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Original article

Synthesis of new C5-(1-substituted-1,2,3-triazol-4 or 5-yl)-2′-deoxyuridines and their antiviral evaluation

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ABSTRACT

The synthesis and antiviral evaluation of a series of C5-(1,4- and 1,5-disubstituted-1,2,3-triazolo)-nucleoside derivatives is described. The key steps of this synthesis are regioselective Huisgen's 1,3-dipolar cycloaddition, using either copper-catalyzed azide-alkyne cycloaddition (CuAAC) or ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) under microwave activation. Some compounds among the **5a**–**l** series possess activity against herpes simplex viruses 1 and 2, varicella-zoster virus, human cytomegalovirus and vaccinia virus. Their cytostatic activities were determined against murine leukemia cells, human T-lymphocyte cells and cervix carcinoma cells. Compounds were also evaluated on a wide panel of RNA viruses, including Vesicular stomatitis virus, influenza viruses type A (H1N1 and H3N2) and B in MDCK cell cultures, parainfluenza-3 virus, reovirus-1, Sindbis virus and Punta Toro virus in Vero cell cultures and Vesicular stomatitis, Coxsackie B4 and respiratory syncytial virus, with no specific antiviral effect.

1. Introduction

C5-substituted pyrimidine nucleosides have taken up an important role in the therapy of virus infection and cancer [1]. For instance, significant progress in the study of anti-herpes nucleosides has been made by the advent of 5-substituted pyrimidine nucleosides such as 5-iodo-, 5-(2-chloroethyl)-, and (*E*)-5-(2-bromovinyl)- derivatives of 2′-deoxyuridine.

In recent years, our group reported [2] and patented [3] a series of C5-monohalogenated ethynyl or dihalogenated vinyl-modified nucleosides as antiviral drugs against *flaviviridae* viruses, and especially HCV, meanwhile some 5-*iso*xazol-5-yl were recently developed by Kim's group [4] (Fig. 1). Nearly at the same time, we became interested in [3 + 2] cycloaddition reaction pioneered by Huisgen [5] between acetylenes and azides. The copper-catalyzed (CuAAC) [6] or ruthenium-catalyzed (RuAAC) [7] Huisgen azide-alkyne cycloadditions, recently reviewed by Amblard et al. [8] allowed us to synthesize several base- or sugar-modified nucleosides [9]. These catalyzed reactions are highly specific, irreversible and chemo-selective and offer complete regioselectivity. Thus, based on these aforementioned C5-substituted nucleoside derivatives and their antiviral activity, we designed and synthesized some C5-triazolo-2′-deoxyuridines (Fig. 2) starting from our previously described C5-ethynyl-2′-deoxyuridine through either a CuAAC and RuAAC reaction [10] with various substituted phenyl azides generated *in situ*.

The influence of the substituted at the phenyl group and the effect of the regioselectivity (1,4 and 1,5) on the antiviral data will be discussed. Among all synthesized compounds (**5a**–**l** and **7b**, **d**, **h**, **l**), **5a** was already described [11] to study the effect of a stacking triazole and aromatic groups in the major grooves of nucleic acid duplex stability, but not for its antiviral properties.

2. Results and discussion

2.1. Chemistry

To introduce the 1,2,3-triazol scaffold, we decided that the Huisgen reaction would be carried out from C5-ethynyl-2′-deoxyuridine [2a] and a variety of substituted phenyl azides (chosen from polar to apolar and bulky substituents). Thus, treatment of known

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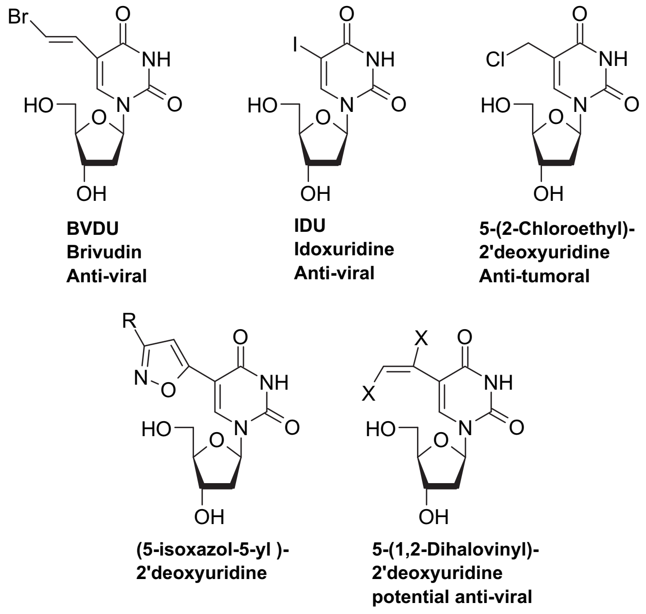


Fig. 1. Antiviral or anticancer C5-substituted nucleosides.

acetylated 2′-deoxyuridine (**1**) with elemental iodine and ceric ammonium nitrate (CAN) at 80 °C gave the corresponding protected 5-iodouracil nucleoside **2**. After reaction, under Sonogashira conditions, of **2** with trimethylsilylacetylene (TMS) in the presence of Et_3N, CuI and $PdCl_2(PPh_3)_2$ in anhydrous DMF at room temperature (**3a**), and following removal of the trimethylsilyl group with n-Bu_4NF, the corresponding protected 5-ethynyl-2′-deoxyuridine (**3b**) was obtained in good yields (Scheme 1).

Since all aromatic azides are not commercially available, we decided to convert commercial substituted anilines into their corresponding azides, which were directly engaged into the CuAAC reaction following a procedure reported in 2007 by Barral et al. [12] Thus azidation is achieved by treatment of substituted aniline with *tert*-butyl-*O*-nitrite and an equimolar quantity of azido-trimethylsilane in acetonitrile, respectively (Scheme 2).

Without any purification, the freshly synthesized substituted phenyl azides were directly reacted with alkynyl nucleoside **3b** in the presence of copper sulfate and ascorbic acid sodium salt. Triazolo-appended nucleosides **4a–l** were obtained in moderate to good yields (from 60 to 92%). No traces of 1,5-regioisomer were observed. After deacylation ($MeOH/NH_3$), compounds **5a–l** were evaluated against various viral strains. It appears that compounds **5b**, **5e**, **5h** and **5l** exhibited interesting biological activities against DANN viruses, respectively, (see Table 1 hereafter).

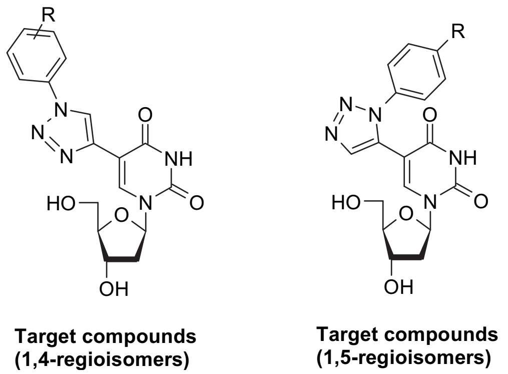
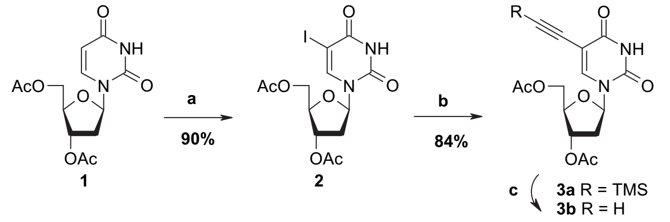


Fig. 2. C5-(1,2,3)-triazoles-2′-deoxyuridines obtained.



Scheme 1. Synthesis of acetylated **3b**. Reagents and conditions: (a) I_2, CAN, CH_3CN, reflux; (b) TMS-acetylene, CuI, $PdCl_2(PPh_3)_2$, DMF, Et_3N; (c) n-Bu_4NF, CH_3CN.

Therefore we decided to study the regioisomeric 1,5 or 1,4 influences on biological activity of the some active **5b**, **5h**, **5l** and inactive **5d** 1,4-regioisomers. We have previously investigated the optimal conditions [9d] for microwaves-assisted [13] RuAAC synthesis of 1,5-disubstituted-1,2,3-triazolo-nucleosides (Scheme 3). Thus, the protected C5-ethynyl-uridine (**3b**) was reacted with freshly synthesized aromatic azides [12], 5 mol% $Cp^*RuCl(PPh_3)_2$ catalyst (**8**) in THF at 100 °C, during 5 min under microwave irradiation. The corresponding nucleosides **6b**, **6d**, **6h** and **6l** were obtained in good yields (70–80%), respectively. A purification by column chromatography, on silica gel was necessary to remove the small amount of 1,4-regioisomers formed (4–5%) as observed by TLC. The final deacylation by ammoniac in methanol during 5 h at 0 °C gave the corresponding nucleosides **7b**, **7d**, **7h** and **7l** in good yields, respectively.

