Preparation of 1,4-disubstituted-1,2,3-triazolo ribonucleosides by $Na_2CuP_2O_7$ catalyzed azide-alkyne 1,3-dipolar cycloaddition

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DOI: http://dx.doi.org/10.3998/ark.5550190.0013.807

Abstract

In this study, we describe the synthesis of 1,4-disustituted-1,2,3-triazolo-ribonucleosides by means of 1,3-dipolar cycloaddition between various N-1 propargyl-pyrimidines and 1'-azido-2',3',5'-tri-*O*-benzoylribose catalyzed by $Na_2CuP_2O_7$/sodium ascorbate. All obtained compounds were evaluated for their anti-HCV activity in vitro.

Keywords: 1,2,3-Triazolo ribonucleosides, $Na_2CuP_2O_7$, click chemistry

Introduction

Triazole derivatives occupy a prominent place in medicinal chemistry because of their therapeutic properties. Compounds containing a triazole moiety have found tremendous application in the field of pharmaceutical,[1] biology,[2] and material sciences.[3] On the other hand, triazole nucleosides such as Ribavirine (Virazole) or 1,2,3-triazole TSAO analogues are used for the treatment of HCV and HIV[4,5] respectively. Thus, the pharmaceutical importance of triazoles has prompted the design and synthesis of various triazolonucleosides.[6-7] We previously reported the preparation of various 1,2,3-triazole acyclonucleosides from the propargylated nucleobases by copper-free Huisgen 1,3-dipolar cycloaddition at high temperature and long duration and the

evaluation of the resulting compounds for their HIV activity.[8] Recently, we also reported the preparation of several triazoloacyclic nucleoside phosphonates using copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition between azidoalkylphosphonates and propargylated nucleobases and their evaluation for their HIV and HCV activity.[9]

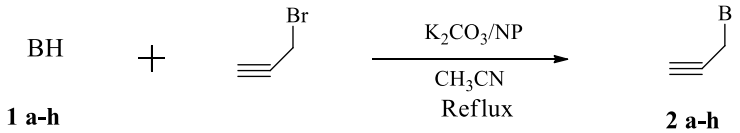
The click reaction[10] has become a basic tool in organic or in bioorganic for the preparation of 1,2,3-triazole. To reach this aim, a number of procedures have been developed including the use of Cu(I)-Zeolite[11], Cu/C[12], Cu(OH)x/TiO_2[13] . The results obtained by any of these methods are, in general, excellent. On the other hand, looking for a new catalyst having a great efficiency to carry on the 1,3-dipolar cycloaddition reaction is still in demand.

In addition to our previous research on using phosphate derivatives as catalyst[14] and in continuation of our drug discovery program, we report herein the synthesis of new 1,4-disubstituted-1,2,3-triazolo-ribonucleosides using, for the first time, $Na_2CuP_2O_7$ as catalyst for Huisgen 1,3-dipolar cycloaddition. The anti-HCV activity of the prepared 1,2,3-triazole ribonucleosides was also determined.

Results and Discussion

After a series of trials with various copper catalysts, we were pleased to find that $Na_2CuP_2O_7$ could be used for the smooth preparation of 1,4-substituted 1,2,3-triazole nucleosides under mild conditions. The synthetic phosphate $Na_2CuP_2O_7$ was prepared by reaction between Na_2CO_3, CuO and $(NH_4)_2HPO_4$ as previously reported[15]. The final product was identified by X-ray powder diffraction using a Siemens D-500 diffractometer (CuKα radiation 1.5406 Å; Space group: triclinic P1bar; a = 5.361 Å, b = 7.029 Å and c = 8.743 Å) and infrared spectroscopy IR. FTIR-spectrum of the $Na_2CuP_2O_7$ compound exhibited prominent multiple absorption bands especially in three frequency regions (i.e. at ν1 = 2350.6 cm−1, ν2 = 1629.7 cm^{-1} and ν3 = 1260–499.3 cm^{-1}). The vibration at 2350.6 cm^{-1} is attributed due to the stretching of Cu O Cu bonding and 1629.7 cm^{-1} is due to the stretching of Na O bonding. The strong vibration bands in the range of 1260–499.3 cm^{-1} are due to the presence of P O P bonding.

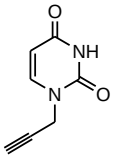
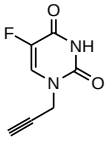
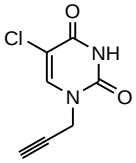
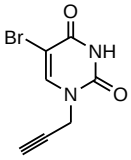
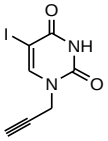
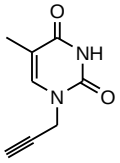
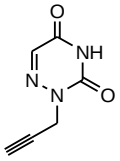
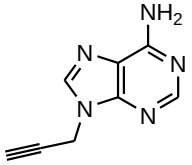
We have developed a new and easy synthesis of the propargyl pyrimidines and purine using K_2CO_3/Natural Phosphate (1/5) as a basic catalyst[14] (Scheme 1). The yields obtained were 45 to 65% after 2 to 3 h. The major advantage of this method is the ease of the work-up. This procedure appears to be regioselective and gives only the N-1 isomer for pyrimidines and N-9 isomer for adenine (Table 1). The structures of the nucleosides **2a-h** were determined from their spectral (NMR ^1H, ^{13}C, and Mass) data and found to be in agreement with the literature [8d].



BH= base: Uracil **1a**, 5-F-uracil **1b**, 5-Cl-uracil **1c**, 5-Br-uracil **1d**,5-I-uracil **1e**, Thymine **1f**, 6-Azauracil **1g**, Adenine **1h**.

Scheme 1

Table 1. N-Alkylation of nucleobases using K_2CO_3/natural phosphate

Products	Time (h)	Yield %
 **2a**	2	50
 **2b**	3	52
 **2c**	3	48
 **2d**	3	53
 **2e**	5	62
 **2f**	3	56
 **2g**	2	46
 **2h**	2	55

In preliminary experiments, azido-2,3,5-tri-*O*-benzoylribose[16] (azidosugar) **3** was chosen for the template reaction with propargyl-uracil **2a**. Initially, $Na_2CuP_2O_7$ was used alone, with Dioxane/Water (2/1, V/V) as solvent. No product was isolated when the reaction was conducted at room temperature overnight in the presence of 10 mol% $Na_2CuP_2O_7$ (entry 1, Table 2).

