalysis.

Results and Discussion

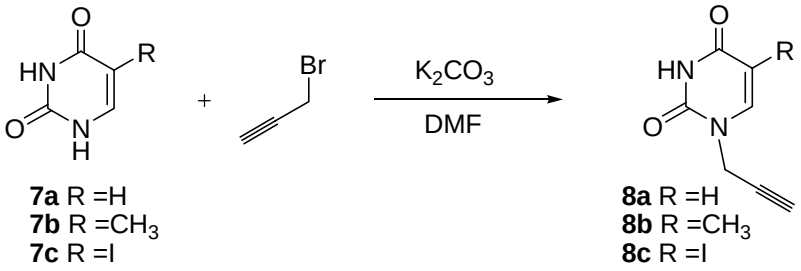
The most widely used methods for the synthesis of triazoles is the Huisgen 1,3-dipolar cycloaddtion of alkynes with organic azides. This route to triazoles is often conducted at high temperature for a prolonged period of time, and usually leads to a mixture of 1,4-disubstituted and 1,5- disubstituted 1,2,3-triazoles.[7] Copper-catalyzed click chemistry involving azides and terminal acetylenes has enabled practical and efficient preparation of 1,4-disubstituted-1,2,3-triazoles, from a wide range of substrates with excellent selectivity.[8-13] We decided to explore the feasibility of the "click"chemistry for the synthesis of novel 1,2,3-triazole acyclonucleosides with different heterocyclic bases connected *via* a flexible methylene linker. At first, several attempts were made in order to optimize the reaction conditions.

The synthetic approach to 1,4-disubstituted-1,2,3-triazoles analogues of ACV involved first the preparation of the known [(2-acetoxyethoxy)methyl]azide **6** from the [(2-acetoxyethoxy)methyl]bromide **2** and sodium azide at 90-95°C for 4h (Scheme 1)[7].



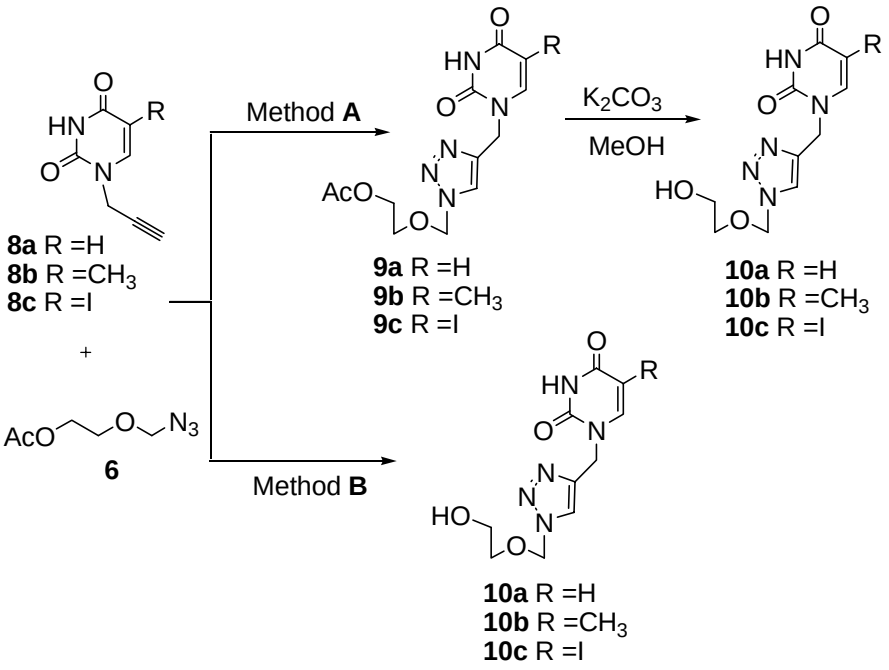
Scheme 1. Synthesis of the known azide **6** from bromide **5** and sodium azide.

The second step of the synthesis was the preparation the propargylated nucleobases. For this, uracil, thymine and iodouracil, were used as starting materials which were treated with propargylbromide in the presence of K_2CO_3. All reactions were carried out in DMF, as it is an excellent solvent for dissolving nucleobases[7] (Scheme 2). The pyrimidine derivatives were exclusively alkylated at the N-1 position, **8a-c** as confirmed by ^{1}H NMR spectra.



Scheme 2. N-1-alkylation of heterocyclic bases **7a-7c** with propargylbromide.

