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Graphical Abstract

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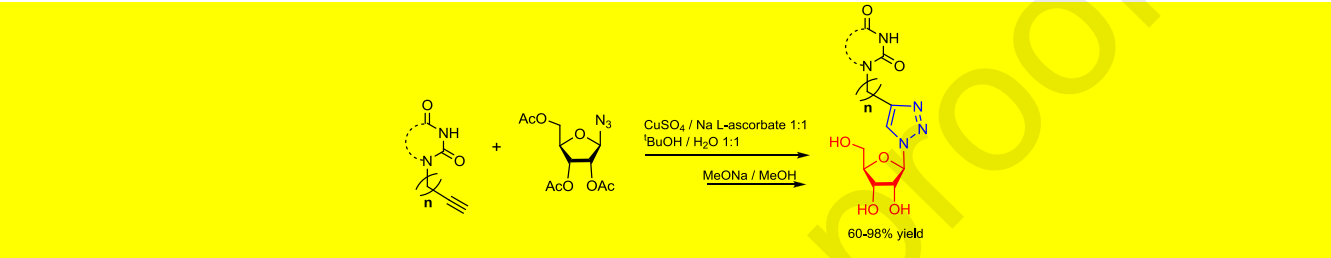

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ABSTRACT

A series of novel 1,2,3-triazolyl nucleoside analogues was synthesized *via* the CuAAC reaction of *N*1-alkynyl uracil, 6-methyluracil, 3,6-dimethyl uracil, thymine and quinazolin-2,4-dione with protected azido β-*D*-ribofuranose. The obtained compounds differ in both the nature of the pyrimidine-2,4-dione fragment and the length of the polymethylene linker connecting it with the β-*D*-ribofuranosyl-1,2,3-triazol-4-yl moiety. The 1,2,3-triazolyl nucleoside analogues were evaluated for their cytotoxicity *in vitro*.

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The hundred-year study of nucleic acids and, as an apotheosis, the discovery of their structure in the 1950s, finally made it possible to understand their fundamental importance for cell viability *in vivo* [1]. Almost immediately, the idea appeared that the nucleoside components of DNA or some of their derivatives or analogues can affect the biochemical processes in the cells of bacteria and viruses. In the early 1960s, the first nucleoside analogues azidothymidine and didanosine which suppressed HIV DNA replication in monocytes and macrophages *in vitro* were synthesized. Over the next 50 years, numerous nucleoside analogues have been created and used to treat human immunodeficiency viruses, hepatitis B and C viruses, herpes simplex virus and cytomegalovirus as well as for the treatment of various types of cancer [2]. Recently, 1,2,3-triazolyl nucleoside analogues have been synthesized [3]. In these compounds the 1,2,3-triazole ring plays not only the role of a passive linker between the nucleic base and the sugar residue; the 1,2,3-triazole moiety readily associate with biological targets due to the formation of hydrogen bonds and dipole interactions [4].

The introduction of click chemistry reactions in medicinal chemistry have drawn attention to 1,2,3-triazole as an attractive bridge group (linker or spacer), which could connect two pharmacophores to produce novel bifunctional molecules and at ~~the same~~ time is resistant to hydrolysis, oxidation or reduction [5a]. Moreover, since the 1,2,3-triazole units are not present in natural products, they are remarkably stable to metabolic transformations and are therefore utilised in various drugs [5b,c]. The first reported synthesis of 1,2,3-triazole nucleoside derivatives [6] using Cu alkyne-azide cycloaddition (CuAAC) was followed by analogous syntheses of modified pyrimidine nucleosides in which the 1,2,3-triazole ring was attached either directly to the C5 position of 2'-deoxyuridine [7a,b] or *via* a methylene unit [7c,d]. Generation of the 1,2,3-triazole moiety at the C5' position of uridine [8a,b] and at the C3' position of several nucleosides [8c,d] *via* CuAAC has been also reported. The synthesized 1,2,3-triazolyl nucleoside analogues showed anticancer [7a,8b,8c], antiviral [7b], antitubercular [7c,d] and antimicrobial [8a,b] activities. In 2012 a series of 1,4-disubstituted-1,2,3-triazolonucleosides was synthesized for the first time *via* CuAAC between 1-deoxy-1-azido-2,3,5-tri-*O*-benzoyl-*D*-ribofuranose and various *N*1-propargyl pyrimidines [9a-c]. None of the new compounds were found to inhibit HCV replication *in vitro* [9a], but 1,2,3-triazolyl analogs **2a-e** (Fig. 1) appeared to be potent competitive inhibitors of RNase A with low μM inhibition constant values [9c]. Recently, evaluation of the bioactivity of 5-substituted uridines **1a-e** and their corresponding 1,2,3-triazolyl analogs **2a-e** (Fig. 1) revealed their ability to inhibit the angiogenic activity of hAng *in vivo* [9d],