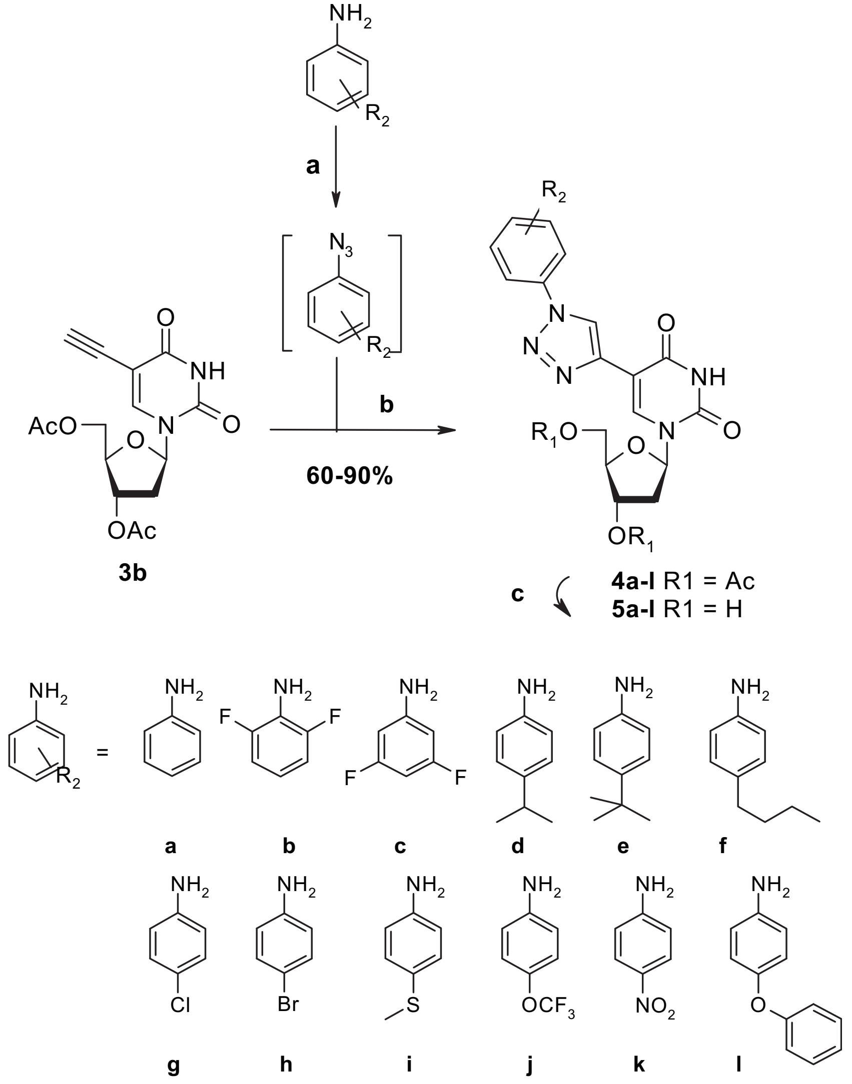
2.2. *Antiviral activity*

Compounds **5a–l** and **7b**, **7d**, **7h**, and **7l** were evaluated against a wide variety of viruses, to determine their antiviral activity, as the effective concentration required to reduce virus-induced cytopathicity by 50% (EC_{50}). Data for vaccinia virus (VV), herpes simplex virus-1(KOS) (HSV-1), HSV-1(TK^-), HSV-2(G), varicella-zoster virus (VZV TK^+ and TK^-), human cytomegalovirus (AD-169 and Davis strains) in HEL cell cultures are summarized in Table 1.

Several of the synthesized compounds showed activities against several DNA viruses. Especially, the EC_{50} against VZV was 3.1 μM for **5b**, 2.6 μM for **5h** and 1.4 μM for **5l**. None of compounds **5a–l** displayed a specific antiviral effect against a wide panel of other viral strains including Vesicular stomatitis virus, influenza viruses type A (H1N1 and H3N2) and B in MDCK cell cultures, parainfluenza-3 virus, reovirus-1, Sindbis virus and Punta Toro virus in Vero cell cultures and Vesicular stomatitis, Coxsackie B4 and respiratory syncytial virus in HeLa cell cultures and HIV-1(III_B) or HIV-2(ROD) in CEM cell cultures (data not shown). However, the active compounds are also endowed with a pronounced cytostatic activity. The compounds' active against DNA virus replication is also quite cytostatic. Therefore, it is currently unclear whether the activity observed for these compounds is due to a specific antiviral effect or to an a-specific cellular toxic activity. It is interesting to quote that the (1,5)-regioisomers, **7b**, **7d**, **7h**, **7l** were found inactive against this wide panel of viruses and not toxic.

2.3. *Cytostatic activity*

The *in vitro* inhibitory effects of **5a–l** on the proliferation of murine leukemia cells (L1210), human T-lymphocyte cells (CEM) and cervix carcinoma cells (HeLa) are reported in Table 2. Several compounds showed a cytostatic activity with an $IC_{50} \sim \leq 1$ μM (**5b**, **5h** and **5l**) or an IC_{50} between 1 and 10 μM (**5d–g**). The 4-phenoxyphenyl triazolyl derivative **5l** exhibits a pronounced cytostatic activity with all IC_{50} values <1 μM ($IC_{50} = 0.5$ μM for L1210, $IC_{50} = 0.8$ μM for CEM, $IC_{50} = 0.28$ μM for HeLa), whereas the



Scheme 2. CuAAC synthesis of triazoles **5a**–**l**. Reagents and conditions: (a) *t*-BuONO, TMSN$_3$, CH$_3$CN; (b) CuSO$_4$, sodium ascorbate, *t*BuOH/H$_2$O; (c) NH$_3$, MeOH.

regioisomer **7l** displays no cytostatic activity. Compound **5l** has a comparable antiproliferative activity as 5-fluorouracil (5-FU) against L1210 and HeLa cells. It is superior to 5-FU against CEM cells.

3. Conclusion

A set of C5-(1,4- and 1,5-disubstituted-1,2,3-triazolo) nucleoside derivatives were designed and synthesized through a regioselective CuAAC or RuAAC, as potential antiviral agents. Both series were low molecular weight compounds with leadlike properties suitable for a medicinal chemistry optimization program. They have been evaluated against several DNA viruses and their cytostatic activities were determined against murine leukemia cells, human T-lymphocyte cells and cervix carcinoma cells. Some cellular activity was observed, which most likely implies that the compounds are able to penetrate into cells. Several of the synthesized compounds showed activities against several DNA viruses in the micromolar range. Whereas the 1,4-regioisomers exhibited antiviral activity, it is interesting to quote that the (1,5)-regioisomers, were found inactive against this wide panel of viruses and display no toxicity. In order to design compounds with a significantly increased potency, it will be necessary to study their phosphorylation by human and viral kinases; this process would be greatly aided by a co-crystal structure of the best compounds bound in the enzyme active sites. Also, it will be of interest to investigate the properties of their monophosphorylated derivatives against thymidylate synthase and their triphosphorylated derivatives against the viral and cellular DNA polymerases to reveal the mechanism of biological action.

4. Experimental

4.1. Chemistry

Commercially available chemicals were of reagent grade and used as received. Acetonitrile was distilled from CaH$_2$. The reactions were monitored by thin layer chromatography (TLC) analysis using silica gel plates (Kieselgel 60F$_{254}$, E. Merck). Column chromatography was performed on Silica Gel 60M (0.040–0.063 mm, E. Merck). Melting points are uncorrected and were measured on a Kofler apparatus. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova$_{\text{Unity}}$ 400 spectrometer (400 MHz) in (d_4) methanol, CDCl$_3$ and DMSO, shift values in parts per million relative to SiMe$_4$ as internal reference. High Resolution Mass spectra were performed by the Mass Spectrometry Center of Blaise Pascal University (Program Masslynx 4.0) (Aubière, France). The purity was determined by HRMS, ^{1}H, ^{13}C and a semi-preparative HPLC (Hypersil

Table 1
Antiviral and cytotoxic activity of compounds **5a**–**l** and **7b**, **d**, **h**, **l** against vaccinia (VV), herpes simplex virus-1(KOS) (HSV-1), varicella-zoster virus (VZV TK$^+$ and TK$^-$), human cytomegalovirus (AD-169 strain and Davis strain) in HEL cells.

Compound	Antiviral activity EC$_{50}$ (μM)[a]								Cytotoxicity (μM)	
	HSV-1 (KOS)	HSV-1 (TK$^-$ KOS ACV^R)	HSV-2 (G)	VZV		HCMV		VV	(MCC)[b]	(CC$_{50}$)[c]
				(TK$^+$) OKA	(TK$^-$) 07-1	AD-169 strain	Davis strain			
5a	>50	>50	>50	>270	>270	>270	>270	>50	270	270
5b	36	31	≥50	3.1	6.1	29	18	38	≥10	1.5
5c	>220	>220	>220	>50	>50	>50	>50	>220	220	36
5d	>10	>10	>10	20	97	240	185	>10	>240	7.4
5e	>50	>50	>50	7.7	35	>50	>50	37	230	12.4
5f	>50	>50	>50	>50	>50	>50	>50	>50	230	147
5g	>240	>240	>240	41	48	>240	>131	>240	>240	7.4
5h	132	132	≥100	2.6	14	45	25	31	≥44	1.0
5i	>50	>50	>50	27	>50	>50	>50	>50	>230	27
5j	>50	>50	>50	>50	>50	>220	>220	>50	>220	47
5k	>50	>50	>50	>50	>50	>50	>50	>50	240	136
5l	31	8.6	≥43	1.4	5.7	19.4	16.4	4.3	130	0.45
7b	>100	>100	>100	–	–	–	–	>100	>100	–
7d	>100	>100	>100	–	–	–	–	>100	>100	–
7h	>100	>100	>100	–	–	–	–	>100	>100	–
7l	>100	>100	>100	–	–	–	–	>100	>100	–
Brivudin	0.02	6.0	180	0.003	54.4	–	–	2.0	>250	>250
Cidofovir	0.8	0.8	1.4	–	–	0.3	0.4	6.0	>250	>250
Acyclovir	0.4	10	0.2	1.0	16.5	–	–	>250	>50	>130
Ganciclovir	0.01	0.1	0.04	–	–	–	–	>100	>250	>250
Ribavirin	>250	>250	>250	–	–	>100	>100	>250	>250	>250

[a] Effective concentration required to reduce virus-induced cytopathicity by 50%.

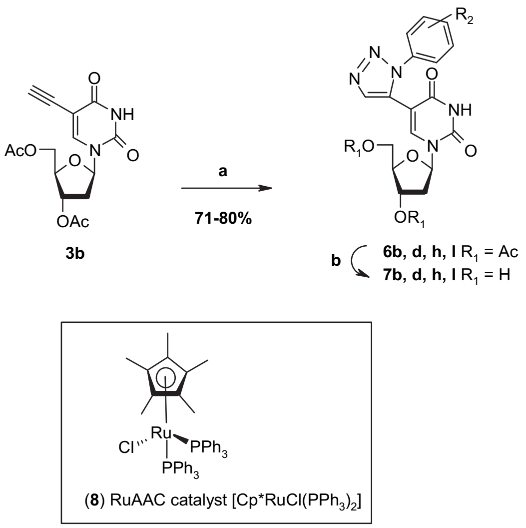
[b] Minimum cytotoxic concentration that causes a microscopically detectable alteration of cell morphology.

[c] Cytotoxic concentration required to reduce cell growth by 50%.

100; C-18; 5 μm); with an appropriate gradient of acetonitrile:H_2O and was found >98%.