Therefore, we tried heating and increasing the amount of $Na_2CuP_2O_7$. To our delight, the reaction gave the corresponding 1,2,3-triazole nucleoside **4a** in a range of 15-26% yield (entries: 2-5, Table 2) at 90°C. We decided to explore the feasibility of the 'click' chemistry with the novel catalyst $Na_2CuP_2O_7$ for the construction of novel 1,2,3-triazole nucleosides. In the standard procedure for regioselective Cu(I)-catalyzed alkyne-azide coupling, the catalyst can be directly introduced as a Cu(I) salt or generated in situ by reduction of a Cu(II) salt, usually in organic-aqueous systems[17]. Two reaction conditions that favour either process were selected:

Condition A[18]:

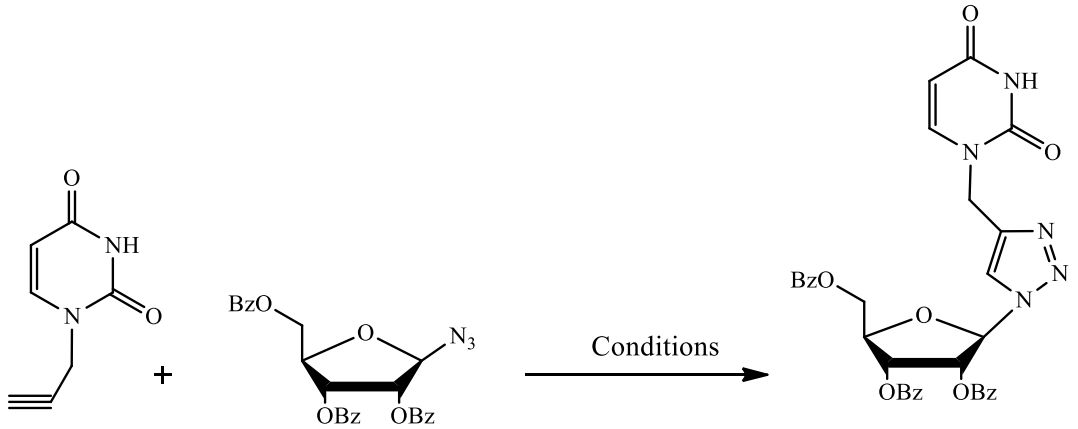
azidosugar + propargyl–uracil + $Na_2CuP_2O_7$ (0.5mmol) + $(Et)_3N$ + Dioxane/water (90°C, 2h): these conditions produced no reaction .

Condition B:

azidosugar + propargyl–uracil + $Na_2CuP_2O_7$(0.5mmol)/Na Ascorbate(0.5 mmol) + Dioxane/water (90°C, 2h) .

Condition B gave the 1,2,3- triazole nucleoside **4a** with 72% yield.

Encouraged by this result, the reaction was carried out increasing the amount of Na ascorbate(0.1 mmol- 1 mmol) the optimal reaction condition was as follows: $Na_2CuP_2O_7$ (0.5 mmol)/Na Ascorbate(0.5 mmol) as catalyst and Dioxane/water(2/1, v/v) as solvent and reflux 90°C for 2 h. We deduced that the catalyst is generated in situ from Cu(II) (Na2CuP2O7) via reduction with sodium ascorbate. Under the present conditions when simpler alkyne **5** was used in the reaction with the azides **3a** or **3b** (Scheme 2, 3) led to the corresponding 1,4-disubstituted 1,2,3-triazole derivatives **6**, and **7** in 66% and 62% yields respectively as shown in Table 3. These results are in the same range as those reported in the literature[19] using CuSO4/Na Ascorbate as catalyst for the preparation of 1,2,3-triazolo-nucleosides.

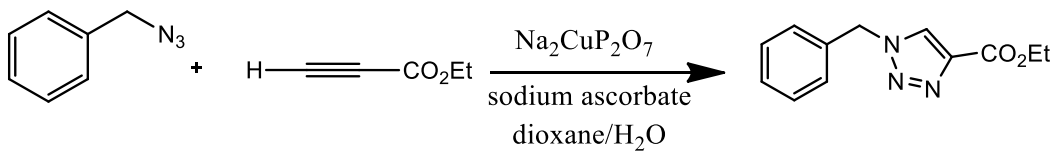


2a **3a** **4a**

Scheme 2

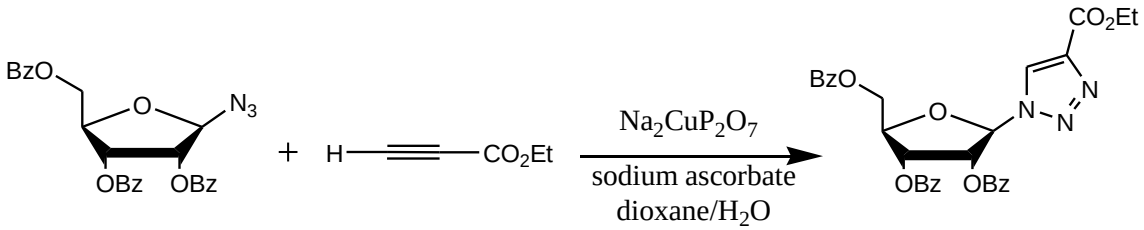
Table 2. Optimization of the $Na_2CuP_2O_7$ catalyzed model reaction for the synthesis of 1,4-disubstituted-1,2,3-triazole ribonucleoside **4a** using different catalysts and solvents at 90°C

Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	$Na_2CuP_2O_7$ (0.1 mmol)	Dioxane/water	2/RT	0
2	$Na_2CuP_2O_7$ (0.1 mmol)	Dioxane/water	2	15
3	$Na_2CuP_2O_7$ (0.5 mmol)	Dioxane/water	2	20
4	$Na_2CuP_2O_7$ (0.75 mmol))	Dioxane/water	2	24
5	$Na_2CuP_2O_7$ (1 mmol))	Dioxane/water	2	26
6	$Na_2CuP_2O_7$ (0.1 mmol) Na Ascorbate (0.1 mmol)	Dioxane/water	2	45
7	$Na_2CuP_2O_7$ (0.25 mmol) Na Ascorbate (0.25 mmol)	Dioxane/water	2	51
8	$Na_2CuP_2O_7$ (0.5 mmol) Na Ascorbate (0.5 mmol)	Dioxane/water	2	72
9	$Na_2CuP_2O_7$ (0.75 mmol) Na Ascorbate (0.75 mmol)	Dioxane/water	2	60
10	$Na_2CuP_2O_7$ (1 mmol) Na Ascorbate (1 mmol)	Dioxane/water	2	16
11	$Na_2CuP_2O_7$ (0.5 mmol) Na Ascorbate (0.5 mmol)	Dioxane	2	0
12	$Na_2CuP_2O_7$ (0.5 mmol) Na ascorbate (0.5 mmol)	Water	2	33



3b **5** **6**

Scheme 3

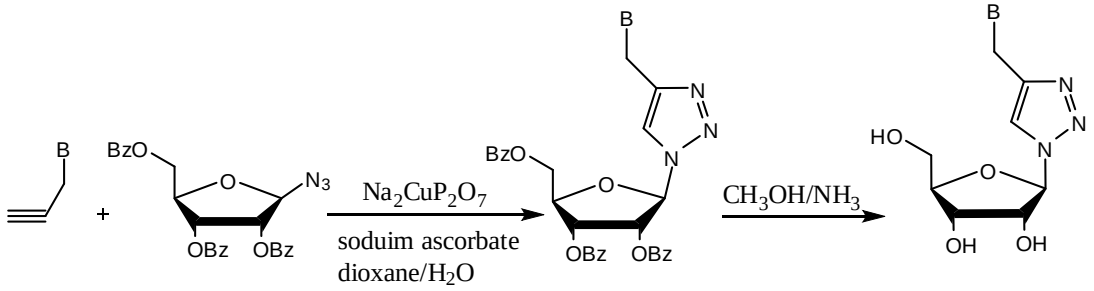


3 b **5** **7**

Scheme 4

Table 3. 1, 3-Dipolar cycloaddition of **3a** and **3b** to **5**

Entry	Products	Time (h)	Yield (%)
1	**6**	2	66
2	**7**	2	62



2a-h **3** **8b-h** **9a-h**

B= nucleobase : uracil **1a**, 5-F-uracil **1b**, 5-Cl-uracil **1c**, 5-Br-uracil **1d**, 5-I-uracil **1e**, Thymine **1f**, 6-Azauracil **1g**, Adenine **1h.**

Scheme 5

The optimised reaction conditions were successfully applied to a variety of terminal alkynes (Table 4). Propargylated uracil, 5-fluorouracil, 5-chlorouracil, 5-bromouracil, 5-iodouracil,

thymine, 6-azauracil, and adenine were combined with azidosugar **3**. All reactions were highly regioselective towards the corresponding 1,2,3-triazole nucleosides **8a-h** and were obtained in excellent isolated yields (Table 4). Deblocking of the benzoyl protecting groups was performed using methanolic ammonia (saturated at 0°C) at room temperature and gave 1,2,3-triazole ribonucleosides **9a-h** in a 40-55% yield. The structures of the nucleosides were determined from their spectral (^{1}H, ^{13}C NMR and Mass) data.

The mechanism for this $Na_2CuP_2O_7$ -catalyzed synthesis of 1,2,3-triazole ribonucleosides need much more studies, but we offer the following tentative hypothesis. A plausible mechanism (Scheme 6) might follow the same steps as for a bimetallic mechanism where the alkyne was coordinated to one Cu center, and the azide interacts with the second Cu center.[20]

Finally, we were also interested in studying the biological activity of 1,2,3-triazole ribonucleosides **9a-h**. These derivatives were tested *in vitro* in the aim to evaluate their anti-HCV activity. None of the new compounds were found to inhibit HCV replication *in vitro* (Table 5).

Antiviral activity was assessed in a 3 day cell culture assay using the HCV-replicon-containing cell line, AVA5 (genotype 1b, CON1) (provided by Apath, Inc. to GUMC) as previously described[21].

Finally, we were also interested in studying the biological activity of 1,2,3-triazole ribonucleosides **9a-h**. These derivatives were tested *in vitro* with the aim to evaluate their anti-HCV activity. None of the new compounds were found to inhibit HCV replication *in vitro* (Table 5).

Table 4. Synthesis of 1, 4-disubstituted-1,2,3-triazole ribonucleosides **8a-h** with different alkynes