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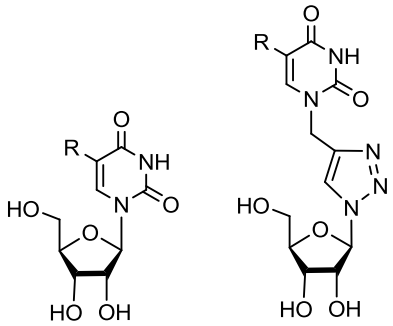
wi h 3-being more potent than the ones without. The strongest inhibitor **2a** in the series of compounds **2a-e** completely inhibited the angiogenic activity of hAng, blocking both the entrance of hAng into the cell and its ribonucleolytic activity [9d]. Analysis of the obtained data [9d] revealed that introduction of the 1,2,3-triazole bridge group between the pyrimidine and ribose moieties substantially enhances the ability of uridine **1a** and its 5-substituted derivatives **1b-e** to inhibit the angiogenic activity of hAng.

Taking into account these findings we decided to study the effect of the distance between the pyrimidine and *D*-ribofuranosyl-1,2,3-triazol-4-yl moieties on the ability to inhibit the angiogenic activity of hAng. Moreover it would be of interest to determine the effect of replacing uracil and thymine in 1,2,3-triazolyl nucleoside analogues **2a,b** with 6-methyluracil, 3,6-dimethyluracil and quinazoline-2,4-dione on the inhibitory ability. Herein, we report the syntheses of novel 1,2,3-triazolyl nucleoside analogues in which the above mentioned uracil derivatives are bonded with the *D*-ribofuranosyl-1,2,3-triazol-4-yl moiety by a polymethylene linker of variable length.



R	Compd	Compd
H	**1a**	**2a**
CH_3	**1b**	**2b**
Br	**1c**	**2c**
Cl	**1d**	**2d**
F	**1e**	**2e**

Figure. 1. 5-Substituted uridines **1a-e** and their 1,2,3-triazolyl analogues **2a-e** which inhibited the angiogenic acivity of hAng *in vivo* [9d].

To obtain the target 1,2,3-triazolyl nucleoside analogues, we used a convergent approach consisting of pyrimidine and carbohydrate routes (Scheme 1). The first route focused on the synthesis of uracil derivatives **3a**,**b**; **4a-c**; **5a,b**; **6a**,**b** bearing ω-alkyne substituents at the *N*1 atom. The conventional method for the alkylation of uracil and its 3-, 5-, 6-methyl derivatives is conversion to a monosodium salt using sodium hydride in DMF, followed by the reaction with alkyl halides [10]. The reaction proceeds non-selectively and affords a mixture of mono- and di-*N*-alkylated products which can be separated by column