4.1.1. *3′,5′-Di-O-acetyl-5-iodo-2′-deoxyuridine (**2**)*

A solution of acetylated 2′-deoxyuridine (**1**) (15 mmol) in dry CH_3CN (150 mL), CAN (4.94 g, 0.6 eq) and I_2 (2.28 g, 0.6 eq) was refluxed until completion (typically 1 h, checked by TLC). After cooling to room temperature, solvents were evaporated under reduced pressure and the dark oily residue was dissolved in AcOEt (300 mL) and H_2O (50 mL). The biphasic mixture was cooled in an ice bath and a saturated $Na_2S_2O_3$ solution was smoothly added until complete decolouration. The organic layer was washed with water (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The white foam was triturated with pentane (50 mL), filtrated and dried under reduced pressure to afford pure iodinated **2**. The physico-chemical data of **2** are in accordance to those previously published.



Scheme 3. RuAAC synthesis of triazoles **7b**, **7d**, **7h** and **7l**. Reagents and conditions: (a) R-N_3, [Ru] Catalyst, CH_2Cl_2, MW; (b) NH_3, MeOH.

4.1.2. *3′,5′-Di-O-acetyl-5-trimethylsilylethynyl-2′-deoxyuridine (**3a**)*

Iodinated nucleoside **2** (5 mmol) was dissolved in a mixture of dry DMF (15 mL), dry Et_3N (2.06 mL, 3 eq) and trimethylsilylacetylene (2.06 mL, 3 eq). CuI (190 mg, 0.2 eq) and $PdCl_2(PPh_3)_2$ (350 mg, 0.1 eq) were then added and the reaction mixture was stirred at room temperature until completion (typically 5–20 h, checked by TLC). Solvents were evaporated under reduced pressure. The oily residue was dissolved in AcOEt (250 mL) then washed with water (5 × 40 mL) and brine (40 mL). The organic layer was dried over $MgSO_4$ and the solvents were evaporated under reduced pressure to dark oil. A purification using a short path flash

Table 2
Cytostatic activity of compounds **5a**–**5l** and **7b**, **d**, **h**, **l** against murine leukemia cells (L1210), human T-lymphocyte cells (CEM) and human cervix carcinoma cells (HeLa).

Compound	Cytostatic activity [IC$_{50}$ (μM)[a]]		
	L1210	CEM	HeLa
5a	204 ± 0	75 ± 8	56 ± 0
5b	2.9 ± 0.5	1.5 ± 0.5	0.51 ± 0.09
5c	nd	nd	nd
5d	29 ± 7	22 ± 0.2	6.2 ± 0.7
5e	15 ± 11	11 ± 5	9 ± 0
5f	15 ± 1	60 ± 49	23 ± 21
5g	14.8 ± 0.2	13 ± 4	4 ± 3
5h	4.6 ± 0.6	1.8 ± 0.2	1.37 ± 0.02
5i	62 ± 0	50 ± 0	23 ± 10
5j	50 ± 0	35 ± 4	37 ± 2
5k	>100	>100	>100
5l	0.5 ± 0.4	0.8 ± 0.3	0.28 ± 0.02
7b	10 ± 2	12 ± 1	5 ± 3
7d	>200	>200	>200
7h	61 ± 5	47 ± 2	8 ± 4
7l	134 ± 6	107 ± 70	42 ± 6
5-FU[b]	0.56 ± 0.31	14 ± 2	0.57 ± 0.23

[a] 50% Inhibitory concentration, or compound concentration required to inhibit tumor cell proliferation by 50%.

[b] 5-fluorouracil as reference compound.

chromatography (eluent: hexanes/AcOEt 7/3 then 1/1) afforded the desired compound **3a**. The physico-chemical data of **3a** are in accordance to those previously published [2a].

*4.1.3. 3′,5′-Di-O-acetyl-5-ethynyl-2′-deoxyuridine (**3b**)*

Compound **3a** (2 mmol) was dissolved in dry CH_3CN (20 mL). TBAF monohydrate (583 mg, 1.05 eq) was added and the resulting solution was stirred at room temperature until completion (typically 30 min to 2 h, checked by TLC). Solvents were evaporated under reduced pressure at room temperature and the oily residue was submitted to a flash column chromatography (eluent: hexanes/AcOEt 1/1 then AcOEt then MeOH/AcOEt 98/2) to afford pure 5-ethynyl nucleoside **3b** as white solid in 74% yield. mp = 183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H, NH), 7.93 (s, 1H, H_6), 6.30 (t, J = 7.1 Hz, 1H, $H_{1'}$), 5.25 (m, 1H, $H_{3'}$), 4.30–4.45 (m, 3H, $H_{4'}$ and $H_{5'}$), 3.21 (s, 1H, CH alkyne), 2.55 (m, 1H, $H_{2'a}$), 2.25 (m, 1H, $H_{2'b}$), 2.07 (s, 3H, OAc), 2.05 (s, 3H, OAc); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.5, 170.3, 161.1, 149.2, 142.9, 99.8, 85.7, 82.4, 74.6, 74.0, 63.9, 38.5, 21.0, 20.9. HRMS ($M^{+}H$) found 336.3048 calculated for $C_{15}H_{17}N_2O_7$ 336.3052.

*4.1.4. General procedure to compounds **4a–l***

Aniline derivative (1 eq) was dissolved, in anhydrous acetonitrile (4 mL by mmol of aniline derivative) in a round-bottom flask and cooled to 0 °C. To this mixture, *t*-BuONO (1.5 eq) followed by $TMSN_3$ (1.2 eq) was added dropwise and the resulting solution was stirred at room temperature for 2 h. To the crude mixture containing the azido derivative, compound **3b** (1 eq), aqueous solution of $CuSO_4$ (0.05 eq) and sodium ascorbate (0.2 eq) were added and the reaction was stirred overnight at room temperature. After evaporation of all volatiles, the residue was purified on silica gel eluting with (petroleum ether/ethyl acetate, 4/6) to give pure compounds **4a–l**, respectively.

*4.1.4.1. 3′,5′-Di-O-acetyl-5-(1-phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**4a**).* Compound **4a** has been synthesized according to the corresponding procedure as a white solid in 80% yield. mp = 201 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H, NH), 8.61 (s, 1H, $H_{triazol}$), 8.60 (s, 1H, H_6), 7.77–7.66 (m, 2H, H_{arom}), 7.45 (t, J = 7.8 Hz, 2H, H_{arom}), 7.36 (t, J = 7.4 Hz, 1H, H_{arom}), 6.42 (dd, J = 5.7, 8.6 Hz, 1H, $H_{1'}$), 5.33 (dt, J = 1.5, 6.5 Hz, 1H, $H_{3'}$), 4.44 (dd, J = 3.0, 12.3 Hz, 1H, $H_{5'a}$), 4.38 (dd, J = 2.8, 12.3 Hz, 1H, $H_{5'b}$), 4.34 (q, J = 2.7 Hz, 1H, $H_{4'}$), 2.57 (ddd, J = 1.6, 5.7, 14.6 Hz, 1H, $H_{2'a}$), 2.37 (ddd, J = 6.5, 8.6, 14.6 Hz, 1H, $H_{2'b}$), 2.26 (s, 3H, OAc), 2.07 (s, 3H, OAc); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.16, 170.59, 161.26, 149.85, 139.64, 137.15, 135.85, 129.93, 128.94, 120.68, 120.39, 106.97, 85.46, 82.88, 74.79, 64.19, 38.20, 21.25, 21.14. IR (cm^{-1}): 1713.0, 1228.7, 749.3. HRMS ($M^{+}H$) found 456.1538, calcd for $C_{21}H_{22}N_5O_7$ 456.1519.

*4.1.4.2. 3′,5′-Di-O-acetyl-5-(1-[2,6-difluoro]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**4b**).* Compound **4b** has been synthesized according to the corresponding procedure as a white solid with a yield of 67%. mp = 215 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H, NH), 8.70 (s, 1H, $H_{triazol}$), 8.49 (s, 1H, H_6), 7.50 (td, J = 4.3, 8.6 Hz, 1H, H_{arom}), 7.14 (t, J = 8.1 Hz, 2H, H_{arom}), 6.50 (dd, J = 5.6, 8.7 Hz, 1H, $H_{1'}$), 5.33 (dt, J = 1.5, 6.5 Hz, 1H, $H_{3'}$), 4.44 (dd, J = 2.9, 13.0 Hz, 1H, $H_{5'a}$), 4.37 (dd, J = 2.6, 13.0 Hz, 1H, $H_{5'b}$), 4.32 (q, J = 2.3 Hz, 1H, $H_{4'}$), 2.55 (ddd, J = 2.0, 5.6, 14.0 Hz, 1H, $H_{2'a}$), 2.38 (ddd, J = 6.5, 8.7, 14.0 Hz, 1H, $H_{2'b}$), 2.33 (s, 3H, OAc), 2.13 (s, 3H, OAc); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.16, 170.59, 160.92, 155.97, 149.69, 139.05, 135.96, 131.69, 124.99, 112.84, 112.61, 106.81, 85.31, 82.88, 74.79, 64.20, 38.24, 21.21, 21.14; IR (cm^{-1}): 1739.9, 1694.6, 1234.3, 755.7. HRMS ($M^{+}H$) found 492.1334, calcd for $C_{21}H_{20}N_5O_7F_2$ 492.1331.

*4.1.4.3. 3′,5′-Di-O-acetyl-5-(1-[3,5-difluoro]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**4c**).* Compound **4c** has been synthesized according to the corresponding procedure as a white solid with a yield of 71%. mp = 217 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H, NH), 8.72 (s, 1H, $H_{triazol}$), 8.68 (s, 1H, H_6), 7.44 (dd, J = 2.1, 7.2 Hz, 2H, H_{arom}), 6.89 (m, 1H, H_{arom}), 6.48 (dd, J = 5.7, 8.5 Hz, 1H, $H_{1'}$), 5.33 (dt, J = 1.5, 6.4 Hz, 1H, $H_{3'}$), 4.44 (dd, J = 2.8, 12.0 Hz, 1H, $H_{5'a}$), 4.38 (dd, J = 2.4, 12.0 Hz, 1H, $H_{5'b}$), 4.34 (q, J = 2.4 Hz, 1H, $H_{4'}$), 2.57 (ddd, J = 1.5, 6.0, 14.0 Hz, 1H, $H_{2'a}$), 2.37 (ddd, J = 6.4, 8.5, 14.0 Hz, 1H, $H_{2'b}$), 2.32 (s, 3H, OAc), 2.13 (s, 3H, OAc); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.08, 170.60, 160.86, 149.53, 140.17, 136.24, 120.03, 106.46, 104.23, 104.15, 103.93, 85.53, 82.95, 74.74, 64.19, 38.34, 21.24, 21.13. IR (cm^{-1}): 1740.1, 1693.2, 1481.0, 1235.6, 754.6. HRMS ($M^{+}H$) found 492.1313, calcd for $C_{21}H_{20}N_5O_7F_2$ 492.1331.