Next, the terminal triple bonds of propargylated nucleobases were ligated to the azide residue of the pseudosugar using the copper(I)-catalyzed 1,3-dipolar cycloaddition in water-acetonitrile and Et_3N at room temperature leading to the 1,4-disubstituted regioisomer within 3h (method A)[14] (84 and 86% yields). In order to obtain these triazole acyclonucleosides in higher yields with shorter reaction times under mild reaction conditions, we turned our attention to microwave irradiation. The use of microwave-assisted organic synthesis has attracted considerable interest over the last two decades, leading often to remarkable decreases in reaction times, significant enhancements of yields, easier workups and better regioselectivity.[15]



Scheme 3. Reagents and conditions: Method A: CuI, Et_3N, H_2O/CH_3CN, RT. Method B: 1) MW, CuI, Et_3N; 2) MeOH/ K_2CO_3.

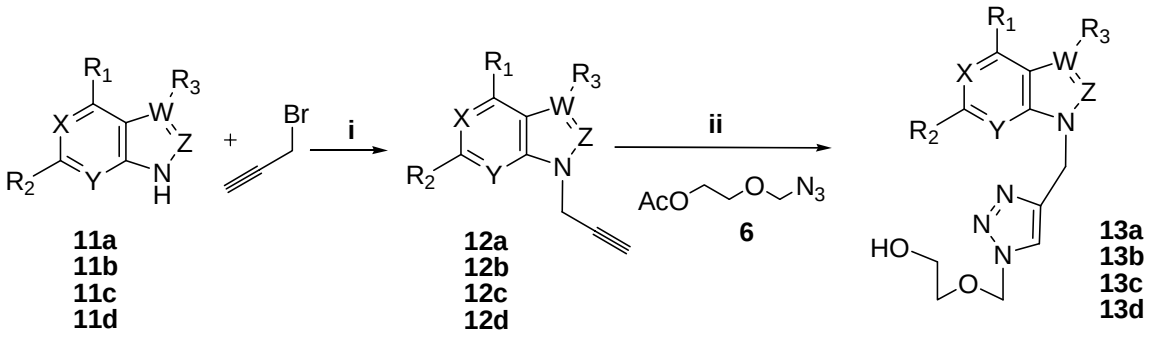
Herein, we report a rapid, facile and practical protocol for the formation of the triazole ring. The cycloaddition of propargylated nucleobases and azide carried out under microwave conditions with CuI as catalyst and without solvent lead to the desired products in a quantitative yield and reaction time of one minute (Scheme 3) (Method B). Consequently, Method B was selected as the best practical protocol for the synthesis of triazole acyclonucleosides, because it gave the best results.

Table 1. Synthesis of 1,4-disubstituted 1,2,3-triazole analogues of ACV catalysed by CuI under different reaction conditions

Compound	Azide equivalent	Method A		Method B	
		Yield (%)	Reaction time	Yield (%)	Reaction Time
10a	5 eq	84	3 h	92	1 min
10b	5 eq	86	3 h	93	1 min
10c	5 eq	85	3 h	91	1 min

Method A: In water at room temperature.
Method B: under microwave

To extend the general applicability of the microwave assisted click reaction, for the synthesis of triazole acyclonucleosides of purines and modified nucleobases.