halogenoprop-1-ynes in DMF in the presence of K_2CO_3 also proceeds non-selectively [11]. To achieve selectivity in the alkylation, uracil or thymine were first converted to their bis (trimethylsilyl) ethers by treatment with a mixture of hexamethyldisilazane (HMDS) and chlorotrimethylsilane (TMSCl) [12a,b]. Next, the bis (trimethylsilyl) derivatives were alkylated by treatment with an appropriate alkyl halide in DMF or 1,2-dichloroethane [12a,b]. The reactions proceeded selectively with the formation of exclusively *N*1 substituted pyrimidines [12a, b]. We then used this approach to synthesize *N*-1-ω-alkyne uracil derivatives **3a**,**b**; **4b,c**; **5a,b**. However, the reactions of bis silylated derivatives **7** of the starting pyrimidine-2,4-diones **3-5** with propargyl bromide, 5-chloro-1-pentyne, and 6-chloro-1-hexyne afforded the target compounds **3a**,**b**; **4b,c**; **5a,b** in low yields (5-10%). Moreover, the silylation reaction of quinazolin-2,4-dione **6** under conventional conditions [12a,b] (quinazolin-2,4-dione **6**, HMDS, TMSCl, reflux, 20 h) did not lead to the corresponding bis silylated derivative. Therefore, *N*-1-ω-alkyne derivatives of uracil **3a**,**b**; **4b,c**; **5a,b** and quinazolin-2,4-dione **6a**,**b** were synthesized according to the previously described procedure [13]. Firstly, starting compounds **3**–**6** were reacted with an excess of HMDS in toluene in the presence of H_2SO_4 at reflux for 8 hours to afford the required bis silylated derivatives **7** which were then engaged in the alkylation without purification (Scheme 1). For the alkylation of bis silylated uracil derivatives **7**, we used the ω-iodo-α-alkynes prepared from commercially available ω-chloro-α-alkynes *via* the Finkelstein reaction. Alkyne derivatives of uracil **3a**,**b**; **4b,c**; **5a,b** and quinazolin-2,4-dione **6a**,**b** were obtained in 33-71% yield. It should be noted that this procedure was not suitable for the synthesis of propargyl derivative of 6-methyluracil **4a**. The reactions led to mixtures of the regioisomeric products *N*1-(prop-2-yn-1-yl)- and *N*-3-(prop-2-yn-1-yl)-6-methyluracils which could not be separated. Therefore, for the selective *N*1 propargylation of 6-methyluracil **4**, firstly, its monopotassium salt was prepared by reaction of **4** with KOH in water, followed by alkylation with propargyl bromide in toluene at reflux, which afforded the required *N*1 monopropargylated 6-methyluracil **4a** in 34% yield (Scheme 1). Since the preparation of *N*1 alkyne derivatives of 3,6-dimethyluracil **8** did not require any selectivity, the conventional approach [10] was used (Scheme 1). First, the monosodium salt of uracil derivative **8** was obtained by the reaction with sodium hydride in DMF, followed by alkylation with ω-bromo-α-alkynes to afford alkyne derivatives **8a-c** in good yields (72-94%).

The carbohydrate route focused on the synthesis of 2,3,5-tri-*O*-acetyl-β-*D*-ribofuranosyl azide **9c** (Scheme 1). Firstly, commercially available *D*-ribose **9** was converted into methyl *D*-α/β-ribofuranoside [14] which was immediately acetylated [15] to afford a mixture of α- and β-anomers of methyl 2,3,5-tri-*O*-acetyl-*D*-ribofuranoside **9a** which were separated by silica gel flash chromatography. Next, the methoxy group of the β-anomer of sugar **9a** was substituted for an acetoxy group by the treatment of **9a** with glacial AcOH and Ac_2O in the presence of H_2SO_4 [14]. The obtained β-*D*-ribofuranose 1,2,3,5-tetraacetate **9b** was reacted with trimethylsilyl azide ($TMSN_3$) in the presence of tin tetrachloride [16] to afford the protected azido ribofuranose **9c** in 95% yield.

