Synthesis and Application of C-5'-triazolyl-nucleosides

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Abstract: Modified nucleosides are the core precursor nucleic acid, and it has a significant contribution medicinal chemistry and drug discovery. So that, prepare different triazolyl scaffolds, ruthenium and copper catalysed azide-alkyne 1,3-dipolar cycloaddition reactions also known as click reaction have developed as a facile and efficient unique tool because of its simplicity and ideal conditions. Introduction of a triazole ring in nucleosides, improves their therapeutic value and different photophysical attributes. In this article, discussed the synthesis and application of C-5'-triazolyl nucleosides.

Key words: Triazole, nucleoside, click chemistry, anti-cancer, anti-viral.

INTRODUCTION

Nucleosides are the building block of biological system and it has a long and rich history in the area of drug discovery.[1] Presently, several nucleosides and their derivatives are used in the treatment of different viruses, cancers, parasites, as well as fungal and bacterial infections.[2] Apart from this, several candidates of this class are presently at the stage of clinical and preclinical trials of drug discovery.[1,3] Continuously in search of new clinically fruitful nucleosides analogous, in literature it was found that 1,2,3-triazole scaffold is a remarkable and well recognized pharmacophore[4] and is the bioisostere of ester, amide, carboxylic acid and other heterocycles. During the last twenty years, triazole scaffold has achieved special attention for the development of novel antibiotics medicine because several compounds carrying 1,2,3-triazole scaffold such as tazobactam, cephalosporin, and cefatrizine. Therefore, 1,2,3-triazole could be a powerful pharmacophore that play a crucial role in bioconjugation. Ribavirin (A) (Figure 1) is the first FDA accepted triazole based nucleoside medicine, that is used contrary to HCV and the progress of azidothymidine (AZT, B) (Figure 1) is used as HIV.[5] Triazole containing nucleosides also demonstrated a wide spectrum of pharmacological activities like antiviral[6], anti-microbial[7], antitumor properties[8], anti-proliferative[9], etc. Beside this, different triazolyl nucleoside analogues demonstrated photophysical attributes and other applications.[10, 11] Surely, triazolyl nucleosides and their analogues, might be a promising candidate for future drug discovery and development.

Figure 1. Structure of drugs Ribavirin A and Zidovudine B.

In 1960s, Huisgen et al .[12] prepared a triazole compound *via* 1,3-dipolar cycloaddition reaction between alkynes and azides through thermal reaction conditions. Further, the idea of triazole preparing heterocyclic ring through copper-catalyzed azides-alkynes cycloaddition, that is also known as "click chemistry" was recognized first by Medal and then by Sharpless.[13] Click chemistry provide a simple and regioselective 1,4-isomeric compound via mild reaction conditions. Subsequently, Jia research group has been also developed regioisomer 1,5-disubstituted triazolyl compound through ruthenium catalysed azide-alkyne cycloaddition.[14] It is significant to recognize that the emergence of click chemistry has been given a golden platform in drug discovery and development[15,16] such as lead discovery via target-templated *in vitro* chemistry, bio-conjugation process and combinatorial chemistry. Due to the

extraordinary utility of triazolyl nucleoside compounds in pharmacological applications, in this paper, we have been discussed the synthesis as well as biological utility of modified nucleosides carrying triazole scaffold at C-5' positions of the nucleoside.

1. Synthesis

Kumar research group[17] synthesised a library of C-5'-triazolo nucleosides (6a-g, 7a-i) by copper(I) - catalysed 1,3-dipolar cycloaddition reaction of propargylated nucleoside and substituted fluoro aryl azides in good to excellent yield (Scheme 1). Firstly, compound 2 was synthesised from uridine 1 by the reaction of uridine in 70% acetone and $HClO_4$.In the next step, compound 2 was treated with propargylbromide under base DBU in acetonitrile solvent to afford propargylated nucleosides 3. Further, unmasking of 3 with dil. HCl in methanol solvent to give the nucleoside 4 in good yield. The reaction of nucleoside 4 and substituted aryl azide under click chemistry condition to give the triazolyl nucleosides 6a-g in good to excellent yield. Lastly, treatment of 3 with substituted aryl azide 5 under click chemistry to afford the protected triazolyl nucleosides 7a-l in quantitative yield. All synthesised compounds have been characterised by spectroscopic techniques such as mass spectroscopy, ^{1}HNMR, ^{13}C NMR etc. Further, all synthesised compounds have been evaluated for their antibacterial activity in vitro against Xanthomonas citri pv. Bacillus siamensis, malvacearum, Pseudomonas aeruginosa and Ralstonia solanacearum. All synthesised nucleosides demonstrated antibacterial activity contrary to four bacterial strains in the range of 0.318 mm to 3.596 mm.