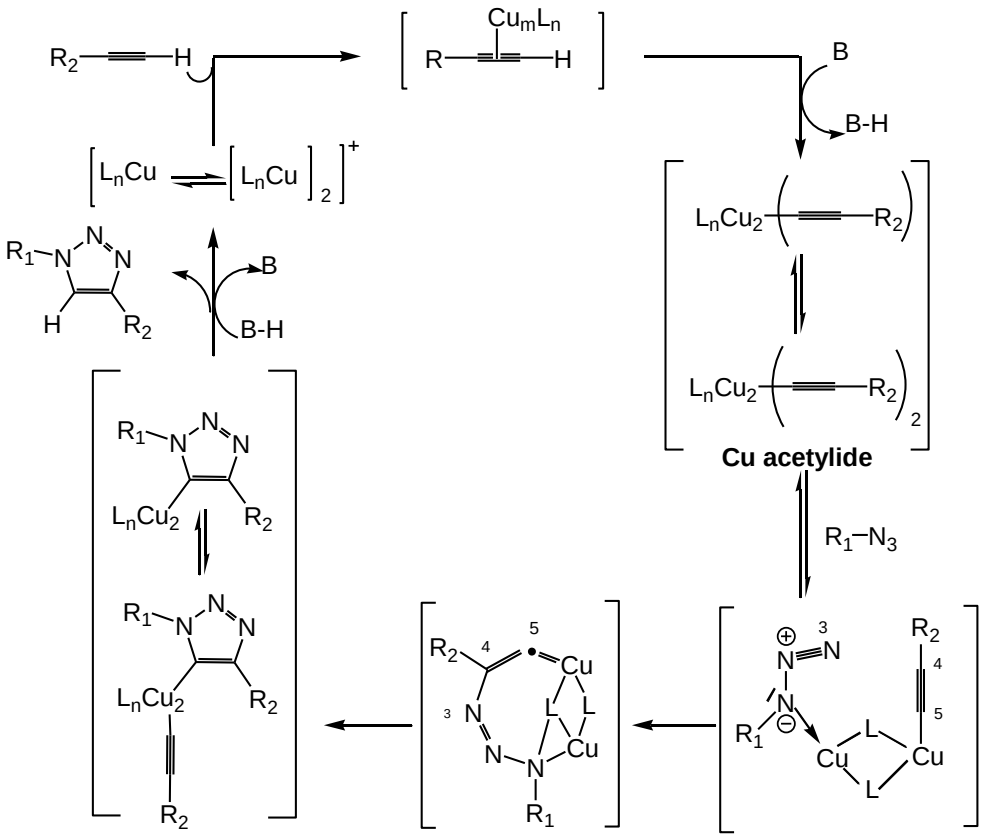
Entry	Bases/products[a]	Time (h)	Yield (%)[b]
1	Uracil/**4a**	2	72
2	5-Fluorouracil/**8b**	2	68
3	5-Chlorouracil/**8c**	2	88
4	5-Bromouracil/**8d**	2	72
5	5-Iodouracil/**8e**	2	84
6	Thymine/**8f**	2	67
7	6-azauracil/**8g**	2	69
8	Adenine/**8h**	2	73

[a] Reaction conditions: azidosugar **3** (1 mmol), **2** (1.1 mmol), $Na_2CuP_2O_7$(0.5 mmol) Na ascorbate (0.5 mmol) in dioxane/water at 90°C. [b] Isolated yield after column chromatography.

Table 5. Anti-HCV activity of compounds **9a-f, h**

Compound	CC_{50} (μM)[a]	EC_{50} (μM)[b]	SI[c]
9a	>100	> 10	>10
9b	> 100	> 10	>10
9c	> 100	> 10	>10
9d	> 100	> 10	>10
9e	> 100	> 10	>10
9f	> 100	> 10	>10
9h	> 100	> 10	>10
2CmeCyt	>300	1,5	200
aIFNB2	>10000[d]	1,5 [d]	6667

[a] CC_{50} Concentrations of compound required for 50% extinction of Huh 5.2 cells. [b] IC_{50} Concentrations of compound achieving 50% inhibition of the replicon system. [c] SI selectivity index = CC_{50}/ $IC_{50.}$ [d] Interferon reported as IU/ml.



Scheme 6

Conclusions

We have shown for the first time that 1,4-disubstituted 1,2,3-triazole ribonucleosides can be prepared from protected azidosugar **3** and propargyl-nucleobases **2a-h** by using the couple $Na_2CuP_2O_7$/Na ascorbate as a new catalyst. The major advantages of this method is the ease of the work-up, short reaction times and use of various substrates which make it a useful strategy for the synthesis of 1,2,3-triazole ribonucleosides in comparison to high temperature cycloaddition[8] which resulted in a mixture of regioisomers.

Experimental Section

General. The NMR spectra were recorded on a Bruker spectrometer (AC 300 MHz). Chemical shifts are reported as δ values (ppm) relative to TMS as a standard and the coupling constants *J* values are given in Hz. FAB mass spectra were recorded on a Varian MAT 311A spectrometer. TLC was performed on 60 F254 precoated plastic plates silica gel (Merck). Column chromatography was performed on silica gel (30-60 μm). All solvents were distilled and dried before using.

Preparation of K_2CO_3/NP

500 mg of K_2CO_3 were dissolved in 5 ml of water and then 2.5 g of Natural Phosphate (NP) were added to the solution. After 15 min stirring, the mixture was evaporated to dryness and used as catalyst.

Typical procedure for alkylation reactions

To a mixture of nucleobase (1 mmol), 200 mg of the catalyst K2CO3/NP (1/5) and 5ml of CH3CN was added propargyl bromide (1.1 mmol).The latter, was heated under reflux. After 30 min heating, an additional 100 mg of K2CO3/NP were added. After 2 to 3 h heating the reaction was quenched by adding two drops of acetic acid, and filtered. The precipitate was washed with MeOH. The solvent was evaporated and the residue was purified by flash column (silica gel) (Table 1).

Typical procedure for 1,3-dipolar cycloaddition

The propargylated base **2a-h** (1.1 mmol), azidosugar **3** (1 mmol) and $Na_2CuP_2O_7$ (0.5 mmol), sodium ascorbate (0.5 mmol) were suspended in Dioxane/water (2/1, v/v) and stirred at reflux 90°C for 2 h. Then, the solution was evaporated, and the residue was applied to flash column (silica gel).