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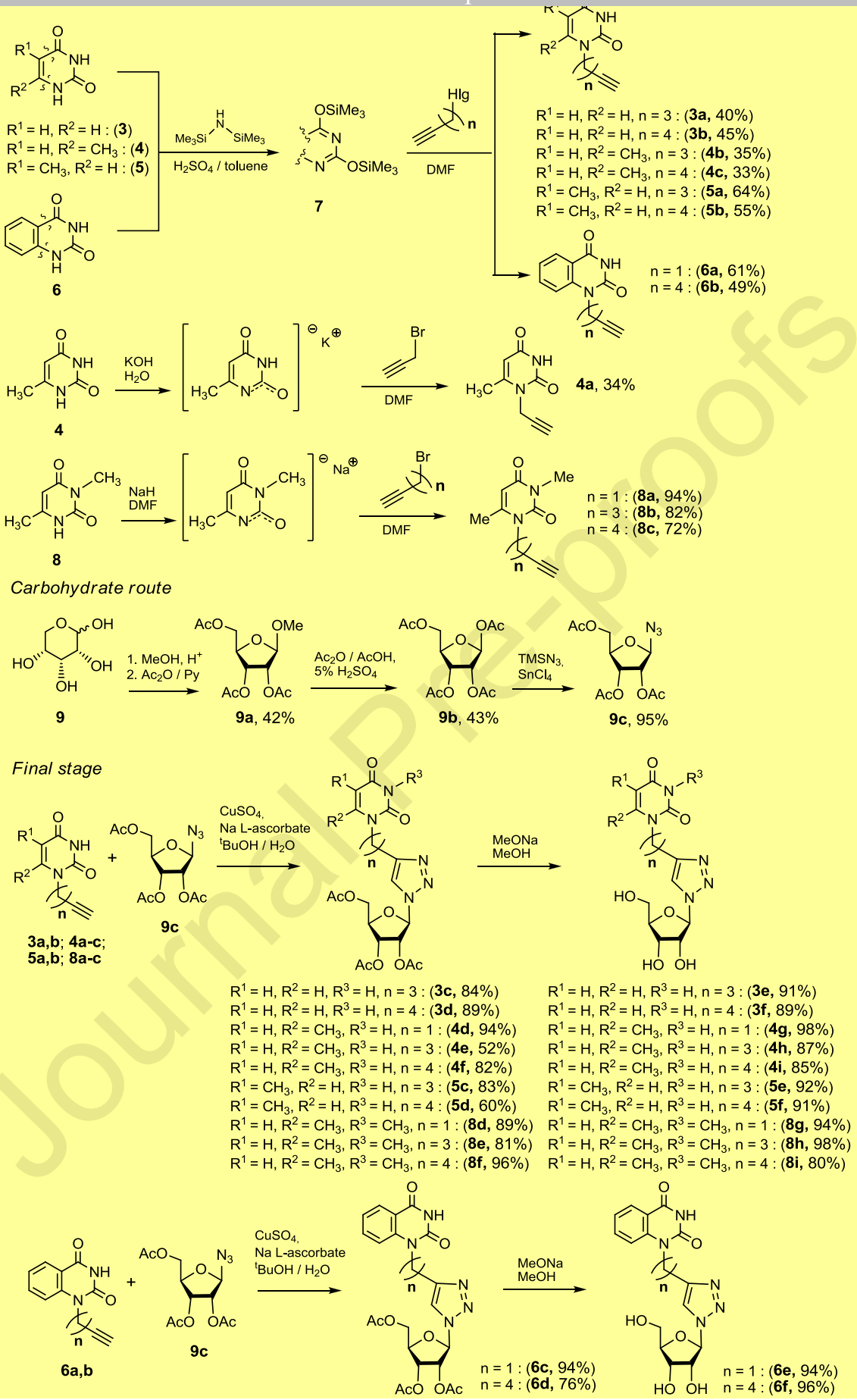

Scheme 1. Convergent synthesis of 1,2,3-triazolyl nucleoside analogues containing uracil, thymine, 6-methyluracil, 3,6-dimethyluracil, and quinazolin-2,4-dione.

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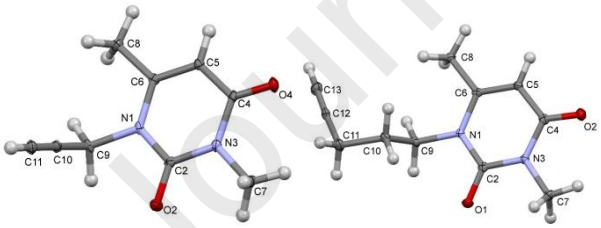
synthesis and couple the protected azido ribofuranose **9c** with *N*1-alkynylated uracil derivatives **3a**,**b**; **4a-c**; **5a**,**b**; **6a**,**b**, and **8a-c** (Scheme 1). The CuAAC reactions were performed in *t*-BuOH / H_2O (1:1) using equimolar amounts of the reactants, $CuSO_4 \cdot 5H_2O$ (10 mol%), and sodium ascorbate (20 mol%). These conditions were found to be optimum in terms of the solvent and the amount of catalyst [5a, 6, 7, 8]. 1,2,3-Triazolyl nucleoside analogues with protected OH groups **3c**,**d**; **4d-f**; **5c**,**d**; **6c**,**d**; **8d-f** were obtained in good yields (84-94%). The formation of the 1,2,3-triazole ring was indicated by the presence in the ^{1}H NMR spectra of **3c**,**d**; **4d-f**; **5c**,**d**; **6c**,**d**; **8d-f** of the signal for the triazolyl proton C5"-H within the range 7.50-7.97 ppm. Triazolyl carbons C4" in the ^{13}C NMR spectra resonated within the range 142.9-147.7 ppm and the signals of triazolyl carbons C5" were observed within the range 120.1-123.5 ppm. These facts were in full accordance with the characteristic features of the ^{1}H and ^{13}C NMR spectra of 1,2,3-triazoles previously described in the literature [7-9, 17]. It is worth noting that all performed CuAAC reactions provided 1,2,3-triazolyl nucleoside analogues **3c**,**d**; **4d-f**; **5c**,**d**; **6c**,**d**; **8d-f** as β-glycosides. Their ^{1}H NMR spectra displayed the anomeric protons of the acetylated *D*-ribofuranose moieties as doublets within the range 5.98-6.13 ppm with vicinal coupling constants within the range 3.5-4.2 Hz. This strongly suggested a β-orientation of the glycosidic bond in compounds **3c**,**d**; **4d-f**; **5c**,**d**; **6c**,**d**; **8d-f** in full accordance with the literature data [16]. Finally, removal of the *O*-acetyl protective groups of **3c**,**d**; **4d-f**; **5c**,**d**; **6c**,**d**; **8d-f** with 0.1N MeONa/MeOH solution furnished the target 1,2,3-triazolyl nucleoside analogues **3e**,**f**; **4g-i**; **5e**,**f**; **6e**,**f**; **8g-i** bearing unprotected OH groups in good yields (89-98%).