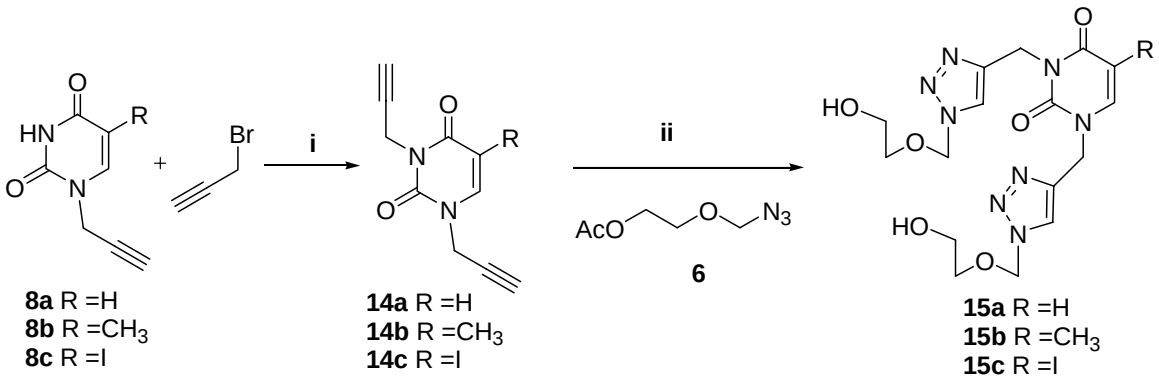


Compound	X	Y	W	Z	R_1	R_2	R_3
11a	N	N	N	C	NH_2	H	-
11b	N	N	N	C	OH	NHAc	-
11c	C	C	C	N	H	NO_2	Cl
11d	C	C	C	N	H	NO_2	Br
12a	N	N	N	C	NH_2	H	-
12b	N	N	N	C	OH	NHAc	-
12c	C	C	C	N	H	NO_2	Cl
12d	C	C	C	N	H	NO_2	Br
13a	N	N	N	C	NH_2	H	-
13b	N	N	N	C	OH	NH_2	-
13c	C	C	C	N	H	NO_2	Cl
13d	C	C	C	N	H	NO_2	Br

Scheme 4. Reagents and conditions: (i) K_2CO_3, DMF. (ii) 1) CuI, Et_3N, MW; 2) MeOH/ K_2CO_3.

N-9-propargyladenine, *N*-9-Propargyl-*N*-2-acetylguanine, *N*-1-propargyl-3-chloro and *N*-1-propargyl-3-bromoindazole were prepared by using the same reaction conditions discussed above. Using the copper(I)-catalyzed 1,3-dipolar cycloaddition under click reaction conditions the desired products were obtained in a quantitative yield and reaction time of only one minute (Scheme 4).

With this promising procedure in hand, we extended the scope of substrates to include other alkinyle derivatives, as outlined in Scheme 5. Analogously to the preparation of N-1-proparglated pyrimidine, the N-1, N-3-bis-propargylated pyrimidines were prepared from starting material N-1-propargylated uracil, thymine and 5-iodouracil (Scheme 5), (Yields 80-88%). The bis-propargylated pyrimidines were converted into the bis-triazoles acyclonucleosides using the same reaction conditions in quantitative yield.



Scheme 5. Reagents and conditions: (i) K_2CO_3, DMF. (ii) 1) CuI, Et_3N, MW; 2) MeOH/ K_2CO_3

Using the copper(I)-catalyzed 1,3-dipolar cycloaddition under click reaction conditions the bis-propargyl-5-iodouracil 14c unexpectedly leads to bis-triazoluracil 15a in a quantitative yield and reaction time of one minute. This structure was established on the basis of ^1H, ^{13}C NMR spectra, mass spectrum and comparison with the spectroscopic data of 15a. This transformation can best be explained by a deiodination of N-1, N-3-bis-alkylated 5-iodouracil in the presence of CuI.

The structure of all compounds was confirmed on the basis of ^1H, ^{13}C NMR spectra and mass spectra. The formation of 1,4-disubstituted triazoles was unequivocally established through the characteristic chemical shift value of the triazolyl proton (5-CH) at δ = 8.07-8.54 ppm. The triazole ring formation can also be identified from the 13C-spectra with the new signals of the olefinic C-atoms of the 1,2,3-triazole moiety at (δ (C5) = 122.5-125 ppm) and (δ(C4) =140-144 ppm).

Table 2. Synthesis of 1,4-disubstituted 1,2,3-triazoles analogue of ACV catalysed by CuI under microwave irradiation (Method B).

Compound	Azide equivalent	Reaction time	Yield (%)
13a	5 eq	1min	92
13b	5 eq	1min	90
13c	5 eq	1min	94
13d	5 eq	1min	93
15a	5 eq	1min	91
15b	5 eq	1min	90

Conclusions

In summary, we report a short and efficient synthesis of 1,2,3-triazole and bis-1,2,3-triazoles acyclonucleoside analogues of ACV. We accomplished a straightforward convenient methodology for the synthesis of novel 1,2,3-triazole nucleosides using the Cu(I)-catalyzed alkyne-azide cycloaddition reaction. These products are under investigation for their biological activities.

Experimental Section

General. Melting points were determined in open capillary tubes and are uncorrected. NMR spectra were recorded at 300 MHz (^{1}H, ^{13}C) Bruker in (DMSO-d_6, $CDCl_3$) using TMS as an internal reference. All chemical shifts (δ) are expressed in parts per million and coupling constant (*J*) are given in Hertz; T (1,2,3-triazole) and B (heterocyclic base). Mass spectra were obtained by using ESI/MS and (FAB^+). Reactions were performed in a domestic microwave oven Model AVM510/WP/WH. DMF and MeCN were distilled prior to use and stored over molecular sieves 4A. Precoated Merck Silica Gel 60F-254 plates were used for thin layer chromatography (TLC) and the spots were detected under UV light (254 nm). Column chromatography (CLC) was performed using silica gel (0.063-0.2 mm) Fluka. All reagents used were purchased from Aldrich.