*4.1.4.4. 3′,5′-Di-O-acetyl-5-(1-[4-iso-propyl]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**4d**).* Compound **4d** has been synthesized according to the corresponding procedure as a white solid with a yield of 89%. mp = 137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H, NH), 8.59 (s, 1H, $H_{triazol}$), 8.57 (s, 1H, H_6), 7.61 (d, J = 8.5 Hz, 2H, H_{arom}), 7.29 (d, J = 8.5 Hz, 2H, H_{arom}), 6.42 (dd, J = 5.7, 8.6 Hz, 1H, $H_{1'}$), 5.26 (dt, J = 1.4, 6.7 Hz, 1H, $H_{3'}$), 4.37 (dd, J = 3.1, 12.3 Hz, 1H, $H_{5'a}$), 4.30 (dd, J = 2.7, 12.3 Hz, 1H, $H_{5'b}$), 4.25 (q, J = 2.3 Hz, 1H, $H_{4'}$), 2.90 (sept, 1H, CH), 2.48 (ddd, J = 1.3, 5.7, 14.5 Hz, 1H, $H_{2'a}$), 2.33 (ddd, J = 6.6, 8.6, 14.5 Hz, 1H, $H_{2'b}$), 2.25 (s, 3H, OAc), 2.06 (s, 3H, OAc), 1.21 (d, J = 6.9 Hz, 6H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.45, 170.57, 161.38, 149.83, 135.71, 134.6, 127.82, 120.69, 107.07, 85.47, 82.94, 74.30, 64.26, 38.15, 33.99, 24.05, 21.22, 21.11; IR (cm^{-1}): 1710.1, 1227.9, 1032.9, 835.8. HRMS ($M^{+}H$) found 498.1994, calcd for $C_{24}H_{28}N_5O_7$ 498.1989.

*4.1.4.5. 3′,5′-Di-O-acetyl-5-(1-[4-tert-butyl]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**4e**).* Compound **4e** has been synthesized according to the corresponding procedure as a white solid with a yield of 90%. mp = 143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H, NH), 8.67 (s, 1H, $H_{triazol}$), 8.64 (s, 1H, H_6), 7.74–7.64 (m, 2H, H_{arom}), 7.57–7.48 (m, 2H, H_{arom}), 6.50 (dd, J = 5.7, 8.7 Hz, 1H, $H_{1'}$), 5.34 (dt, J = 1.3, 6.8 Hz, 1H, $H_{3'}$), 4.37 (dd, J = 3.1, 12.3 Hz, 1H, $H_{5'a}$), 4.30 (dd, J = 2.8, 12.3 Hz, 1H, $H_{5'b}$), 4.25 (q, J = 2.4 Hz, 1H, $H_{4'}$), 2.56 (ddd, J = 1.6, 5.6, 14.5 Hz, 1H, $H_{2'a}$), 2.33 (ddd, J = 6.5, 8.6, 14.5 Hz, 1H, $H_{2'b}$), 2.33 (s, 3H, OAc), 2.14 (s, 3H, OAc), 1.36 (s, 9H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.16, 161.26, 152.23, 149.57, 139.59, 135.88, 134.70, 126.80, 120.37, 107.10, 85.41, 82.86, 74.81, 64.18, 38.07, 34.97, 31.45, 21.25, 21.14; IR (cm^{-1}): 1710.1, 1230.6, 754.2 cm^{-1}. HRMS ($M^{+}H$) found 512.2151, calcd for $C_{25}H_{30}N_5O_7$ 512.2145.

*4.1.4.6. 3′,5′-Di-O-acetyl-5-(1-[4-butyl]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**4f**).* Compound **4f** has been synthesized according to the corresponding procedure as a white solid with a yield of 84%. mp = 140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H, NH), 8.66 (s, 1H, $H_{triazol}$), 8.63 (s, 1H, H_6), 7.66 (d, J = 8.4 Hz, 2H, H_{arom}), 7.31 (d, J = 8.4 Hz, 2H, H_{arom}), 6.49 (dd, J = 5.7, 8.6 Hz, 1H, $H_{1'}$), 5.32 (dt, J = 1.4, 6.7 Hz, 1H, $H_{3'}$), 4.44 (dd, J = 3.1, 12.3 Hz, 1H, $H_{5'a}$), 4.37 (dd, J = 2.8, 12.3 Hz, 1H, $H_{5'b}$), 4.32 (q, J = 2.6 Hz, 1H, $H_{4'}$), 2.66 (t, J = 7.6 Hz, 2H, CH_2), 2.54 (ddd, J = 1.3, 5.5, 14.5 Hz, 1H, $H_{2'a}$), 2.39 (ddd, J = 6.6, 8.6, 14.5 Hz, 1H, $H_{2'b}$), 2.32 (s, 3H, OAc), 2.13 (s, 3H, OAc), 1.62 (dt, J = 7.6, 12.9 Hz, 2H, CH_2), 1.36 (tq, J = 7.3, 14.8 Hz, 2H, CH_2), 0.93 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.15, 170.58, 161.32, 149.93, 144.05, 139.49, 135.72, 134.98, 129.77, 120.61, 120.39, 107.08, 85.41, 82.85, 74.80, 64.18, 38.16, 35.56, 33.63, 22.43, 21.23, 21.12, 14.09. IR (cm^{-1}): 1710.1, 1231.5, 755.0. HRMS ($M^{+}H$) found 512.2144, calcd for $C_{25}H_{30}N_5O_7$ 512.2145.

*4.1.4.7. 3′,5′-Di-O-acetyl-5-(1-[4-chloro]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**4g**).* Compound **4g** has been synthesized according to the corresponding procedure as a white solid with a yield of 60%. mp = 192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H, NH), 8.70

(s, 1H, $H_{triazol}$), 8.66 (s, 1H, H_6), 7.75 (d, *J* = 8.7 Hz, 2H, H_{arom}), 7.48 (d, *J* = 8.7 Hz, 2H, H_{arom}), 6.47 (dd, *J* = 5.7, 8.5 Hz, 1H, $H_{1'}$), 5.33 (dt, *J* = 1.4, 6.9 Hz, 1H, $H_{3'}$), 4.44 (dd, *J* = 3.0, 12.4 Hz, 1H, $H_{5'a}$), 4.40 (dd, *J* = 2.8, 12.4 Hz, 1H, $H_{5'b}$), 4.30 (q, *J* = 2.6 Hz, 1H, $H_{4'}$), 2.50 (ddd, *J* = 1.8, 5.4, 14.5 Hz, 1H, $H_{2'a}$), 2.40 (ddd, *J* = 6.5, 8.6, 14.5 Hz, 1H, $H_{2'b}$), 2.31 (s, 3H, OAc), 2.14 (s, 3H, OAc); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.10, 170.59, 149.85, 135.98, 135.64, 135.64, 134.59, 130.06, 121.74, 85.91, 82.91, 74.79, 64.17, 60.59, 38.23, 21.22, 21.14, 14.39. IR (cm^{-1}): 1715.4, 1232.9, 756.6. HRMS (M^+H) found 490.1131, calcd for $C_{21}H_{21}N_5O_7Cl$ 490.1130.

*4.1.4.8. 3′,5′-Di-O-acetyl-5-(1-[4-bromo]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**4h**).* Compound **4h** has been synthesized according to the corresponding procedure as a white solid with a yield of 62%. mp = 198 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H, NH), 8.67 (s, 1H, $H_{triazol}$), 8.65 (s, 1H, H_6), 7.72–7.62 (m, 4H, H_{arom}), 6.48 (dd, *J* = 5.6, 8.7 Hz, 1H, $H_{1'}$), 5.33 (dt, *J* = 1.5, 6.9 Hz, 1H, $H_{3'}$), 4.44 (dd, *J* = 3.1, 12.3 Hz, 1H, $H_{5'a}$), 4.38 (dd, *J* = 2.8, 12.3 Hz, 1H, $H_{5'b}$), 4.33 (q, *J* = 2.3 Hz, 1H, $H_{4'}$), 2.56 (ddd, *J* = 1.7, 5.6, 14.6 Hz, 1H, $H_{2'a}$), 2.38 (ddd, *J* = 6.5, 8.6, 14.6 Hz, 1H, $H_{2'b}$), 2.32 (s, 3H, OAc), 2.14 (s, 3H, OAc); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.10, 170.59, 160.95, 149.59, 139.93, 135.99, 133.12, 122.60, 122.02, 120.07, 106.73, 85.49, 82.92, 74.78, 64.20, 38.27, 21.26, 21.15; IR (cm^{-1}): 1715.4, 1230.6, 757.8 cm^{-1}. HRMS (M^+H) found 534.0612, calcd for $C_{21}H_{21}N_5O_7{}^{79}Br$ 534.0624.

*4.1.4.9. 3′,5′-Di-O-acetyl-5-(1-[4-thiomethyl]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**4i**).* Compound **4i** has been synthesized according to the corresponding procedure as a white solid with a yield of 67%. mp = 161 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H, $H_{triazol}$), 8.60 (s, 1H, H_6), 8.30 (s, 1H, NH), 7.69 (d, *J* = 8.7 Hz, 2H, H_{arom}), 7.38 (d, *J* = 8.7 Hz, 2H, H_{arom}), 6.48 (dd, *J* = 5.7, 8.7 Hz, 1H, $H_{1'}$), 5.33 (dt, *J* = 1.5, 6.6 Hz, 1H, $H_{3'}$), 4.44 (dd, *J* = 3.0, 12.3 Hz, 1H, $H_{5'a}$), 4.38 (dd, *J* = 2.8, 12.3 Hz, 1H, $H_{5'b}$), 4.35 (q, *J* = 2.7 Hz, 1H, $H_{4'}$), 2.55 (ddd, *J* = 1.6, 5.6, 14.5 Hz, 1H, $H_{2'a}$), 2.54 (s, 3H, SMe), 2.38 (ddd, *J* = 6.5, 8.7, 14.5 Hz, 1H, $H_{2'b}$), 2.33 (s, 3H, OAc), 2.14 (s, 3H, OAc); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.16, 170.65, 160.94, 149.46, 149.29, 139.81, 136.08, 135.45, 122.59, 122.12, 120.31, 106.74, 85.55, 82.98, 74.82, 64.25, 38.33, 21.30, 21.20. IR (cm^{-1}): 1716.6, 1261.6, 1229.9, 757.2. HRMS (M^+H) found 502.1412, calcd for $C_{22}H_{24}N_5O_7S$ 502.1396.