Ethyl-[(2,3,5-Tri-*O*-benzoyl-ß-D-erythro-pentofuranosyl)-1,2,3-triazol]-4-carboxylate (6). NMR ^{1}H ($CDCl_3$) (300MHz) δ (ppm): 1.30 (t, 3H, CH_3), 4.29 (q, 2H, CH_2) 4.42(s, 2H, H5'),

4.90 (m, 1H, H2'), 5.60 (m, 1H, H3'), 5.62 (m, 1H, H4'), 6.20 (m, 1H, H1'), 7.50 (m, Ar-H), 8.10 (m, Ar-H), 8.38 (s, 1H, CH =C). ^{13}C NMR ($CDCl_3$, 75 MHz): 14.10 (CH_3), 70.01 (CH_2), 63.81 (C5'), 70.00 (C2'), 71.69 (C3'), 76.67 (C4'), 90.4 5(C1'), 125.21 (C5), 128.44-133.87 (Ar-C), 166.93 (CO_2). MS/ESI$^+$ m/z 586.57 $(M+H)^+$**.**

Ethyl-benzyl-1*H*-1,2,3-triazole-4-carboxylate (7). NMR ^{1}H ($CDCl_3$) (300MHz) δ (ppm): 1.32 (t, 3H, CH_3), 4.29 (q, 2H, CH_2), 4.99 (s, 2H, CH_2), 7.10-7.56 (m, 5H, Ar-H),. 8.42 (s, 1H, CH =C)^{13}C NMR ($CDCl_3$, 75 MHz): 14.10 (CH_3), 56.71 (CH_2), 70.01 (CH_2), 125.47 (C5), 128.44-133.87 (Ar-C), 166.81 (CO_2). MS/ESI$^+$ m/z 232.26$(M+H)^+$

2-[(2,3,5-Tri-O-benzoyl-ß-D- erythro-pentofuranosyl)-1,2,3-triazol-4-yl-methyl]Uracil (4a). RMN ^{1}H ($CDCl_3$) (300MHz) δ (ppm): 4.30 (m, 2H, CH_2), 4.42(s, 2H, H5'), 4.90 (m, 1H, H2'), 5.60 (m, 1H, H3'), 5.62 (m, 1H, H4'), 5.80 (d, 1H, H5), 6.20 (m, 1H, H1'), 7.90 (d, 1H, H6), 7.50 (m, Ar-H), 8.10 (m, Ar-H), 8.26 (s, 1H, CH =C), 10.20 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): 48.57 (CH_2), 63.81 (C5'), 70.00 (C2'), 71.69 (C3'), 76.67 (C4'), 90.4 5(C1'), 102.87 (C5), 124.01 (C9), 128.44-133.87 (Ar-C), 142.21 (C6), 143.89 (C8), 150.59 (2C=O), 163.99 (4C=O), 166.11 (CO_2). MS/ESI$^+$ m/z 638.47 $(M+H)^+$

2-[(2,3,5-Tri-O-benzoyl-ß-D-erythro-pentofuranosyl)-1,2,3-triazol-4-yl-methyl]5-FluoroUracil (8b). RMN ^{1}H ($CDCl_3$) (300MHz) δ (ppm): 4.30 (m, 2H, CH_2), 4.42(m, 2H, H5'), 4.90 (m, 1H, H2'), 5.60 (m, 1H, H3'), 5.62 (m, 1H, H4'), 6.20 (m, 1H, H1'), 7.19 (d, 1H, H6), 7.50 (m, Ar-H), 8.10 (m, Ar-H), 8.16 (s, 1H, CH=C), 9.20 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): 48.57 (CH_2), 62.80 (C5'), 70.00 (C2'), 71.69 (C3'), 76.67 (C4'), 90.45 (C1'), 102.41 (C5), 124.01 (C9), 128.44-133.87 (Ar-C), 143.21 (C6), 143.09 (C8), 150.59 (2C=O), 163.99 (4C=O), 166.11 (CO_2). MS/ESI$^+$ m/z 656.49 $(M+H)^+$**.**

2-[(2,3,5-Tri-O-benzoyl-ß-D-erythro-pentofuranosyl)-1,2,3-triazol-4-yl-methyl]5-Chloro-Uracil(8c). RMN ^{1}H ($CDCl_3$) (300MHz) δ (ppm): 4.30 (m, 2H, CH_2), 4.42(m, 2H, H5'), 4.90 (m, 1H, H2'), 5.60 (m, 1H, H3'), 5.62 (m, 1H, H4'), 6.54 (m, 1H, H1'), 7.97 (s, 1H, H6), 7.50 (m, Ar-H), 8.10 (m, Ar-H), 8.26 (s, 1H, CH=C), 10.30 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): 48.77 (CH_2), 62.81 (C5'), 71.00 (C2'), 71.69(C3'), 76.67 (C4'), 91.35 (C1'), 106.47 (C5), 124.04 (C9), 128.44-133.87 (Ar-C), 142.21 (C6), 143.89 (C8), 150.59 (2C=O), 163.99 (4C=O), 166.11 (CO_2). MS/ESI$^+$ m/z 672.49 $(M+H)^+$**.**

2-[(2,3,5-Tri-O-benzoyl-ß-D-erythro-pentofuranosyl)-1,2,3-triazol-4-yl-methyl]5-Bromo-Uracil (8d). RMN ^{1}H ($CDCl_3$) (300MHz) δ (ppm): 4.30 (s, 2H, CH_2), 4.51(m, 2H, H5'), 4.90 (m, 1H, H2'), 5.60 (m, 1H, H3'), 5.62 (m, 1H, H4'), 6.51 (m, 1H, H1'), 7.50 (m, Ar-H), 8.10 (m, Ar-H), 8.16 (s, 1H, CH=C), 8.26 (d, 1H, H6), 9.55 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): 48.57 (CH_2), 62.81 (C5'), 70.00 (C2'), 71.69(C3'), 76.67 (C4'), 90.45 (C1'), 97.47 (C5), 122.01 (C9), 128.44-133.87 (Ar-C), 143.21 (C6), 143.89(C8), 150.59 (2C=O), 159.99 (4C=O), 166.11 (CO_2). MS/ESI$^+$ m/z 716.90 $(M+H)^+$**.**

2-[(2,3,5-Tri-O-benzoyl-ß-D- erythro-pentofuranosyl)-1,2,3-triazol-4-yl-methyl]5-IodoUracil(8e). RMN ^{1}H ($CDCl_3$) (300MHz) δ (ppm): 4.30 (m, 2H, CH_2), 4.42 (m, 2H, H5'), 4.90 (m, 1H, H2'), 4.96 (m, 1H, H3'), 5.12 (m, 1H, H4'), 6.20 (m, 1H, H1'), 7.50 (m, Ar-H), 8.10 (m, Ar-H), 8.01 (s, 1H, CH=C), 8.04 (d, 1H, H6), 9.55 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75