[(2-Acetoxyethoxy)methyl]bromide[7] 5. To 106 mmol (13 g) of distilled acetyl bromide, was added 100 mmol of 1,3-dioxolane drop wise while agitating and cooling by a bath of ice. The reaction is fast and exothermic. After the addition, the reaction is agitated further during 30 min at room temperature. Afterwards the reaction mixture was distilled under reduced pressure. ^{1}H NMR, $CDCl_3$, δ 2.1 (s, 3H, CH_3COO), 3.88 (t, 2H, OCH_2), 4.27 (t, 2H, CH_2O), 5.72 (s, 2H, OCH_2Br).

[(2-acetoxyethoxy)methyl]azide[7] 6. To a solution of 10 mmol (2g) of [(2-acetoxyethoxy) methyl]bromide in 60 ml of anhydrous DMF is added 15 mmol (0,9g) of sodium azide (NaN_3). The mixture was brought up to a temperature of 90-95°C during 4h. After cooling, the solution was extracted with ether (2 x 50 ml) then washed with brine, and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the residual oil was purified on a silica gel column with hexane (95 %). ^{1}H NMR, $CDCl_3$, δ 2.1 (s, 3H, CH_3COO); 3.8 (t, 2H, OCH_2); 4.2 (t, 2H, CH_2O); 4.65 (s, 2H, OCH_2N_3).

General procedure for the synthesis of the monopropargyl heterocyclic bases[7]

The mixture of 1 mmol of the heterocyclic base (thymine, uracil, iodouracil, adenine, N-2acetylguanine, 3-bromo-6-nitroindazole or 3-chloro-6- nitroindazole), 0,5 mmol of K_2CO_3 and 1 mmol of propargylbromide in 20 ml of anhydrous DMF was stirred at room temperature

during 24h. After removal of the solvent under reduced pressure the residue obtained was purified on silica gel column CH_2Cl_2 and MeOH (99/1).

***N*-1-Propargyluracil 8a.** (54 %), Solid, mp 154–166°C, ^{1}H NMR, DMSO-d_6, δ 3.43(t, 1H, CH, *J*= 2.3 Hz); 4.57 (d, 2H, CH_2N, *J*= 2.3 Hz); 5.7 (d, 1H, H-5, *J*= 7.8 Hz); 7.75(d,1H, H-6, *J*= 7.8 Hz); 11.44 (s,1H, NH). ^{13}C NMR, DMSO-d_6: 36.60; 75.79; 78.42; 101.67; 144.42; 150.35; 163.50. FAB-MS, $C_7H_6N_2O_2$ m/z 151 $(M+H)^+$.

***N*-1-Propargylthymine 8b.** (56%), Solid, mp 154–156 °C, ^{1}H NMR, DMSO-d_6, δ 1.75 (s, 3H, CH_3); 3, 37 (t, 1H, CH, *J*= 2.2 Hz); 4.46 (d, 2H, CH_2N *J*= 7,8 Hz); 7.55(s, 1H, H-6); 11.35 (s, 1H, NH). ^{13}C NMR, DMSO-d_6: 11.87; 36.30; 75.58; 78.61; 109.38; 140.04; 150.33; 164.09. FAB-MS, $C_8H_8N_2O_2$ m/z 165 $(M+H)^+$.

***N*-1-Propargyl-5-iodouracil 8c.** (62%), Solid, mp180-182 °C, ^{1}H NMR, DMSO-d_6, δ 3.42(t, 1H, CH, *J*= 2.6 Hz); 4.58 (d, 2H, CH_2N, *J*= 2.6 Hz); 8.28(d,1H,, H-6); 12.02 (s,1H, NH). ^{13}C NMR, DMSO-d_6: 36.94; 68.85; 75.98; 78.31; 148.69; 150.05; 160.87. FAB-MS, $C_7H_5IN_2O_2$ m/z 277 $(M+H)^+$.