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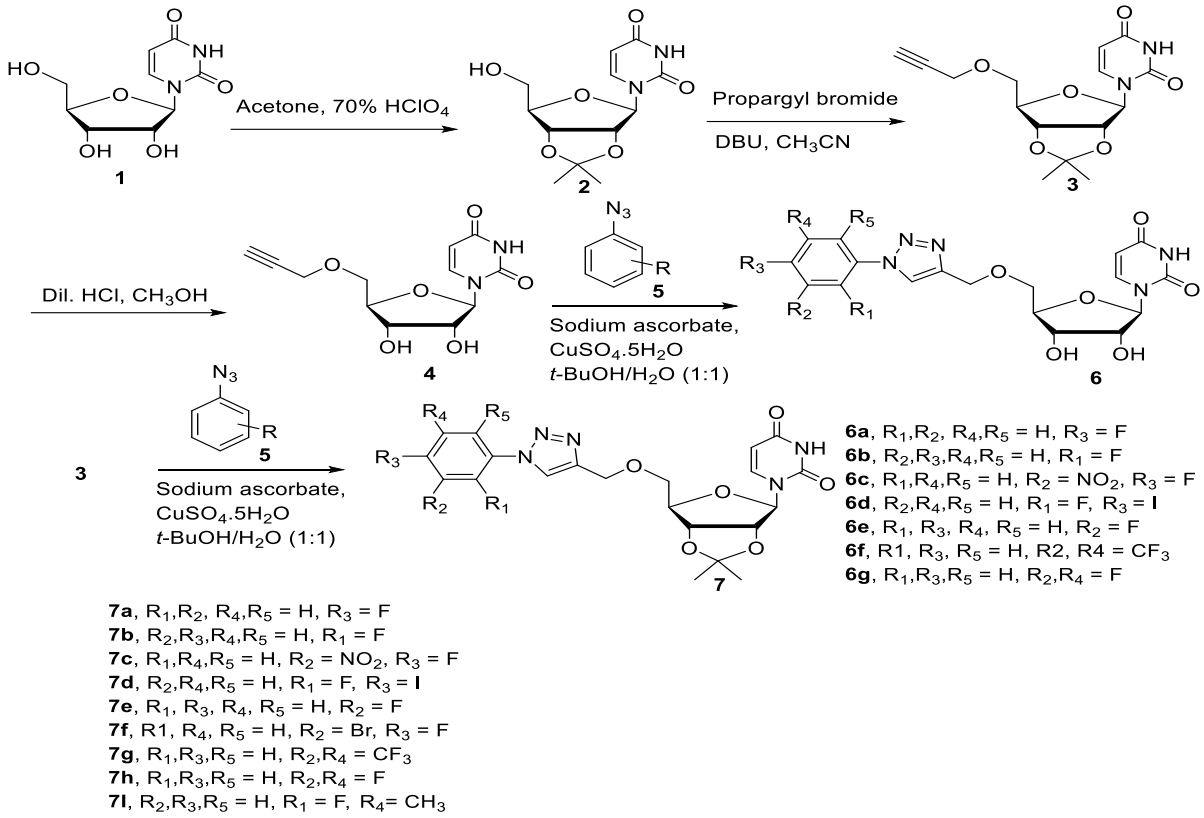

Scheme 1. Synthesis of triazolyl nucleosides **6a-g** and **7a-i**.

Kosiova research group[18] has been synthesized a library of coumarin conjugated thymidine nucleosides **10a-e** and **12a-e** (**Scheme 2**). The substituted alkynes have been treated with 5'-azido-5'-deoxyuridine (**8**) and 5'-azido-5'-deoxythymidine (**119**) under click chemistry conditions via CuSO4 and sodium ascorbate to give nucleosides **10a-e** and **12a-e**, respectively.