*4.1.4.10. 3′,5′-Di-O-acetyl-5-(1-[4-trifluoromethoxy]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**4j**).* Compound **4j** has been synthesized according to the corresponding procedure as a white solid with a yield of 71%. mp = 200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H, NH), 8.67 (s, 1H, $H_{triazol}$), 8.66 (s, 1H, H_6), 7.84 (d, *J* = 9.0 Hz, 2H, H_{arom}), 7.39 (d, *J* = 8.5 Hz, 2H, H_{arom}), 6.48 (dd, *J* = 5.6, 8.6 Hz, 1H, $H_{1'}$), 5.33 (dt, *J* = 1.5, 6.6 Hz, 1H, $H_{3'}$), 4.44 (dd, *J* = 3.1, 12.3 Hz, 1H, $H_{5'a}$), 4.38 (dd, *J* = 2.7, 12.3 Hz, 1H, $H_{5'b}$), 4.35 (q, *J* = 2.4 Hz, 1H, $H_{4'}$), 2.56 (ddd, *J* = 1.5, 5.6, 14.9 Hz, 1H, $H_{2'a}$), 2.38 (ddd, *J* = 6.5, 8.6, 14.9 Hz, 1H, $H_{2'b}$), 2.32 (s, 3H, OAc), 2.14 (s, 3H, OAc). ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.11, 170.59, 160.89, 149.40, 149.23, 139.75, 136.03, 135.40, 122.53, 122.07, 120.26, 106.69, 85.50, 82.92, 74.76, 64.20, 38.28, 21.15, 21.14. IR (cm^{-1}): 1715.4, 1261.9, 1230.8, 759.1. HRMS (M^+H) found 540.1339, calcd for $C_{22}H_{21}N_5O_8F_3$ 540.1342.

*4.1.4.11. 3′,5′-Di-O-acetyl-5-(1-[4-nitro]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**4k**).* Compound **4k** has been synthesized according to the corresponding procedure as a white solid with a yield of 60%. mp = 212 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H, $H_{triazol}$), 8.70 (s, 1H, H_6), 8.47 (s, 1H, NH), 8.43 (d, *J* = 9.1 Hz, 2H, H_{arom}), 8.03 (d, *J* = 9.1 Hz, 2H, H_{arom}), 6.48 (dd, *J* = 5.6, 8.6 Hz, 1H, $H_{1'}$), 5.34 (dt, *J* = 1.5, 6.6 Hz, 1H, $H_{3'}$), 4.45 (dd, *J* = 3.1, 12.3 Hz, 1H, $H_{5'a}$), 4.40 (dd, *J* = 2.7, 12.3 Hz, 1H, $H_{5'b}$), 4.35 (q, *J* = 2.4 Hz, 1H, $H_{4'}$), 2.58 (ddd, *J* = 1.6, 5.7, 14.2 Hz, 1H, $H_{2'a}$), 2.38 (ddd, *J* = 6.5, 8.6, 14.8 Hz, 1H, $H_{2'b}$), 2.32 (s, 3H, OAc), 2.14 (s, 3H, OAc). ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.09, 170.57, 160.87, 149.38, 149.21, 139.73, 136.01, 135.38, 122.51, 122.05, 120.24, 106.67, 85.48, 82.90, 74.74, 64.18, 38.26, 21.13, 21.12. IR (cm^{-1}): 1708.5, 1526.7, 1342.7, 1227.4, 1024.5, 854.3. HRMS (M^+H) found 501.1385, calcd for $C_{21}H_{21}N_6O_9$ 501.1370.

*4.1.4.12. 3′,5′-Di-O-acetyl-5-(1-[4-phenoxy]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**4l**).* Compound **4l** has been synthesized according to the corresponding procedure as a white solid with a yield of 79%. mp = 191 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H, NH), 8.66 (s, 1H, $H_{triazol}$), 8.62 (s, 1H, H_6), 7.71 (d, *J* = 8.9 Hz, 2H, H_{arom}), 7.38 (t, *J* = 7.9 Hz, 2H, H_{arom}), 7.21–7.01 (m, 5H, H_{arom}), 6.49 (dd, *J* = 5.7, 8.6 Hz, 1H, $H_{1'}$), 5.33 (dt, *J* = 1.5, 6.6 Hz, 1H, $H_{3'}$), 4.44 (dd, *J* = 3.0 Hz, 12.3 Hz, 1H, $H_{5'a}$), 4.38 (dd, *J* = 2.8 Hz, 12.3 Hz, 1H, $H_{5'b}$), 4.33 (q, *J* = 2.3 Hz, 1H, $H_{4'}$), 2.56 (ddd, *J* = 1.2, 5.6, 14.3 Hz, 1H, $H_{2'a}$), 2.39 (ddd, *J* = 6.5, 8.6, 14.9 Hz, 1H, $H_{2'b}$), 2.33 (s, 3H, OAc), 2.13 (s, 3H, OAc). ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.14, 170.59, 161.15, 158.06, 156.56, 149.76, 139.61, 135.81, 132.36, 130.22, 124.32, 122.44, 120.53, 119.58, 119.53, 106.98, 85.43, 82.88, 74.79, 64.19, 38.34, 21.24, 21.13. IR (cm^{-1}): 1717.0, 1260.7, 1230.0, 756.4. HRMS (M^+H) found 548.1799, calcd for $C_{27}H_{26}N_5O_8$ 548.1781.

4.1.5. General procedure to **5a–l**

Compounds **4a–l** were respectively dissolved in a solution of NH_3 in methanol 7N. The mixture was stirred at 0 °C overnight. After evaporation of the solvents, the residual solid was purified on silica gel eluting with ethyl acetate to give compounds **5a–l**, respectively.

*4.1.5.1. 5-(1-Phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**5a**).* Compound **5a** has been synthesized according to the corresponding procedure and obtained to give a white solid with a yield of 99%. mp = 244 °C. ^{1}H NMR (400 MHz, MeOD) δ 8.80 (s, 1H, $H_{triazol}$), 8.75 (s, 1H, H_6), 7.88 (d, *J* = 8.1 Hz, 2H, H_{arom}), 7.64–7.55 (m, 2H, H_{arom}), 7.54–7.46 (m, 1H, H_{arom}), 6.38 (dt, *J* = 6.6, 9.0 Hz, 1H, $H_{1'}$), 4.46 (dt, *J* = 3.3, 5.6 Hz, 1H, $H_{3'}$), 4.00 (q, *J* = 3.6 Hz, 1H, $H_{4'}$), 3.87 (dd, *J* = 3.4, 12.0 Hz, 1H, $H_{5'a}$), 3.79 (dd, *J* = 4.0, 12.0 Hz, 1H, $H_{5'b}$), 2.47–2.27 (m, 2H, $H_{2'}$). ^{13}C NMR (400 MHz, DMSO) δ 171.71, 161.10, 149.68, 140.08, 138.68, 136.81, 136.56, 129.89, 128.64, 120.15, 120.05, 111.42, 104.70, 87.68, 84.86, 70.62, 61.36. IR (cm^{-1}): 3133.7, 1680.6, 1475.4, 1246.3, 1051.8, 759.7. HRMS (M^+H) found 372.1316, calcd for $C_{17}H_{18}N_5O_5$ 372.1308.

*4.1.5.2. 5-(1-[2,6-Difluoro]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**5b**).* Compound **5b** has been synthesized according to the corresponding procedure and obtained to give a white solid with a yield of 92%. mp = 256 °C. ^{1}H NMR (400 MHz, MeOD) δ 8.82 (s, 1H, $H_{triazol}$), 8.61 (s, 1H, H_6), 7.67 (tt, *J* = 6.2, 8.6 Hz, 1H, H_{arom}), 7.32 (t, *J* = 8.4 Hz, 2H, H_{arom}), 6.38 (t, *J* = 6.7 Hz, 1H, $H_{1'}$), 4.48 (dt, *J* = 3.5, 6.8 Hz, 1H, $H_{3'}$), 4.00 (q, *J* = 3.5 Hz, 1H, $H_{4'}$), 3.88 (dd, *J* = 3.4, 11.9 Hz, 1H, $H_{5'a}$), 3.80 (dd, *J* = 4.0, 11.9 Hz, 1H, $H_{5'a}$), 2.44–2.34 (m, 2H, $H_{2'}$). ^{13}C NMR (400 MHz, MeOD) δ 163.36, 157.47, 151.78, 151.57, 141.23, 138.78, 133.81, 126.46, 113.92, 113.72, 106.40, 89.32, 87.23, 72.50, 63.06, 41.75. IR (cm^{-1}): 3328.1, 1693.4, 1087.0, 1045.5, 881.8. HRMS (M^+H) found 408.1125, calcd for $C_{17}H_{16}N_5O_5$ 408.1120.

*4.1.5.3. 5-(1-[3,5-Difluoro]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**5c**).* Compound **5c** has been synthesized according to the corresponding procedure and obtained to give a white solid with a yield of 94%. mp = 258 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.75 (s, 1H, NH), 9.05 (s, 1H, $H_{triazol}$), 8.70 (s, 1H, H_6), 7.87 (dd, *J* = 2.0, 7.9 Hz, 2H, H_{arom}), 7.48–7.37 (m, 1H, H_{arom}), 6.25 (t, *J* = 6.7 Hz, 1H, $H_{1'}$), 5.30 (d, *J* = 4.1 Hz, 1H, $H_{3'}$), 3.88 (q, *J* = 3.1 Hz, 1H, $H_{4'}$), 3.67–3.56 (m, 2H, $H_{5'}$), 2.21 (dd, *J* = 4.7, 6.5, 2H, $H_{2'}$). ^{13}C NMR (400 MHz, MeOD) δ 163.36, 157.47, 151.78, 151.57, 141.23, 138.78, 133.81, 126.46, 113.92, 113.72, 106.40, 89.32, 87.23, 72.50, 63.06, 41.75. IR (cm^{-1}): 3327.5, 1695.6, 1087.8, 1046.4, 880.2. HRMS (M^+H) found 408.1104, calcd for $C_{17}H_{16}N_5O_5F_2$ 408.1120.