***N*-9-Propargyladenine 12a.** (80%) Solid, mp 213-214 °C, ^{1}H NMR, DMSO-d_6, δ: 3.56(t, 1H, CH); 5.03(d, 2H, CH_2-N); 7.3 (s, 2H, NH_2); 8.18 (2s,2H, H-2 and H-8). ^{13}C NMR, DMSO-d_6: 32.23; 75.81; 78.29; 118.51; 140.07; 149.08; 152.69; 155.99. FAB-MS, $C_8H_7N_5$ m/z 174 $(M+H)^+$.

***N*-9-Propargyl-N-2-acetylguanine 12b.** (40%), Solid, mp 285–286 °C, ^{1}H NMR, DMSO-d_6, δ 2.2 (s, 3H, CH_3CON); 3.55 (t, 1H, CH); 4.95 (d, 2H, CH_2-N); 7.35(bs, 2H, NH_2); 8.08 (s, 1H, H-8). ^{13}C NMR, DMSO-d_6: 25.36; 32.90; 72.85; 78.30; 117.51; 143.60; 152.43; 153.30. 158.58; 170.63. FAB-MS, $C_{10}H_9N_5O_2$ m/z 233 $(M+H)^+$.

***N*-1-Propargyl(3-bromo-6-nitroindazole) 12c.** (91%) Solid, mp 128 °C, ^{1}H NMR, DMSO-d_6, δ 3.50(t, 1H, CH); 5.55(d, 2H,CH_2-N); 7.86-8.07(m, 2H, H5-, H-4);8.90(d,1H, H-7), ^{13}C NMR, DMSO-d_6: 40.91; 77.23; 78.42; 108.19; 117.13; 121.44; 121.96; 126.79; 139.47; 147.82.

***N*-1-Propargyl(3-chloro-6-nitroindazole) 12d.** (90%) Solid, mp 121 °C, ^{1}H NMR, DMSO-d_6, δ 3.51(t, 1H, CH); 5.554(d, 2H, CH_2-N); 7.95-8.05(m, 2H, H-5, H-4); 8.89(d,1H, H-7), ^{13}C NMR, DMSO-d_6: 41.55; 77.89; 79.01; 108.99; 117.74; 122.02; 124.68; 133.98; 140.47; 148.48.

General procedure for the synthesis of the N-1, N-3-bis-propargylpyrimidines

The mixture of 1mmol of the heterocyclic base (*N*-1-propargyluracil, *N*-1-propargylthymine, *N*-1-propargyl-5-iodouracil), 0,5 mmol of K_2CO_3 and 1.1mmol of propargylbromide in 20 ml of anhydrous DMF was stirred at room temperature during 15h. After removal of the solvent under reduced pressure and purification on silica gel column chromatography, we obtained the desired pure product.

***N*-1,*N*-3-Dipropargyluracil 14a.** (80%), Solid, mp 105 °C**,** ^{1}H NMR, DMSO-d_6, δ 3.10(t, 1H, CH); 3.44(t, 1H, CH); 4.52 (d, 2H, CH_2N); 4.59 (d, 2H, CH_2N); 5.81 (d, 1H, H-5, *J* = 8.1 Hz); 7,79 (d,1H, H-6, *J* = 7.8 Hz).^{13}C NMR, DMSO-d_6: 31,06; 31,90; 74,24; 77.42; 79.37; 80.14; 101.99; 144.76; 151.11; 162.51.

***N*-1,*N*-3-Dipropargylthymine 14b.** (84%), Solid, mp 101 °C, ^{1}H NMR, DMSO-d_6, δ 1.83 (s, 3H, CH_3); 3.08 (t, 1H, CH); 3.39 (t, 1H, CH); 4.55 (m, 4H, 2x(CH_2N)); 7.67 (s, 1H, H-6), ^{13}C NMR, DMSO-d_6: 13.03; 30.68; 38.17; 73.54; 76.56; 78.90; 79.60; 109.19; 139.82; 150.31; 162.64.

***N*-1,*N*-3-Dipropargyliodouracil 14c.** (88%), Solid, mp 123 –126 °C, ^{1}H NMR, DMSO-d_6, δ 3.14 (t, 1H, CH); 3.45(t, 1H, CH); 4.55 (m, 4H, 2x(CH_2N)); 8,33 (d, 1H, H-6, J = 7.8 Hz),^{13}C NMR, DMSO-d_6: 31.46; 38.19; 67.50; 73.43; 76.31; 78.06; 78.58; 147.77; 149.47; 158.99.