MHz): 43.25 (CH_2), 63.71 (C5'), 63.93 (C2'), 71.69 (C3'), 75.67 (C4'), 90.51(C1'), 103.41 (C5), 123.99 (C9), 128.44-133.87 (Ar-C), 148.21 (C6), 143.09 (C8), 150.59 (2C=O), 160.99 (4C=O), 166.11 (CO_2). MS/ESI$^+$ m/z 763.50 $(M+H)^+$**.**

2-[(2,3,5-Tri-O-benzoyl-ß-D- erythro-pentofuranosyl)-1,2,3-triazol-4-yl-methyl]Thymine (8f). RMN ^{1}H($CDCl_3$) (300MHz) δ(ppm):2.10 (d, 3H, CH_3), 4.26 (m, 2H, H5'), 4.30 (m, 2H, CH_2), 5.00 (m, 1H, H2'), 5.10 (m, 1H, H3'), 5.25 (m, 1H, H4'), 6.40 (m, 1H, H1'), 7.25 (m, Ar-H), 7.50 (m, Ar-H), 7,70 (d, 1H, H6), 8.12 (s, 1H, CH=C), 10.70 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): 20.12 (C10), 53.47 (CH_2), 62.81 (C5'), 70.76 (C2'), 72.49 (C3'), 75.17 (C4'), 90.49 (C1'), 110.37 (C5), 124.01 (C9), 128.38-133.87 (Ar-C), 138.46 (C6), 151.19 (C8), 151.59 (2C=O), 163.29 (4C=O), 166.11 (CO_2). MS/ESI$^+$ m/z 652.53 $(M+H)^+$**.**

2-[(2,3,5-Tri-O-benzoyl-ß-D- erythro-pentofuranosyl)-1,2,3-triazol-4-yl-methyl]6-azauracil (8g). RMN ^{1}H ($CDCl_3$) (300MHz) δ(ppm): 4.00 (m, 2H, CH_2), 4.26 (m, 2H, H5'), 4.80 (m, 1H, H2'), 4.90 (m, 1H, H3'), 5.00 (m, 1H, H4'), 6.54 (m, 1H, H1'), 7.11 (s, 1H, H5), 7.40 (m, Ar-H), 8.00 (m, Ar-H), 8.24 (s, 1H, CH=C), 10.96 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): 50.57 (CH_2), 59.61 (C5'), 70.00 (C2'), 71.69 (C3'), 76.67 (C4'), 89.45 (C1'), 102.47 (C5), 120.01 (C9), 128.44-133.87 (Ar-C), 143.89 (C8), 150.59 (2C=O), 163.99 (4C=O), 166.11 (CO_2). MS/ESI$^+$ m/z 639.55 $(M+H)^+$.

7-[(2',3',5'-Tri-O-benzoyl-ß-D- erythro-pentofuranosyl)-1,2,3-triazole-4-yl-methyl]Adenine (8h). RMN ^{1}H ($CDCl_3$) (300MHz) δ(ppm): 4.30 (s, 2H, NH_2), 4.32 (m, 2H, CH_2), 4.10 (m, 2H, H5'), 4.70 (m, 1H, H2'), 4.81 (m, 1H, H3'), 4.93 (m, 1H, H4'), 5.50 (s, 2H, CH_2), 6.25 (m, 1H, H1'), 8.10 (s, 1H, H8), 7.50 (m, Ar-H), 8.15 (m, Ar-H), 8.20 (s, 1H, H2), 8.30 (s, 1H, CH =C). . ^{13}C NMR ($CDCl_3$, 75 MHz): 48.73 (C10), 63.75 (C5'), 71.72 (C2'), 75.01 (C3'), 76.67 (C4'), 90.54 (C1'), 119.40 (C5), 122.87 (C12), 128.44-133.87 (Ar-C), 140.49(C8), 140.59 (C6), 152.09 (C11), 155.59 (C2), 166.11 (CO_2). MS/ESI$^+$ m/z 661.87 $(M+H)^+$**.**

2-[(ß-D- erythro-pentofuranosyl)-1,2,3-triazol-4-yl-methyl]Uracil (9a). RMN ^{1}H (CD_3OD) (339.8447 MHz) δ (ppm): 3.66 (dd, 2H,J = 4.1 Hz, H5'), 3.78 (dd, 2H, J = 3.3 Hz, H5'), 4.11 (m, 1H, H4'), 4.29 (t, 1H, J = 5.1 Hz, H3'), 4.48 (t, 1H, J= 4.3 Hz H2'), 5.01 (s, 1H, CH_2), 5.67 (d, 1H, J= 7.8 Hz, H5), 6.02 (d, 1H, J= 3.9 Hz, H1'), 7.70 (d, 1H, J= 7.8 Hz, H6), 8.25 (s, 1H, CH =C). MS/ESI$^+$ m/z 326.10$(M+H)^+$ Anal. calcd for $C_{12}H_{15}N_50_6$: 326.10251. found: 326.10258. UV(MeOH) 265 nm.

2-[(ß-D- erythro-pentofuranosyl)-1,2,3-triazol-4-yl-methyl]5-FluoroUracil (9b). RMN ^{1}H (CD_3OD) (300MHz) δ(ppm): 3.66 (dd, 2H, J= 4.3 Hz, H5'), 3.81 (dd, 2H, J= 3.1 Hz, H5'), 4.12 (m, 1H, H4'), 4.30 (t, 1H, J= 5 Hz, H3'), 4.48 (t, 1H, J= 4.1 Hz, H2'), 4.99 (s, 2H, CH_2), 6.02 (d, 1H, J= 4.1 Hz, H1'), 7.92 (s, 1H, H6), 8.25 (s, 1H, CH=C), MS/ESI$^+$ m/z 344.1005 $(M+H)^+$ Anal. calcd for $C_{12}H_{14}FN_50_6$: 344.10059. found: 344.10052.UV(MeOH) 273 nm.