All synthesized 1,2,3-triazolyl nucleoside analogues were characterized by NMR spectroscopy, mass spectrometry and elemental analysis (see ESI). Moreover, the structures of 1-alkynyluracils **8a** and **8b**, as well as one of the nucleoside analogues **6c**, were confirmed by single crystal X-ray diffraction analysis. Their structures are shown in Figure 2 and Figure 3. Figure 3 clearly shows that compound **6c** has a β-orientation of the glycosidic bond. The structures of the independent molecules A and B differ significantly. In molecule A the quinazoline ring has a *syn*-orientation relative to the $CH_2OC(O)CH_3$ group at the C4' atom, while in the molecule B the quinazoline ring is oriented in the opposite direction (*anti*-orientation).



8a **8b**

Figure 2. X-ray crystal structures of *N*1-alkynylated uracil derivatives **8a** and **8b**.

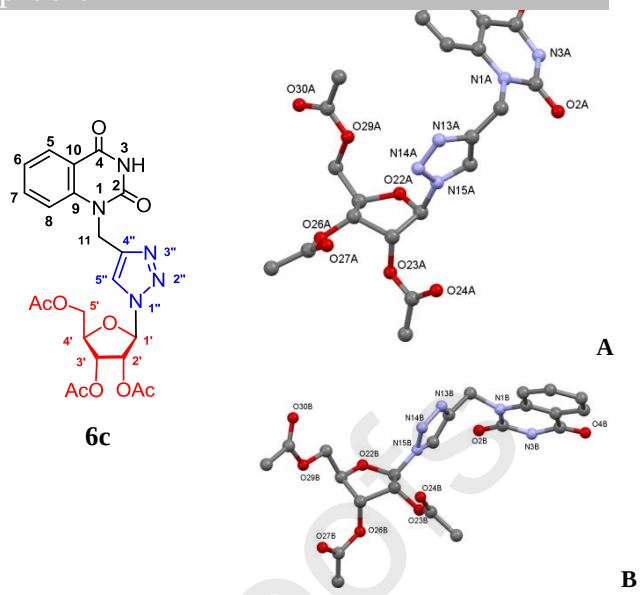


Figure 3. X-ray crystal structure of independent molecules A and B of 1,2,3-triazolyl nucleoside analogue **6c**. Hydrogen atoms are not shown for clarity.

The reason for this is the conformational flexibility of compound **6c** with increasing length of the polymethylene linker between the nucleobase and the 1,2,3-triazolyl ring. Unlike native nucleosides, in 1,2,3-triazolyl analogues **3c-f; 4d-i; 5c-f**; **6c-f; 8d-i** due to the increase in the distance between the nucleobase and the sugar residue, steric and electronic interactions between them are completely eliminated. Such changes in structure may lead to changes in the biological activities. This short communication begins a series of articles devoted to the synthesis and study of the biological activity of 1,2,3-triazolyl nucleoside analogues with a variable linker length between a pyrimidine-2,4-dione and 1,2,3-triazole moieties.