General procedure for the synthesis of the triazole acyclonucleoside derivatives

The synthesis of the 1,2,3-triazole derivatives was carried out by two methods:

Method A. To a solution of 5 mmol of the alkylazide in 10 ml of water/acetonitrile (v/v) was added 1 mmol of N-propargylbase, 1mmol Et_3N and 0,1mmol of CuI for 3h at room temperature. The reaction mixture was diluted with 25 mL of water, cooled in ice, and extracted with CH_2Cl_2 (3 x 15 ml). The combined organic extracts were washed with brine, and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the acetyl groups of the protected nucleosides were then cleaved using 2 mmol of K_2CO_3 in 10 ml of methanol, and the reaction mixture was stirred for 3 h at room temperature.When TLC analysis showed no more starting material, solvent was removed by rotary evaporation, and the residue was purified on silica gel with dichloromethane and methanol to give the desired compound.

Method B. the mixture of alkylazide (5 mmol), Et_3N (1 mmol), N-propargylbase (1 mmol) and 0,1mmol of CuI were irradiated in the microwave oven at power level (300 W) for 1 min without solvent. K_2CO_3 (2 mmol) in 10 ml of methanol were added directly to reaction mixture. The mixture was stirred for additional 3h at room temperature. When TLC analysis showed no starting material, solvent was removed under reduced pressure, and the residue was purified on silica gel with dichloromethane and methanol.

1-[[1-[(2-Hydroxyethoxy)methyl]-1,2,3-triazol-4-yl]methyl]uracil 10a. Solid, mp 154 – 156 °C, ^{1}H NMR, DMSO-d_6, δ 3.47 (m, 4H, CH_2CH_2), 4.67 (s, 1H, OH), 4.95 (s, 2H, T-CH_2-B), 5.7(s, 2H, OCH_2-T); 5.72 (d, 1H, H-5, J= 7,4 Hz); 7.75 (d, 1H, H-6, J=7,5 Hz), 8.2 (s, 1H, H-5(triazole)), 11.3 (s, 1H, NH).^{13}C NMR, DMSO-d_6: 42.31; 59.70; 70.95; 78.20; 101.25; 123.97; 142.76; 145.48; 150.71; 163.69. ESI-MS, $C_{10}H_{13}N_5O_4$ m/z = 267.

1-[[1-[(2-Hydroxyethoxy)methyl]-1,2,3-triazol-4-yl]methyl]thymine 10b. Solid, mp 118 – 120 °C, ^{1}H NMR, DMSO-d_6, δ 1.7 (s, 3H, CH_3), 3.46 (m, 4H, CH_2CH_2), 4.57 (s, 1H, OH), 4.91 (s, 2H, T-CH_2-B), 5.69 (s, 2H, OCH_2N); 7.62 (s, 1H, H-6), 8.21 (s, 1H, H5 triazole), 11.31 (s, 1H, NH).^{13}C NMR, DMSO-d_6: 12.50; 42.74; 63.16; 67.73; 78.50; 109.47; 124.61; 141.72; 143.16; 151.28; 164.84, ESI-MS; $C_{11}H_{15}N_5O_4$ m/z = 281.

1-[[1-[(2-Hydroxyethoxy)methyl]-1,2,3-triazol-4-yl]methyl]iodouracil 10c. Solid, mp 155 °C, ^{1}H NMR, DMSO-d_6, δ 3.71 (m, 4H, CH_2CH_2); 4.92 (m, 1H, OH); 5.18 (s, 2H, T-CH_2-B), 5.91(s, 2H, OCH_2-T); 8.44 (s, 1H, H-5(triazole)); 8.53 (s, 1H, H-6); 11.3 (s, 1H, NH).^{13}C NMR, DMSO-d_6: 43.20; 60.32; 69.09; 71.57; 78.82; 124.61; 143.24; 150.31; 151.01; 161.64. ESI-MS, $C_{10}H_{12}N_5O_4I$ m/z = 393.7.

9-[[1-[(2-Hydroxyethoxy)methyl]-1,2,3-triazol-4-yl]methyl]adenine 13a. Solid, mp 209 – 212 °C, ^{1}H NMR, DMSO-d_6, δ: 3.4 (m, 4H, CH_2CH_2), 4.65 (s, 1H, OH), 5.45 (s, 2H, T-CH_2-B), 5.7 (s, 2H, OCH_2N); 7.22 (s, 2H, NH_2), 8.05 (s, 1H, H-5(triazole)), 8.2 and 8.25 (s, 2H, H-2 and H-8). FAB-MS, $C_{11}H_{14}N_8O_2$ m/z 291 $(M+H)^+$.