2-[(ß-D- erythro-pentofuranosyl)-1,2,3-triazol-4-yl-methyl]5-chloroUracil (9c). RMN ^{1}H (CD_3OD) (300MHz) δ(ppm): 3.66 (dd, 2H, J= 4.3 Hz, H5'), 3.81 (dd, 2H, J= 3.1 Hz, H5'), 4.12 (m, 1H, H4'), 4.29 (t, 1H, J= 5 Hz, H3'), 4.48 (t, 1H, J= 4.1 Hz, H2'), 5.03 (s, 2H, CH_2), 6.02 (d, 1H, J= 4.1 Hz, H1'), 8.04 (s, 1H, H6), 8.26 (s, 1H, CH=C), MS/ESI$^+$ m/z 360.0716 $(M+H)^+$ Anal. calcd for $C_{12}H_{14}ClN_50_6$: 360.07164. found: 360.07161.UV(MeOH) 278 nm.

2-[(ß-D- erythro-pentofuranosyl)-1,2,3-triazol-4-yl-methyl]5-BromoUracil (9d). RMN ^{1}H (CD_3OD) (300MHz) δ(ppm): 3.66 (dd, 2H, J= 4.3 Hz, H5'), 3.81 (dd, 2H, J= 3.1 Hz, H5'), 4.12 (m, 1H, H'4), 4.30 (t, 1H, J= 5 Hz, H'3), 4.48 (t, 1H, J= 4.1 Hz, H'2), 5.03 (s, 2H, CH_2), 6.02 (d, 1H, J= 4.1 Hz, H'1), 7.92 (s, 1H, H6), 8.25 (s, 1H, CH=C), MS/ESI$^+$ m/z 404.0204 $(M+H)^+$ Anal. calcd for $C_{12}H_{14}N_50_6$: 404.02042. found: 404.02043. UV(MeOH) 284 nm.

2-[(ß-D- erythro-pentofuranosyl)-1,2,3-triazol-4-yl-methyl]5-IodoUracil(9e). RMN ^{1}H (CD_3OD) (300MHz) δ(ppm): 3.68 (dd, 2H, J= 4.3 Hz, H5'), 3.80 (dd, 2H, J= 3.1 Hz, H5'), 4.12 (m, 1H, H4'), 4.29 (t, 1H, J= 5 Hz, H3'), 4.48 (t, 1H, J= 4.1 Hz, H2'), 5.02 (s, 2H, CH_2), 6.02 (d, 1H, J= 4.1 Hz, H1'), 8.20 (s, 1H, H6), 8.25 (s, 1H, CH=C), MS/ESI$^+$ m/z 452.0062 $(M+H)^+$ Anal. Calcd. for $C_{12}H_{14}IN_50_6$: 452.00615. found: 452.00623.UV(MeOH) 224 nm, 290 nm.

2-[(ß-D- erythro-pentofuranosyl)-1,2,3-triazol-4-yl-methyl]thymine(9f). RMN ^{1}H(CD_3OD) (399.844MHz) δ(ppm):1.86 (s, 3H, CH_3), 3.66 (dd, 2H, J= 4.3, H5'), 3.78 (dd, 2H, J= 3.2, H5'), 4.11 (m, 1H, H4'), 4.29 (t, 1H, J= 5.1 Hz, H3'), 4.48 (t, 1H, J= 4.3, H3'), 4.99 (s, 1H, CH_2), 6.02 (d, 1H, J= 4.1Hz, H1'), 7.53 (s, 1H, H6), 8.23 (s, 1H, CH=C), MS/ESI$^+$ m/z 340.1251 $(M+H)^+$ Anal. Calcd. for $C_{13}H_{17}N_50_6$: 340.12516. found: 340.12518. UV(MeOH) 270 nm.

2-[(ß-D- erythro-pentofuranosyl)-1,2,3-triazol-4-yl-methyl]6-azauracil(9g). RMN ^{1}H (CD_3OD) (300MHz) δ(ppm): 3.68 (dd, 2H, J= 4.3 Hz, H5'), 3.78 (dd, 2H, J= 3.1 Hz, H5'), 4.09 (m, 1H, H4'), 4.29 (t, 1H, J= 5 Hz, H3'), 4.46 (t, 1H, J= 4.1 Hz, H2'), 5.15 (s, 2H, CH_2), 6.00 (d, 1H, J= 4.1 Hz, H1'), 7.41 (s, 1H, H5), 8.20 (s, 1H, CH=C), MS/ESI$^+$ m/z 327.1041 $(M+H)^+$ Anal. Calcd. for $C_{11}H_{14}N_60_6$: 321.10416. found: 321.10413.UV(MeOH) 260 nm.

9-[(ß-D- erythro-pentofuranosyl)-1,2,3-triazol-4-yl-methyl]Adenine(9h). RMN 1H(CD_3OD) (399.844MHz) δ(ppm): 3.66 (dd, 2H, J= 4.3, H5'), 3.78 (dd, 2H, J= 3.2, H'5), 4.11 (m, 1H , H4'), 4.27 (t, 1H, J= 5.1 Hz, H3'), 4.46 (t, 1H, J= 4.3, H3') 5.53 (s, 1H, CH_2), 6.01 (d, 1H, J= 4.1Hz, H1'), 8.19 (s, 1H, H2), 8.21 (s, 1H, H8), 8.30 (s, 1H , CH=C), MS/ESI$^+$ m/z 349.1371 $(M+H)^+$ Anal. calcd for C13H16N804: 349.13713. found: 349.13718.UV(MeOH) 260 nm.