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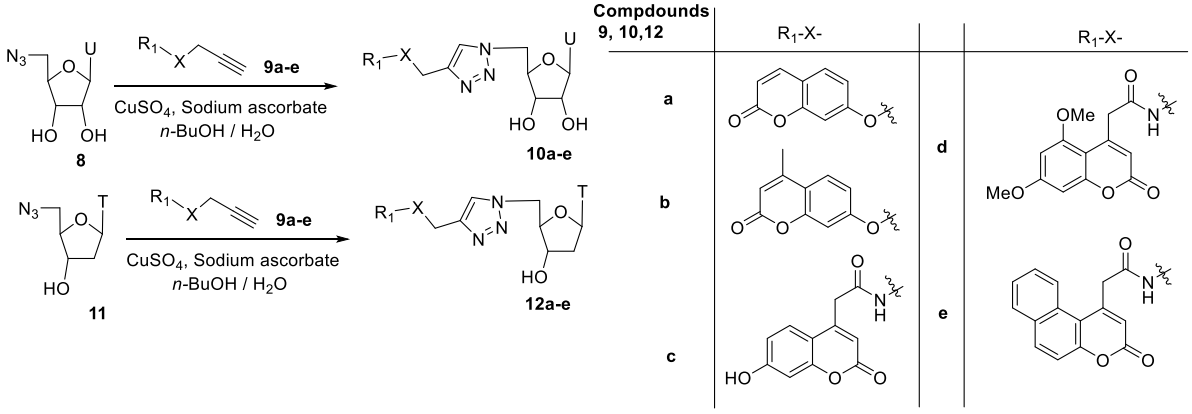
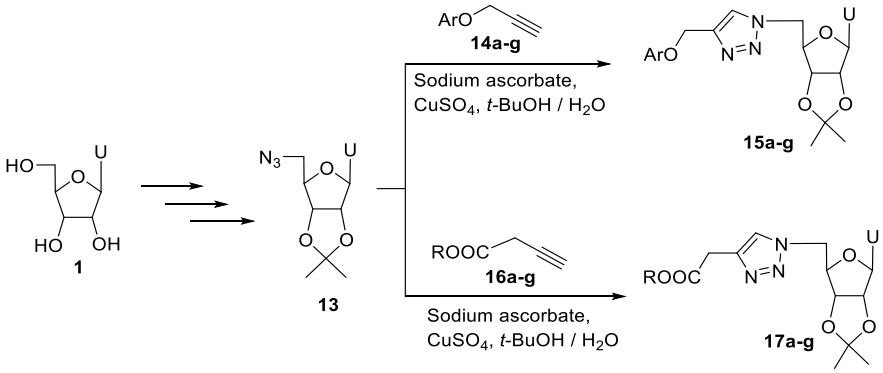
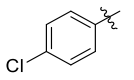
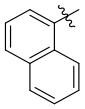
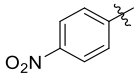
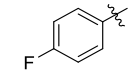
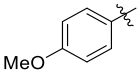
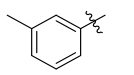


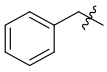
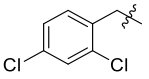
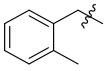
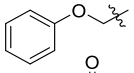
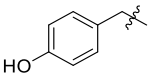
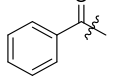
Scheme 2. Synthesis of coumarin conjugated triazolyl-thymidine/uridine nucleosides **10a-e** and **12a-e**.

Chaudhary research group[19] explored new click reaction facilitated nucleosides as potential chitin synthase inhibitors. Uridine (**1**) was transferred into the key precursor 5'-azido-5'-deoxyuridine (**13**) in multiple steps. Firstly, uridine **1** was reacted with dimethoxy propane in acetone solvent in the availability of *para*-toluenesulfonic acid, followed by para toluene sulfonyl chloride in pyridine and

sodium azide & DMF in second and third steps, respectively to give nucleoside **13 (Scheme 3**). Further, compound **13** was treated with different alkynes **14a-g** and **16a-g**, through sodium ascorbate and copper sulphate in a solvent mixture of *t*-BuOH and water. It afforded two series of nucleosides i.e. **15a-g** and **17a-g**, respectively. Nucleoside **15d**, **15e**, **15f**, and **17f** have been observed the most potent chitin synthase inhibitors in comparison to nikkomycin. Triazolyl nucleosides **15a-d** and **17a-b** have been observed to possess better antifungal attributes against human and plant pathogens.