9-[[1-[(2-Hydroxyethoxy)methyl]-1,2,3-triazol-4-yl]methyl]guanine 13c. Solid, mp 209 – 212 °C, ^{1}H NMR, DMSO-d_6, δ 3.5 (m, 4, CH_2CH_2); 4.65 (sl, 1, OH); 5.55 (s, 2, T-CH_2-B); 5.7 (s, 2, OCH_2N); 6.3 (bs, 2, NH_2); 8.0 (s, 1H, H-5(triazole)); 8.2 (s, 1, H-8); FAB-MS, $C_{13}H_{16}N_8O_4$ m/z 307 $(M+H)^+$.

1-[[1-[(2-Hydroxyethoxy)methyl]-1,2,3-triazol-4-yl]methyl](3-chloro-6-nitro indazole) 13d. Solid, mp 89 – 92 °C, , ^{1}H NMR, DMSO-d_6, δ 3.50 (m, 4H, CH_2CH_2), 4.71 (s, 1H, OH), 5.69 (s, 2H, T-CH_2-B), 5.93 (s, 2H, OCH_2N); 7.22 (s, 2H, NH_2), 7.94;8.05 (m, 2H, H-5, H-4); 8.33 (s, 1H, H-5 (triazole)), 8.99(d, 1H, H-7).^{13}C NMR, DMSO-d_6: 45.05; 60.44; 71.58; 78.85; 108.70; 116.84; (2xC) 121.19; (2xC) 124.35; 140.05; 142.97; 147.75. ESI-MS, $C_{13}H_{13}N_2O_4Cl$ m/z = 352.9

1-[[1-[(2-Hydroxyethoxy)methyl]-1,2,3-triazol-4-yl]methyl](3-bromo-6-nitroindazole) 13c. Solid, mp 116 – 119 °C, ^{1}H NMR, DMSO-d_6, δ 3.50 (m, 4H, CH_2CH_2); 4.71 (sl, 1H, OH); 5.69 (s, 2H, T-CH_2–B), 5.93 (s, 2H, OCH_2N); 7.22 (s, 2H, NH_2); 8.05; 8.24 (m, 2H, H-5, H-4); 8.54 (s, 1H, H-5 (triazole)); 9.19 (d,1H, H-7). ^{13}C NMR, DMSO-d_6: 45.74; 60.93; 72.20; 79.49; 109.19; 117.49; (2xC) 122.40; (2xC) 125.53; 140.53; 143.64; 148.36. ESI-MS, $C_{13}H_{13}N_2O_4Br$ m/z = 396.8 .

1,3-Bis-[[1-[(2-hydroxyethoxy)methyl]-1,2,3-triazol-4-yl]methyl]uracil 15a. Viscous residue, ^{1}H NMR, DMSO-d_6, δ 3.45 (m, 8H, 2x(CH_2CH_2)); 4,72 (s, 2H, 2x(OH)); 5.05 (s, 4H, 2x(T-CH_2-B)); 5.71 (s, 4H, 2x(OCH_2-T)); 5.79 (d,1H, H-5, *J*= 7.89 Hz); 7.86 (d, 1H, H6, *J*= 7.86 Hz); 8.08 (s, 1H, H-5(triazole)); 8.25 (s, 1H, H-5(triazole)).^{13}C NMR, DMSO-d_6: 44.12; 46.33; 60.33; 63.35; 71.52; 71.59; 78.69; 78.84; 101.12; 124.38; 124.73; 143.12; 143.89; 144.89; 151.33; 162.60. ESI-MS, $C_{16}H_2N_8O_6$ m/z = 422.9

1,3-Bis-[[1-[(2-hydroxyethoxy)methyl]-1,2,3-triazol-4-yl]methyl]thymine 15b. Solid, mp 72 – 76°C; ^{1}H NMR, DMSO-d_6; δ 1.83 (s, 3H, CH_3); 3.48 (m, 8H, 2x(CH_2CH_2)); 4.74 (s, 2H, 2x(OH)); 5.04 (s, 4H, 2x(T-CH_2-B)); 5.19 (s, 4H, 2x(OCH_2-T)); 7.25 (d, 1H, H-6); 8,07 (s, 1H, H-5(triazole)), 8.25 (s, 1H, H-5(triazole)).^{13}C NMR, DMSO-d_6: 12.53; 43.35; 45.75; 59.72; 62.73; 70.92; 70.99; 78.07; 78.23; 108.15; 123.79; 124.09; 140.10; 142.66; 143.06; 150.57; 162.73. ESI-MS, $C_{17}H_{24}N_8O_6$ m/z = 436.9

References

1. Chen, M. D.; Lu, S. J.; Yuag, G. P.; Yang, S. Y.; Du, X. L. *Heterocycl. Commun*. **2000**, *6*, 421.
2. Diana, G. D., Nitz, J. J. EP 566 199, 1993.