*4.1.5.4. 5-(1-[4-i-Propyl]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**5d**).* Compound **5d** has been synthesized according to the corresponding procedure and obtained to give a white solid with a yield of 95%. mp = 183 °C. ^{1}H NMR (400 MHz, MeOD) δ 8.75 (s, 1H, $H_{triazol}$), 8.73 (s, 1H, H_6), 7.77 (d, J = 8.6 Hz, 2H, H_{arom}), 7.47 (d, J = 8.5 Hz, 2H, H_{arom}), 6.37 (t, J = 6.7 Hz, 1H, $H_{1'}$), 4.46 (dt, J = 3.4, 5.9 Hz, 1H, $H_{3'}$), 3.99 (q, J = 3.5 Hz, 1H, $H_{4'}$), 3.87 (dd, J = 3.5, 12.0 Hz, 1H, $H_{5'a}$), 3.78 (dd, J = 4.0, 12.0 Hz, 1H, $H_{5'b}$), 3.00 (sept, J = 3.5 Hz, 1H, H-C1), 2.44–2.27 (m, 2H, $H_{2'}$), 1.31 (d, J = 6.9, 9H, H-C2). ^{13}C NMR (400 MHz, MeOD) δ 163.31, 153.70, 151.66, 141.61, 138.50, 136.03, 128.00, 121.74, 121.27, 106.60, 89.29, 87.16, 72.47, 63.07, 41.71, 35.81, 31.78. IR: 3447.2, 1698.0, 1681.4, 1664.3, 1049.1. HRMS (M^+H) found 414.1779, calcd for $C_{20}H_{24}N_5O_5$ 414.1777.

*4.1.5.5. 5-(1-[4-t-Butyl]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**5e**).* Compound **5e** has been synthesized according to the corresponding procedure and obtained to give a white solid with a yield of 97%. mp = 176 °C. ^{1}H NMR (400 MHz, MeOD) δ 8.73 (s, 1H, $H_{triazol}$), 8.71 (s, 1H, H_6), 7.75 (d, J = 8.8 Hz, 2H, H_{arom}), 7.63 (d, J = 8.8 Hz, 2H, H_{arom}), 6.36 (t, J = 7.0 Hz, 1H, $H_{1'}$), 4.46 (dt, J = 3.4, 6.5 Hz, 1H, $H_{3'}$), 3.99 (q, J = 3.5, 1H, $H_{4'}$), 3.87 (dd, J = 3.4, 12.0 Hz, 2H, $H_{5'a}$), 3.79 (dd, J = 4.0, 12.0 Hz, 2H, $H_{5'b}$), 2.42–2.28 (m, 2H, $H_{2'}$), 1.37 (s, 9H, H-C2). ^{13}C NMR (400 MHz, MeOD) δ 163.31, 153.68, 151.67, 141.63, 138.49, 136.05, 128.00, 121.72, 121.26, 106.60, 89.31, 81.17, 72.49, 63.09, 41.73, 35.81, 31.79, 24.40. IR (cm^{-1}): 3176.4; 1688.0, 1271.9, 755.4. HRMS (M^+N) found 428.1945, calcd for $C_{21}H_{26}N_5O_5$ 428.1934.

*4.1.5.6. 5-(1-[4-Butyl]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**5f**).* Compound **5f** has been synthesized according to the corresponding procedure and obtained to give a white solid with a yield of 93%. mp = 179 °C. ^{1}H NMR (400 MHz, MeOD) δ 8.64 (s, 1H; $H_{triazol}$), 8.63 (s, 1H, H_6), 7.65 (d, J = 8.5 Hz, 2H, H_{arom}), 7.31 (d, J = 8.4 Hz, 2H; H_{arom}), 6.27 (t, J = 6.7 Hz, 1H, $H_{1'}$), 4.36 (m, 1H, $H_{3'}$), 3.89 (q, J = 3.5 Hz, 1H, $H_{4'}$), 3.77 (dd, J = 3.5, 12.0 Hz, 1H, $H_{5'a}$), 3.69 (dd, J = 4.0, 12.0 Hz, 1H, $H_{5'b}$), 2.61 (t, J = 7.7 Hz, 2H, H-C1), 2.25 (dd, J = 7.0, 14.2, 2H, $H_{2'}$), 1.56 (dt, J = 7.7, 15.3 Hz, 2H, H-C3), 1.30 (dd, J = 7.4, 14.9 Hz, 2H, H-C2), 0.87 (t, J = 7.4, 3H, H-C4); ^{13}C NMR (400 MHz, DMSO) δ 161.15, 149.73, 143.16, 139.98, 136.79, 134.52, 129.66, 120.15, 104.81, 87.71, 84.90, 70.67, 61.41, 34.29, 33.00, 21.73, 13.80. IR (cm^{-1}): 3175.7, 1688.9, 1271.4, 755.0. HRMS (M^+H) found 428.1922, calcd for $C_{21}H_{26}N_5O_5$ 428.1934.

*4.1.5.7. 5-(1-[4-Chloro]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**5g**).* Compound **5g** has been synthesized according to the corresponding procedure and obtained to give a white solid with a yield of 97%. mp = 230 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.74 (s, 1H, NH), 8.92 (s, 1H, $H_{triazol}$), 8.67 (s, 1H, H_6), 8.00 (d, J = 8.8 Hz, 2H, H_{arom}), 7.66 (d, J = 8.8 Hz, 2H, H_{arom}), 6.25 (t, J = 6.7 Hz, 1H, $H_{1'}$), 4.30 (m, 1H, $H_{3'}$), 3.87 (q, J = 3.0 Hz, 1H, $H_{4'}$), 3.62 (q, J = 2.7 Hz, 2H, $H_{5'}$), 2.21 (dd, J = 4.8, 6.3 Hz, 2H, $H_{2'}$). ^{13}C NMR (400 MHz, DMSO) δ 161.06, 149.66, 147.61, 140.23, 135.36, 129.81, 124.50, 121.87, 121.24, 120.15, 104.57, 87.68, 84.88, 70.60, 61.34, 27.11. IR (cm^{-1}): 3179.0, 5160.4, 1679.1, 1044.4. HRMS (M^+Na) found 427.6250; calcd for $C_{17}H_{16}N_5O_5ClNa$ 427.6232.

*4.1.5.8. 5-(1-[4-Bromo]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**5h**)*. Compound **5h** has been synthesized according to the corresponding procedure and obtained to give a white solid with a yield of 90%. mp = 228 °C. ^{1}H NMR (400 MHz, MeOD) δ 8.81 (s, 1H, $H_{triazol}$), 8.75 (s, 1H, H_6), 7.87–7.79 (m, 2H, H_{arom}), 7.79–7.72 (m, 2H, H_{arom}), 6.28 (t, J = 6.7 Hz, 1H, $H_{1'}$), 4.31 (m, 1H, $H_{3'}$), 3.94 (q, J = 3.1 Hz, 1H, $H_{4'}$), 3.78 (q, J = 2.9 Hz, 2H, $H_{5'}$), 2.26 (dd, J = 5.0, 6.3 Hz, 2H, $H_{2'}$). ^{13}C NMR (400 MHz, DMSO) δ 161.04, 150.40, 149.66, 142.26, 140.24, 136.91, 135.75, 122.10, 121.23, 120.08, 104.56, 87.68, 84.88, 70.59, 61.33, 41.11, 40.61. IR: 3179.0, 1682.0, 1256.5, 1211.4, 1166.9, 1037.8 cm^{-1}. HRMS (M^+Na) found 472.0250; calcd for $C_{17}H_{16}N_5O_5^{79}BrNa$ 472.0232.

*4.1.5.9. 5-(1-[4-Thiomethyl]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**5i**).* Compound **5i** has been synthesized according to the corresponding procedure and obtained to give a white solid with a yield of 95%. mp = 188 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.84 (s, 1H, $H_{triazol}$), 8.65 (s, 1H, H_6), 7.88 (d, J = 8.7, 2H, H_{arom}), 7.45 (d, J = 8.8, 2H, H_{arom}), 6.24 (t, J = 6.9 Hz, 1H, $H_{1'}$), 5.30 (d, J = 4.1 Hz, 1H, $H_{3'}$), 5.10 (t, J = 4.8 Hz, 1H, $H_{4'}$), 4.34–4.26 (m, 1H, $H_{5'a}$), 3.90 (q, J = 3.4 Hz, 1H, $H_{5'b}$), 2.54 (s, 3H, H_{SCH3}), 2.21 (dd, J = 4.7, 6.7, 2H, $H_{2'}$). ^{13}C NMR (400 MHz, DMSO) δ 161.19, 149.79, 147.94, 140.42, 140.40, 137.07, 135.59, 135.56, 122.69, 122.28, 120.45, 104.69, 87.73, 85.03, 70.75, 61.49. IR: 3341.1, 3192.6, 1652.4, 1387.2 cm^{-1}. HRMS (M^+Na) found 440.0995, calcd for $C_{18}H_{19}N_5O_5SNa$ 440.1005.

*4.1.5.10. 5-(1-[4-Trifluoromethoxy]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**5j**).* Compound **5j** has been synthesized according to the corresponding procedure and obtained to give a white solid with a yield of 96%. mp = 233 °C. ^{1}H NMR (400 MHz, MeOD) δ 8.84 (s, 1H, $H_{triazol}$), 8.77 (s, 1H, H_6), 8.01 (d, J = 9.0 Hz, 2H, H_{arom}), 7.53 (d, J = 8.4 Hz, 2H, H_{arom}), 6.37 (t, J = 6.7 Hz, 1H, $H_{1'}$), 4.47 (dt, J = 2.8, 5.9 Hz, 1H, $H_{3'}$), 4.00 (q, J = 3.5 Hz, 1H, $H_{4'}$), 3.87 (dd, J = 3.4, 12.0 Hz, 2H, $H_{5'a}$), 3.80 (dd, J = 4.0, 12.0 Hz, 2H, $H_{5'b}$), 2.44–2.28 (m, 2H, $H_{2'}$). ^{13}C NMR (400 MHz, DMSO) δ 161.06, 149.66, 147.81, 140.27, 136.94, 135.46, 135.43, 122.56, 122.15, 120.32, 104.56, 87.70, 84.90, 70.62, 61.36, 40.60; IR: 3176.4, 1685.4, 1260.4, 1211.4, 1170.4, 1041.5 cm^{-1}. HRMS (M^+H) found 456.1148, calcd for $C_{18}H_{17}N_5O_6F_3$ 456.1131.