Compds. 14, 15	Ar		Ar		Ar
a		d		g	
b		e			
c		f			

Compds. 16,17	R		R
a		d	
b		e	
c		f	
		g	-CH_2Cl

Scheme 3. Synthesis of triazolyl-uridine nucleosides **15a-g** and **17a-g**.

Yu research group[20] prepared a library of C-5'-triazolonucleosides starting from the furanoside **18.** Firstly, the furanoside has been tosylated at 5'-hydroxyl position in dichloromethane, followed by treated with sodium azide in polar dimethylformamide solvent to afford azido nucleoside **19** (**Scheme 4**). In next step, click chemistry was achieved between the furanoside **19** and substituted alkynes **20a-i** through Cu and $CuSO_4$ in an equimolar mixture of solvent *n*-butanol and water produced 5'-triazolo-furanosides **21a-i**. Further, reaction of triazolofuranosides with silylatednucleobases of thymine, uracil, and N^4-benzol-cytosine afforded **23a-e**, **h-I, 22a-i**, and **24a** in good yields, respectively. Apart from this, antitumor activity has been screened for synthesised compounds and it was observed that due to the conjugation effects of aromatic rings, the synthesised compound exhibited remarkable activity towards extensive range of tumor cell lines as compared to others. Therefore, these results proposed that on the triazole scaffold with the aromatic ring was a significant for bioactivity.

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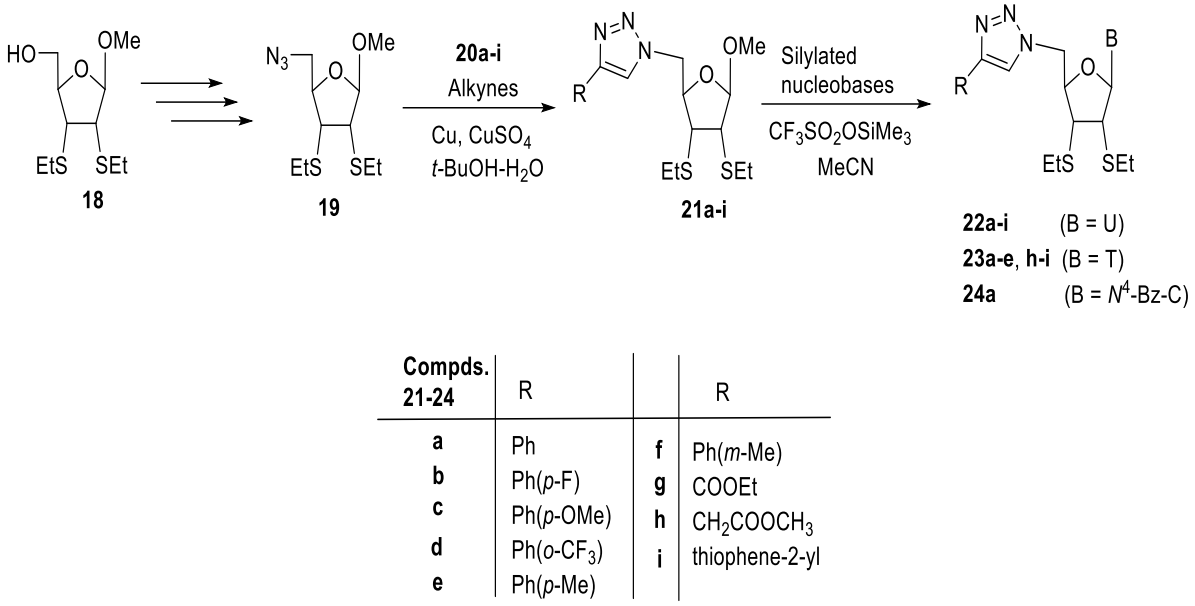
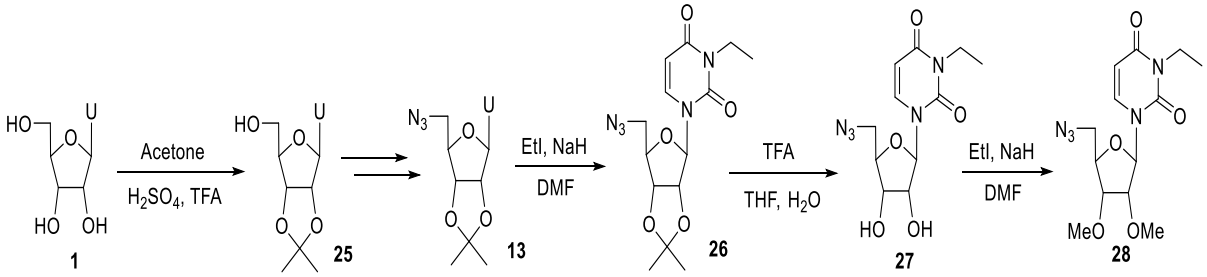