Acknowledgements

This project was supported by the comité mixte inter-universitaire Franco-Marocain programme (A.I. N° = Ma/06/143) and by Centre National de Recherche Scientifique et Technique (Rabat, Maroc). We would like to thank Dr.C. Kwong (Southern Research Institute, Birmingham, Alabama, USA) for reading the manuscript. The author H.B.Lazrek thanks The Southern Research Institute (Birmingham, Alabama, USA) for logistic support and would like to thank all members of the instrumental laboratory for their help (NMR and Mass analysis). The anti-HCV studies were supported by NIAID contract NO1-AI-30046 to GUMC

References

1. Sher, M.; Reinke, H.; Langer, P. *Tetrahedron Lett.* **2007**, *48*, 7923 and references cited therein.
2. Speers, A. E.; Cravatt, B. F. *Chem. Biol*. **2004**, *11*, 535.
3. Diaz, D. D.; Punna, S.; Holzer, P.; McPherson, A. K.; Sharpless, K. B.; Fokin, V. V.; Finn, M. G. *J. Polym. Sci. Part A: Polym. Chem*. **2004**, *42*, 4392.
4. De Clercq, E. *Nat. Rev. Drug Discovery* **2002**, *1*, 13.
5. Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; De Clero, E.; Perno, C-F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185.
6. (a) Amblard, F.; Cho, J. H.; Shinazi, R. F. *Chem. Rev*. **2009**, *109*, 4207. (b) Pradere, U.; Roy, V.; McBrayer, R. T.; Schinazi, R. F.; Agrofoglio, L. A. *Tetrahedron* **2009**, *64*, 9044-9051 and references cited therein. (c) ElAkri, K.; Bougrin, K.; Balzarini, J.; Faraj, A.; Benhida, R. *Bioorg. Med. Chem. Lett.* 2007, *17*, 6656 and references cited therein.
7. Seela, F.; Pujari, S. S.; Schafer, A. H. *Tetrahedron* 2011,doi:10.1016/j.tet.**2011**.07.015.
8. (a) Kabbaj, Y.; Lazrek, H. B.; Barascut, J. L.; Imbach, J. L. *Nucleosides Nucleotides & Nucleic Acids* **2005**, *24*, 161. (b) Redwane, N.; Lazrek, H. B.; Barascut, J. L.; Imbach, J. L.; Balzarini, J.; Witvrouw, M.; De Clerq, E. *Nucleosides Nucleotides & Nucleic Acids* **2001**, *20*, 1439. (c) Lazrek, H. B.; Rochdi, A.; Khaider, H.; Barascut, J. L.; Imbach, J. L.; Balzarini, J.; Witvrouw, M.; Pannecouque, C.; De Clercq, E. *Tetrahedron* **1998**, *54*, 3807. (d) 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. (e) Moukha-Chafiq, O.; Taha, M. L.; Lazrek, H. B.; Vasseur, J. J.; Pannecouque, C.; Witvrouw, M.; De Clercq, E. *Farmaco* **2002**, *57*, 27. (f) Moukha-Chafiq, O.; Taha, M. L.; Lazrek, H. B.; Vasseur, J. J.; Pannecouque, C.; Witvrouw, M.; De Clercq, E. *Nucleosides Nucleotides & Nucleic Acids* **2001**, *20*, 1811.
9. H. Elayadi, V.; Smietana, M.; Pannecouque, C.; Leyssen, P.; Neyts, J.; Vasseur, J. J.; Lazrek, H. B. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7365.
10. (a) Rostovtev, V. V; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596. (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (c) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *24*, 1128. (d) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004. (e) Rodionov, V. O.; Preolski, S. I.; Gardinier, S.; Lim, Y. L.; Finn, M. G. *J. Am. Chem. Soc.* **2007**, *129*, 12705.
11. Chassaing, S.; Kumarraja, A. S.; Sido, S.; Pale, P.; Sommer, J. *Org. Lett.* **2007**, *9*, 883.
12. Lipshutz, B. H.; Taft, B. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 8235.
13. Candeon, N.; Lastecoueres, D.; Diallo, A. K.; Aranzaes, J. R.; Astruc, D.; Vincent, J. M. *Chem. Commun.* **2008**, 741.
14. Sebti, S.; Zahouily, M.; Lazrek, H. B.; Mayoral, M. J.; Macquarrie, D. J. *Current Organic Chemistry* **2008**, *12*, 203 and references cited therein.

15. (a) Erragh, F.; Boukhari, A.; Abraham, F.; El Ouadi, B. J. *Solid State Chem.* **1995**, *120*, 23. (b) Mahesh, M. S.; Gopalakrishna, G. S.; Ashamanjari, K. G. Materials Science and Engineering A. **2007**, *452–453*, 751. (c) Etheredge, K. M. S.; Hwu, S-J. *Inorg. Chem*. **1995**, *34*, 1495.
16. (a) Stimac, A.; Kobe, J. *Carbohydrate Res.* **2000**, 324, 149. (b) Camarasa, M. J.; Alonso, R.; De Las Heras, F. G. *Carbohydrate Res.* **1980**, *83*, 152
17. (a) Lee, L. V.; Mitchell, L.; Huang, S. J.; Fokin, V. V.; Sharpless, K. B.; Wong, C. H. *J. Am. Chem. Soc.* **2003**, 125, 9588. (b) Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, **6**, 3897.
18. Krim, J.; Sillahi, B.; Taourirte, M.; Rakib, E. M.; Engels. J. W. *ARKIVOC* **2009**, *(xii)*, 142. (b) Wu, L-Y.; Xie, Y-X.; Chen, Z-S.; Niu, Y-N.; Liang, Y-M. *Syntlett* **2009**, *9*, 1453.
19. (a) Trakossas, S.; Contouli-Argyropoulon, E.; Hadjipavlou-litina, D. *Tetrahedron Lett.* **2011**, *52*, 1673. (b) Chittepu, P. Sirivolu, V. R.; Seela, F. *Bioorg. Med. Chem*. **2008**, *64*, 8427. (c) Kosiava, I.; Kovackova, S.; Kois, P. *Tetrahedron* 2007, *63*, 312.
20. (a) Astruc, D.; Liang, L. Coord. *Chem. Reviews* **2011**, *255*, 2933. (b) Namitharan, K.; Kumarraja, M.; Pitchumani, K. *Chem. Eur. J.* **2009**, *15*, 2755. (c) Bock, V. D.; Hiemstra, H.; Van Maarseveen, J. H. Eur. *J. Org. Chem.* **2006**, 51. (d) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210.
21. Korba, B. E.; Montero, A. B.; Farrar, K.; Gaye, K.; Mukerjee, S.; Ayers, M.; Rossignol, J. F. *Antivir. Res.* **2008**, *77*, 56.