Novel 1,2,3-triazolyl nucleoside analogues **3c-f**, **4d-i**, **5c-f**, **6c-f**, **8d-i** were subjected to *in vitro* evaluation for cytotoxicity toward a normal human cell line (Chang liver) and a diploid human cell strain (WI-38) composed of fibroblasts. All tested compounds were non-cytotoxic in relation to the normal human cell lines used in these experiments. The obtained IC_{50} values were more than 100 μM. Thus, nucleoside analogs **3c-f**, **4d-i**, **5c-f**, **6c-f**, **8d-i** can be considered as a promising scaffold for the creation of new therapeutic agents.

The study of the ability of nucleoside analogues **3c-f**, **4d-i**, **5c-f**, **6c-f**, **8d-i** to inhibit the angiogenic activity of hAng is currently in progress and will be reported in due course.

In summary, a series of novel 1,2,3-triazolyl nucleoside analogues was synthesized *via* the CuAAC reaction of *N*1-alkynyl uracil, 6-methyluracil, 3,6-dimethyl uracil, thymine and quinazolin-2,4-dione with protected azido β-*D*- ribofuranose. The compounds obtained differ in both the nature of the pyrimidine-2,4-dione fragment and the length of the polymethylene linker connecting it to the β-*D*-ribofuranosyl-1,2,3-triazol-4-yl moiety. All novel 1,2,3-triazolyl nucleoside analogues were non-cytotoxic in relation to a normal human cell line (Chang liver) and a diploid human cell strain (WI-38).

Conflict of interests:

The authors declare they have no conflict of interests.

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Acknowledgments

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Conflict of interest

The authors declare they have no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https:// … . These data include the description of syntheses, characterization of compounds, and crystallographic data for the structures in this article.