*4.1.5.11. 5-(1-[4-Nitro]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**5k**)*. Compound **5k** has been synthesized according to the corresponding procedure and obtained to give a white solid with a yield of 94%. mp = 204 °C . ^{1}H NMR (400 MHz, MeOD) δ 8.99 (s, 1H, $H_{triazol}$), 8.83 (s, 1H, H_6), 8.48 (d, J = 7.1 Hz, 2H, H_{arom}), 8.20 (d, J = 7.1 Hz, 2H, H_{arom}), 6.38 (t, J = 6.8 Hz, 1H, $H_{1'}$), 4.47 (dt, J = 2.9, 6.0 Hz, 1H, $H_{3'}$), 4.00 (q, J = 3.5 Hz, 1H, $H_{4'}$), 3.87 (dd, J = 3.5, 12.0 Hz, 1H, $H_{5'a}$), 3.80 (dd, J = 3.9, 12.0 Hz, 1H, $H_{5'b}$), 2.37 (m, 2H, $H_{2'}$). ^{13}C NMR (400 MHz, DMSO) δ 161.00, 149.60, 147.75, 140.23, 140.21, 136.38, 135.40, 135.37, 122.50, 122.09, 120.26, 104.50, 87.64, 84.84, 70.56, 61.30. IR: 3323.8, 2972.7, 1088.1, 1047.1, 880.5 cm^{-1}. HRMS (M^+Na) found 439.0978, calcd for $C_{17}H_{16}N_6O_7Na$ 439.0978

*4.1.5.12. 5-(1-[4-Phenoxy]phenyl-1,2,3-triazol-4-yl)-2′-deoxyuridine (**5l**).* Compound **5l** has been synthesized according to the corresponding procedure and obtained to give a white solid with a yield of 94%. mp = 277 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.70 (s, 1H, NH), 8.81 (s, 1H, $H_{triazol}$), 8.66 (s, 1H, H_6), 8.05 (d, J = 9.0 Hz, 2H, H_{arom}), 7.45 (t, J = 2.1 Hz, 2H, H_{arom}), 7.25–7.15 (m, 3H, H_{arom}), 7.10 (d, J = 7.6 Hz, 2H, H_{arom}), 6.25 (t, J = 6.7 Hz, 1H, $H_{1'}$), 5.32 (d, J = 4.0 Hz, 1H, $H_{3'}$), 5.07 (t, J = 4.7 Hz, 1H, $H_{4'}$), 4.34–4.26 (m, 1H, $H_{5'a}$), 3.87 (q, J = 3.6 Hz, 1H, $H_{5'b}$), 2.21 (dd, J = 4.7, 6.6, 2H, $H_{2'}$). ^{13}C NMR (400 MHz, DMSO) δ 161.17, 156.96, 156.03, 149.74, 140.05, 136.81, 132.03, 130.31, 124.21, 122.26, 119.29, 119.23, 104.77, 87.72, 84.91, 70.62, 61.41. IR: 3175.9, 1681.0, 1258.6, 1210.9, 1166.1, 1038.9 cm^{-1}. HRMS (M^+H) found 464.1555, calcd for $C_{23}H_{22}N_5O_6$ 464.1570.

*4.1.6. General procedure to compounds **6***

In a microwave sealed reactor, a mixture of azide (1.5 mmol), nucleoside **3b** (1 mmol) and $Cp^*RuCl(PPh_3)_2$ (0.05 mmol) in THF is irradiated during 5 min at 100 °C (200 W, normal mode). The mixture is then evaporated and purified by silica gel column chromatography (Petroleum Ether/AcOEt 3:7) to give pure product **6**.

*4.1.6.1. 3′,5′-Di-O-acetyl-5-(1-[2,6-difluoro]phenyl-1,2,3-triazol-5-yl)-2′-deoxyuridine (**6b**).* Compound **6b** has been synthesized according to the corresponding procedure as a white solid with a yield of 71%.

mp = 208 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H, NH), 8.65 (s, 1H, $H_{triazol}$), 8.52 (s, 1H, H_6), 7.48 (td, $J = 4.2$, 8.6 Hz, 1H, H_{arom}), 7.12 (t, $J = 8.1$ Hz, 2H, H_{arom}), 6.50 (dd, $J = 5.7$, 8.6 Hz, 1H, $H_{1'}$), 5.25 (dt, $J = 1.5$, 6.5 Hz, 1H, $H_{3'}$), 4.40 (dd, $J = 2.7$, 13.0 Hz, 1H, $H_{5'a}$), 4.36 (dd, $J = 2.7$, 13.0 Hz, 1H, $H_{5'b}$), 4.25 (q, $J = 2.7$ Hz, 1H, $H_{4'}$), 2.48 (ddd, $J = 2.1$, 5.8, 14.0 Hz, 1H, $H_{2'a}$), 2.33 (ddd, $J = 6.5$, 8.6, 14.0 Hz, 1H, $H_{2'b}$), 2.30 (s, 3H, OAc), 2.08 (s, 3H, OAc); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.16, 170.59, 160.92, 155.97, 149.69, 139.05, 135.96, 131.69, 124.99, 113.68, 111.58, 107.49, 84.32, 82.88, 73.72, 63.10, 38.44, 21.66, 21.21; IR: 1741.2, 1700.1, 1245.2, 754.3 cm^{-1}; HRMS ($M^{+}Na$) found 514.1136, calcd for $C_{21}H_{20}N_5O_7F_2Na$ 514.1150.

*4.1.6.2. 3′,5′-Di-O-acetyl-5-(1-[4-iso-propyl]phenyl-1,2,3-triazol-5-yl)-2′-deoxyuridine (**6d**).* Compound **6d** has been synthesized according to the corresponding procedure as a white solid with a yield of 80%. mp = 162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H, NH), 8.57 (s, 1H, $H_{triazol}$), 8.50 (s, 1H, H_6), 7.59 (d, $J = 8.7$ Hz, 2H, H_{arom}), 7.32 (d, $J = 8.7$ Hz, 2H, H_{arom}), 6.49 (dd, $J = 5.5$, 8.6 Hz, 1H, $H_{1'}$), 5.29 (dt, $J = 1.5$, 6.9 Hz, 1H, $H_{3'}$), 4.40 (dd, $J = 3.0$, 12.3 Hz, 1H, $H_{5'a}$), 4.28 (dd, $J = 2.6$, 12.3 Hz, 1H, $H_{5'b}$), 4.28 (q, $J = 2.2$ Hz, 1H, $H_{4'}$), 2.88 (sept, 1H, H-C1), 2.51 (ddd, $J = 1.4$, 5.7, 14.4 Hz, 1H, $H_{2'a}$), 2.30 (ddd, $J = 6.5$, 8.7, 14.5 Hz, 1H, $H_{2'b}$), 2.26 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.19 (d, $J = 6.8$ Hz, 6H, H-C2); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.54, 171.02, 163.52, 150.10, 136.21, 133.99, 127.62, 121.03, 107.90, 85.33, 83.01, 74.87, 64.00, 39.20, 34.01, 24.51, 21.33, 21.13; IR: 1709.6, 1228.9, 1031.3, 842.6 cm^{-1}; HRMS ($M^{+}Na$) found 520.1824, calcd for $C_{24}H_{28}N_5O_7Na$ 520.1808.

*4.1.6.3. 3′,5′-Di-O-acetyl-5-(1-[4-bromo]phenyl-1,2,3-triazol-5-yl)-2′-deoxyuridine (**6h**).* Compound **6h** has been synthesized according to the corresponding procedure as a white solid with a yield of 78%. mp = 206 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H, NH), 8.66 (s, 1H, $H_{triazol}$), 8.62 (s, 1H, H_6), 7.70–7.62 (m, 4H, H_{arom}), 6.45 (dd, $J = 5.5$, 8.9 Hz, 1H, $H_{1'}$), 5.29 (dt, $J = 1.4$, 7.0 Hz, 1H, $H_{3'}$), 4.42 (dd, $J = 3.0$, 12.3 Hz, 1H, $H_{5'a}$), 4.37 (dd, $J = 2.8$, 12.3 Hz, 1H, $H_{5'b}$), 4.34 (q, $J = 2.4$ Hz, 1H, $H_{4'}$), 2.56 (ddd, $J = 1.8$, 5.7, 14.6 Hz, 1H, $H_{2'a}$), 2.37 (ddd, $J = 6.4$, 8.6, 14.7 Hz, 1H, $H_{2'b}$), 2.30 (s, 3H, OAc), 2.15 (s, 3H, OAc); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.46, 170.89, 161.02, 149.77, 139.93, 136.04, 132.88, 122.50, 121.99, 119.67, 107.68, 85.78, 83.02, 74.25, 63.99, 38.25, 21.26, 21.13; IR: 1712.3, 1231.2, 1212.25 758.6 cm^{-1}; HRMS ($M^{+}Na$) found 556.0460, calcd for $C_{21}H_{21}N_5O_7{}^{79}BrNa$ 556.0444.

*4.1.6.4. 3′,5′-Di-O-acetyl-5-(1-[4-phenoxy]phenyl-1H-1,2,3-triazol-5-yl)-2′-deoxyuridine (**6l**).* Compound **6l** has been synthesized according to the corresponding procedure as a white solid with a yield of 72%. mp = 202 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H, NH), 8.61 (s, 1H, $H_{triazol}$), 8.59 (s, 1H, H_6), 7.69 (d, $J = 8.8$ Hz, 2H, H_{arom}), 7.41 (t, $J = 8.8$ Hz, 2H, H_{arom}), 7.25–7.01 (m, 5H, H_{arom} OPh), 6.45 (dd, $J = 5.8$ Hz, 8.6 Hz, 1H, $H_{1'}$), 5.30 (dt, $J = 1.4$ Hz, 6.6 Hz, 1H, $H_{3'}$), 4.48 (dd, $J = 3.1$ Hz, 12.3 Hz, 1H, $H_{5'a}$), 4.39 (dd, $J = 2.9$ Hz, 12.3 Hz, 1H, $H_{5'b}$), 4.27 (q, $J = 2.4$ Hz, 1H, $H_{4'}$), 2.59 (ddd, $J = 1.3$ Hz, 5.7 Hz, 14.3 Hz, 1H, $H_{2'a}$), 2.41 (ddd, $J = 6.5$ Hz, 8.7 Hz, 14.5 Hz, 1H, $H_{2'b}$), 2.36 (s, 3H, OAc), 2.15 (s, 3H, OAc); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.28, 170.59, 162.37, 159.04, 156.65, 150.77, 140.40, 133.97, 132.37, 130.22, 124.99, 123.01, 120.00, 119.47, 119.41, 107.25, 85.98, 83.09, 75.08, 64.27, 38.45, 21.78, 21.36. IR: 1719.0, 1259.8, 1227.0, 759.8 cm^{-1}. HRMS ($M^{+}Na$) found 570.1609, calcd for $C_{27}H_{26}N_5O_8$ 570.1601.