3. Manfredini, S.; Vicentini, C. B.; Manfrini, M.; Bianchi, N.; Rutigliano, C.;Mischiati, C.; Gambari, R. *Bioorg. Med. Chem*. **2000**, *8*, 2343.
4. Sidwell, R. W.; Huffman, J. H.; Khare, G. P.; Allen, L. B.; Witkowski, J. T.; Robins, R. K. *Science* **1972**, *177*, 705.
5. (a) De Clercq, E. *Clin. Microbiol. Reviews* **1997**, *10*, 674. (b) De Clercq, E. *Nat. Rev. Drug Discovery* **2002**, *1*, 13. (c) Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; De Clercq, E.; Perno, C.-F.;Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185.
6. Whiting, M.; Tripp, J. C.; Lin, Y. C.; Lindstrom, W.; Olson, A. J.; Elder, J. H.; Sharpless, K. B.; Fokin, V. V. *J. Med. Chem.* **2006**, *49*, 7697.
7. Lazrek, H. B.; Taourirte, M.; Oulih, T.; Barascut, J. L.; Imbach, J. L.; Pannecouque, C.; Witrouw, M.; De Clercq, E. *Nucleosides Nucleotides Nucleic acids* **2001**, *20*, 1949.
8. (a) Kolb, H. C.; Sharpless, K. B. *Drug Discov. Today* **2003**, *8*, 1128. (b) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem*. 2006, 51.
9. (a) Huisgen, R. *Angew. Chem*., *Int. Ed.* **1963**, *2*, 565. (b) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; pp 1–176. (c) *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 4, pp 1069–1109.
10. (a) Moorhouse, A. D.; Santos, A. M.; Gunaratnam, M.;Moore, M.; Neidle, S.; Moses, J. E. *J. Am. Chem. Soc.* **2006**, *128*, 15972. (b) Lee, L. V.; Mitchell, M. L.; Huang, S.-J.; Fokin, V. V.; Sharpless, K. B.; Wong, C.-H. *J. Am. Chem. Soc*. **2003**, *125*, 9588.
11. (a) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.;Scheel, A.; Voit, B.; Pyun, J.; Frechet, J. M. J.; Sharpless,K. B.; Fokin, V. V. *Angew. Chem*., *Int. Ed.* **2004**, *43*, 3928. (b) Wu, P.; Malkoch, M.; Hunt, J. N.; Vestberg, R.;Kaltgrad, E.; Finn, M. G.; Fokin, V. V.; Sharpless, K. B.;Hawker, C. *J. Chem. Commun*. **2005**, 5775. (c) Rozkiewicz, D. I.; Janczewski, D.; Verboom, W.; Ravoo,B. J.; Reinhoudt, D. N. *Angew. Chem., Int. Ed*. **2006**, *45*, 5292.
12. (a)Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. J. Am. Chem. Soc. **2003**, *125*, 3192. 10. (b) Speers, A. E.; Adam, G. C.; Cravatt, B. F. *J. Am. Chem. Soc*. **2003**, *125*, 4686. (c) Speers, A. E.; Cravatt, B. F. *Chem. Biol*. **2004**, *11*, 535. (d) Burley, G. A.; Gierlich, J.; Mofid, M. R.; Nir, H.; Tal, S.; Eichen, Y.; Carell, T. *J. Am. Chem. Soc.* **2006**, *128*, 1398.
13. Chittepu, P.; Sirivolu, V. R.; Seela, F. *Bioorg. Med. Chem*. **2008**, *16*, 8427.
14. Yan, Z. Y.; Zhao, Y. B.; Fan, M. J.; Liu, W. M.; M.Liang, Y. *Tetrahedron* **2005**, *61*, 9331.
15. El Akri, K.; Bougrin, K.; Balzarini, B. J.; Faraj, A.; Benhida, R. *Bioorg. Med. Chem Lett*. **2007**, *17*, 6656.