References

1. Agrofoglio, L. A. *Curr. Org. Chem*. **2006**, *10*, 333-362.
2. Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev*. **2009**, *109*, 4207-4220.
3. (a) Agalave, S. G.; Maujan, S. R.; Pore, V. S. *Chem. Asian. J*. **2011**, *6*, 2696-2718; (b) Ganesh A. *Int. J. Chem. Sci*. **2013**, *11*, 573-578.
4. Kolb, H. C.; Sharpless, K. B. *Drug Discov. Today*. **2003**, *8*, 1128-1137.
5. (a) Tron, G. C., Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A.A. *Med. Res. Rev*. **2008**, *28*, 278-308; (b) Petrova, K. T.; Potewar, T. M.; Correia-da-Silva, P.; Barros, M. T.; Calhelha, R. C.; Ćirik, A.; Soković, M.; Ferreira, I. C. F. R. *Carbohydr. Res*. **2015**, *417*, 66-71; (c) Zhou, C.-H.; Wang, Y. *Curr. Med. Chem*. **2012**, *19*, 239-280.
6. Zhou, L.; Amer, A.; Korn, M.; Burda, R.; Balzarini, J.; De Clercq, E.; Kern, E. R.; Torrence, P. F. *Antiviral Chem. Chemoterapy*. **2005**, *16*, 375-383.
7. (a) Park, S. M.; Yang, H.; Park, S.-K.; Kim. H. M.; Kim, B. H. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 5831-5834; (b) Montagu, A.; Roy, V., Balzarini, J., Snoeck, R.; Andrei, G.; Agrofoglio, L. A. *Eur. J. Med. Chem*. **2011**, *46*, 778-786; (c) Shmalenyuk, E. R.; Chernousova, L. N.; Karpenko, I. L.; Kochetkov, S. N.; Smirnova, T. G.; Andreevskaya, S. N.; Chizhov, A. O.; Efremenkova, O. V.; Alexandrova, L. A. *Bioorg. Med. Chem*. **2013**, *21*, 4874-4884; (d) Alexandrova, L. A.; Efremenkova, O. V.; Andronova, V. L.; Galegov, G. A.; Solyev, P. N.; Karpenko, I. L.; Kochetkov, S. N. *Russ. J. Bioorg. Chem*. **2016**, *42*, 677-684.
8. (a) Chaudhary, P. M.; Chavan, S. R.; Shirazi, F.; Razdan, M.; Nimkar, P., Maybhate, S. P.; Likhite, A. P.; Gonnade, R.; Hazara, B. G.; Deshpande, M. V.; Deshpande, S. R. *Bioorg. Med. Chem*. **2009**, *17*, 2433-2440; (b) Ruddarraju, R. R.; Murugulla, A. C.; Kotla, R.; Tirumalasetty, M. C. B.; Wudayagiri, R.; Donthabakthuni, S.; Maroju, R.; Baburao, K.; Parasa, L. S. *Eur. J. Med. Chem*. **2016**, *123*, 379-396; (c) Kumar, J. M.; Idris, M. M.; Srinivas, G.; Kumar, P. V.; Meghah, V.; Kavitha, M.; Reddy, C. R.; Mainkar, P. S.; Pal, B.; Chandrasekar, S.; Nagesh, N. *PLOS One*. **2013**, *8*, e70798; (d) Chatzileontiadou, D. S. M.; Parmenopoulou, V.; Manta, S.; Kantsadi, A. L.; Kylindri, P.; Griniezaki, M.; Kontopoulou, F.; Telopoulou, A.; Prokova, H.; Panagopoulos, D.; Boix, E.; Balastos, N. A. A.; Komiotis, D.; Leonidas, D. D. *Bioorg. Chem*. **2015**, *63*, 152-165.
9. (a) Elayadi, H.; Mesnaoui, M.; Korba, B. E.; Smietana, M.; Vasseur, J. J.; Secrist, J. A.; Lazrek, H. B. *ARKIVOC*. **2012**, (*viii*), 76-89; (b) Amant, A. H. St.; Bean, L. A.; Guthrie, J. P.; Hudson, R. H. E. *Org. Biomol. Chem*. **2012**, *10*, 6521-6525; (c) Parmenopoulou, V.; Chatzileontiadou, D.S.M.; Manta, M.; Bougiatioti, S.; Maragozidis, P.; Gkaragkouni, D.-N.; Kaffesaki, Zounpoulakis, P.; Balatsos, N.A.A.; Komiotis, D.; Leonidas, D.D. *Bioorg. Med. Chem*. **2012**, *20*, 7184-7193. (d) Chatzileontiadou, D. S. M.; Tsika, A. C.; Diamantopoulou, Z.; Delbé J.; Badet, J.; Courty, J.; Skamnaki, V. T.; Parmenopoulou, V.; Komiotis, D.; Hayes, J. M.; Spyroulias G. A.; Leonidas, D. D. *ChemMedChem*. **2018**, *13*, 259-269.
10. Semenov, V. E.; Akamsin, V. D.; Reznik, V. S. *Russ. J. Gen. Chem*. **2007**, *77*, 1430-1140.
11. Thakur, R. K.; Mishra, A.; Ramakrishna, K. K. G.; Mahar, R., Shukla, S. K.; Srivastava, A. K.; Tripathi, R. P. *Tetrahedron*. **2014**, *70*, 8462-8473.
12. (a) Nowick, J. S.; Chen, J. S.; Noronha, G. *J. Am. Chem. Soc*. **1993**, *115*, 7636-7644; (b) Singh, H., Aggarwal, P.; Kumar, S. *Synthesis*. **1990**, *6*, 520-522.
13. Cai, S. X.; Tian, Y. E.; Hu, X. U.S. Patent 9290460 B2. 2012, WO2012/130166.
14. Forsman, J. J.; Wärnå, J.; Murzin, D. Yu.; Leino, R. *Eur. J. Org. Chem*. **2009**, 5666-5676.
15. Gao, M.; Chen, Y.; Tan, S.; Reibenspies, J. H.; Zingaro, R. A. *Heteroatom Chem*. **2008**, *19*, 199-206.
16. Nisic, F.; Speciale, G.; Bernardi, A. *Chem. Eur. J*. **2012**, *18*, 6895-6906.
17. (a) Fan, W.-Q.; Katritzky, A.R. In *Comprehensive Heterocyclic Chemistry*, Ed. Katritzky, Rees, C.W.; Scriven, E.F.V. Pergamon: Oxford, UK. 1997; Vol. 4; pp 11-14; (b) Romero-Hernández, L.L.; Merino-Montiel, P.; Montiel-Smith, S.; Meza-Reyes, S.; Vega-Báez, J. L.; Abasolo, I.; Schwartz Jr., S.; López, O.; Fernández-Bolanos, J. G. *Eur. J. Med. Chem*. **2015**, *99*, 67-81.

Journal Pre-proofs

- A series of novel 1,2,3-triazolyl pyrimidine nucleoside analogues was synthesized
- The pyrimidine moiety was connected to a triazolyl ring by a linker of variable length
- The obtained compounds differ in the nature of pyrimidine moiety and the linker length
- All obtained compounds were non-cytotoxic in relation to the normal human cell lines

Journal Pre-proofs