*4.1.7. General procedure to compounds **7***

Compounds **6** were dissolved in a solution of NH_3 in methanol 7N, respectively. The mixture was stirred at 0 °C overnight. After evaporation of the solvents, the residual solid was purified on silica gel, eluting with ethyl acetate to give compound **7**, respectively.

*4.1.7.1. 5-(1-[2,6-Difluoro]phenyl-1H-1,2,3-triazol-5-yl)-2′-deoxyuridine (**7b**).* Compound **7b** has been synthesized according to the corresponding procedure and obtained to give a white solid with a yield of 94%. mp = 265 °C. ^{1}H NMR (400 MHz, d_6-acetone) δ 8.89 (s, 1H, $H_{triazol}$), 8.57 (s, 1H, H_6), 7.66 (tt, $J = 6.4$, 8.5 Hz, 1H, H_{arom}), 7.30 (t, $J = 8.4$ Hz, 2H, H_{arom}), 6.30 (t, $J = 6.5$ Hz, 1H, $H_{1'}$), 4.52 (dt, $J = 3.4$, 7.0 Hz, 1H, $H_{3'}$), 3.97 (q, $J = 3.4$ Hz, 1H, $H_{4'}$), 3.85 (dd, $J = 3.5$, 11.9 Hz, 1H, $H_{5'a}$), 3.77 (dd, $J = 4.2$, 11.9 Hz, 1H, $H_{5'a}$), 2.43–2.30 (m, 2H, $H_{2'}$); ^{13}C NMR (400 MHz, d_6-acetone) δ 163.36, 156.39, 152.03, 151.42, 141.04, 137.54, 133.71, 126.46, 114.65, 113.29, 106.40, 90.00, 87.69, 73.07, 62.86, 42.13; IR: 3330.3, 1702.6, 1087.0, 1047.9, 884.8 cm^{-1}; HRMS ($M^{+}H$) found 408.1116, calcd for $C_{17}H_{16}N_5O_5$ 408.1120.

*4.1.7.2. 5-(1-[4-i-Propyl]phenyl-1,2,3-triazol-5-yl)-2′-deoxyuridine (**7d**).* Compound **7d** has been synthesized according to the corresponding procedure and obtained to give a white solid with a yield of 93%. mp = 201 °C. ^{1}H NMR (400 MHz, d_6-acetone) δ 8.75 (s, 1H, $H_{triazol}$), 8.70 (s, 1H, H_6), 7.68 (d, $J = 8.7$ Hz, 2H, H_{arom}), 7.51 (d, $J = 8.7$ Hz, 2H, H_{arom}), 6.36 (t, $J = 6.5$ Hz, 1H, $H_{1'}$), 4.44 (dt, $J = 3.3$, 5.9 Hz, 1H, $H_{3'}$), 4.00 (q, $J = 3.4$ Hz, 1H, $H_{4'}$), 3.88 (dd, $J = 3.6$, 12.0 Hz, 1H, $H_{5'a}$), 3.76 (dd, $J = 4.0$, 12.0 Hz, 1H, $H_{5'b}$), 2.99 (sept, $J = 3.6$ Hz, 1H, H-C1), 2.47–2.29 (m, 2H, $H_{2'}$), 1.25 (d, $J = 6.5$, 9H, H-C2); ^{13}C NMR (400 MHz, d_6-acetone) δ 163.31, 154.23, 152.00, 140.87, 137.66, 136.24, 128.04, 122.54, 123.58, 106.60, 90.01, 87.96, 73.56, 63.47, 42.26, 36.02, 31.58; IR: 3449.2, 1699.5, 1670.4, 999.2 cm^{-1}; HRMS ($M^{+}Na$) found 436.1595, calcd for $C_{20}H_{24}N_5O_5Na$ 436.1597.

*4.1.7.3. 5-(1-[4-Bromo]phenyl-1,2,3-triazol-5-yl)-2′-deoxyuridine (**7h**)*. Compound **7h** has been synthesized according to the corresponding procedure and obtained to give a white solid with a yield of 91%. mp = 231 °C ^{1}H NMR (400 MHz, d_6-acetone) δ 8.75 (s, 1H, $H_{triazol}$), 8.68 (s, 1H, H_6), 7.80–7.74 (m, 2H, H_{arom}), 7.70–7.65 (m, 2H, H_{arom}), 6.30 (t, $J = 6.6$ Hz, 1H, $H_{1'}$), 4.33 (m, 1H, $H_{3'}$), 3.94 (q, $J = 3.6$ Hz, 1H, $H_{4'}$), 3.82 (q, $J = 3.0$ Hz, 2H, $H_{5'}$), 2.32 (dd, $J = 5.1$, 6.3 Hz, 2H, $H_{2'}$); ^{13}C NMR (400 MHz, d_6-acetone) δ 162.08, 151.45, 150.10, 142.26, 139.21, 137.54, 133.69, 123.00, 120.87, 120.07, 103.76, 86.57, 85.06, 71.24, 61.03, 40.75, 40.33. IR: 3212.0, 1682.0, 1248.7, 1172.6, 1042.2 cm^{-1}. HRMS ($M^{+}Na$) found 472.0250; calcd for $C_{17}H_{16}N_5O_5{}^{79}BrNa$ 472.0232.

*4.1.7.4. 5-(1-[4-Phenoxy]phenyl-1,2,3-triazol-5-yl)-2′-deoxyuridine (**7l**).* Compound **7l** has been synthesized according to the corresponding procedure and obtained to give a white solid with a yield of 90%. mp = 256 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.65 (s, 1H, NH), 8.77 (s, 1H, $H_{triazol}$), 8.62 (s, 1H, H_6), 8.12 (d, $J = 9.1$ Hz, 2H, H_{arom}), 7.38 (t, $J = 2.0$ Hz, 2H, H_{arom}), 7.29–7.17 (m, 3H, H_{arom}), 7.10 (d, $J = 7.7$ Hz, 2H, H_{arom}), 6.29 (t, $J = 6.9$ Hz, 1H, $H_{1'}$), 5.39 (d, $J = 3.8$ Hz, 1H, $H_{3'}$), 5.02 (t, $J = 4.8$ Hz, 1H, $H_{4'}$), 4.37–4.27 (m, 1H, $H_{5'a}$), 3.82 (q, $J = 3.7$ Hz, 1H, $H_{5'b}$), 2.25 (dd, $J = 4.8$, 6.8 Hz, 2H, $H_{2'}$); ^{13}C NMR (400 MHz, DMSO) δ 162.25, 157.24, 155.87, 150.84, 139.22, 135.68, 131.84, 129.36, 123.99, 122.04, 118.78, 118.62, 103.89, 88.04, 85.47, 70.41, 61.38. IR: 3180.9, 1704.3, 1265.9, 1202.3, 1020.7 cm^{-1}. HRMS ($M^{+}Na$) found 486.1372, calcd for $C_{23}H_{22}N_5O_6Na$ 486.1390.

4.2. Biology

4.2.1. Antiviral activity assays

The antiviral assays, other than the anti-HIV assays, were based on inhibition of virus-induced cytopathicity or plaque formation in HEL [herpes simplex virus type 1 (HSV-1) (KOS), HSV-2 (G), vaccinia virus, vesicular stomatitis virus, cytomegalovirus (HCMV), and varicella-zoster virus (VZV)], Vero (parainfluenza-3, reovirus-1, Sindbis virus and Coxsackie B4), HeLa (vesicular stomatitis virus, Coxsackie virus B4, and respiratory syncytial virus) or MDCK [influenza A (H1N1; H3N2) and influenza B] cell cultures. Confluent cell cultures (or nearly confluent for MDCK cells) in microtiter 96-well plates were inoculated with 100 $CCID_{50}$ of virus (1 $CCID_{50}$ being the virus dose to infect 50% of the cell cultures) or with 20 plaque forming units (PFU). After 1–2 h virus adsorption period, residual virus was removed, and the cell cultures were incubated in the presence of varying concentrations (200, 40, μM) of the test compounds. Viral cytopathicity was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds. Antiviral activity was expressed as the EC_{50} or concentration required reducing virus-induced cytopathogenicity or viral plaque (VZV) plaque formation by 50%. The minimal cytotoxic concentration (MCC) of the compounds was defined as the compound concentration that caused a microscopically visible alteration of cell morphology. Alternatively, cytotoxicity of the test compounds was measured based on inhibition of cell growth. HEL cells were seeded at a rate of 5×10^3 cells/well into 96-well microtiter plates and allowed to proliferate for 24 h. Then, medium containing different concentrations of the test compounds was added. After 3 days of incubation at 37 °C, the cell number was determined with a Coulter counter. The cytostatic concentration was calculated as the CC_{50}, or the compound concentration required reducing cell proliferation by 50% relative to the number of cells in the untreated controls. The methodology of the anti-HIV assays was as follows: human CEM ($\sim 3 \times 10^5$ cells/cm^3) cells were infected with 100 $CCID_{50}$ of HIV(III_B) or HIV-2(ROD)/ml and seeded in 200 μL wells of a microtiter plate containing appropriate dilutions of the test compounds. After 4 days of incubation at 37 °C, HIV-induced CEM giant cell formation was examined microscopically.

4.2.2. *Cytostatic/toxic activity assays*

Murine leukemia L1210, human lymphocyte CEM and human cervix carcinoma HeLa cells were cultured in RPMI-1640 medium supplemented with 10% foetal calf serum, 2 mM L-glutamine and 0.075% $NaHCO_3$. No antibodies were added to the culture medium. Cells were seeded in 96-well microtiter plates at 50,000 (L1210), 75,000 (CEM) or 20,000 (HeLa) cells per 200 μL-well in the presence of different concentrations of the test compounds. After 2 (L1210), 3 (CEM) or 4 (HeLa) days, the viable cell number was counted using a Coulter counter apparatus. The 50% cytostatic concentration (CC_{50}) was defined as the compound concentration required to inhibit tumor cell proliferation by 50%.

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