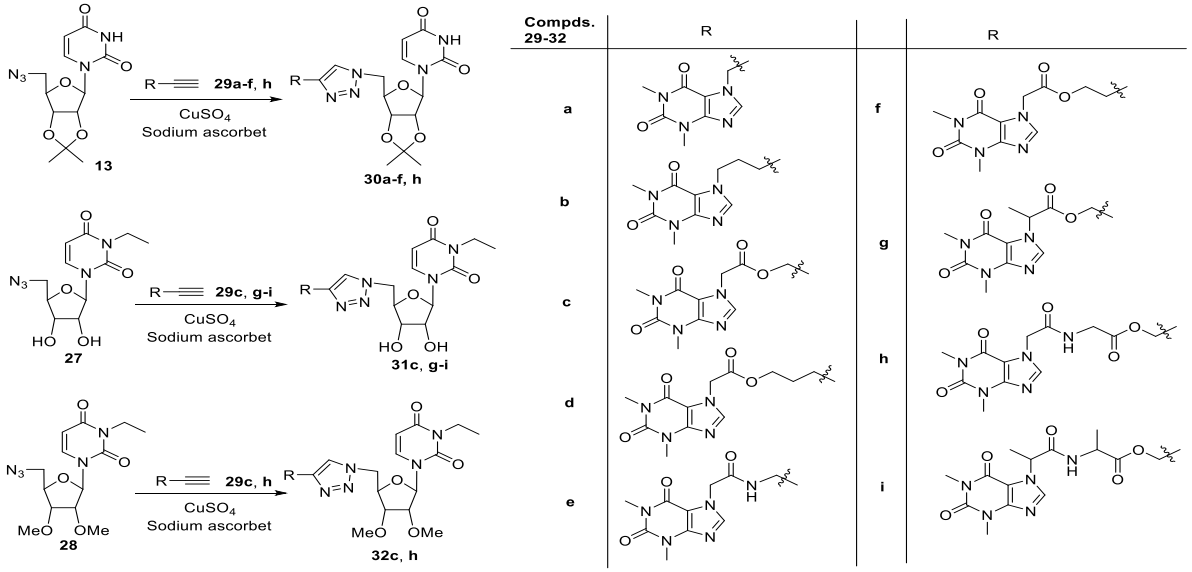
Compds. 21-24	R		R
a	Ph	f	Ph(*m*-Me)
b	Ph(*p*-F)	g	COOEt
c	Ph(*p*-OMe)	h	CH_2COOCH_3
d	Ph(*o*-CF_3)	i	thiophene-2-yl
e	Ph(*p*-Me)		

Scheme 4. Synthesis of triazolyl nucleosides **22a-i**, **23a-e**, **h-i** and **24a**.

Ruddarraju research group[21] designed and synthesised a library of theophylline carrying 5'-triazolo nucleosides and evaluated them contrary to antimicrobial and anticancer activities with *in silico* analysis. Firstly, uridine (**1**) was masking by acetonide and followed by mesylation at the primary hydroxyl and azidation by sodium azide in dimethylformamide, that afforded nucleoside **13** (**Scheme 5**). In next step, *N*-3 of nucleobase uridine was masking by ethyl group through ethyl iodide in dimethylformamide with sodium hydride as a base to afford the corresponding nucleoside **26**. Lastly, reaction of nucleoside **26** with trifluoroacetic acid in an equimolar solvent mixture of tetrahydrofuran and H_2O, followed by methylation of **27** to produce compound **28** in excellent yield (**Scheme 5**). Nucleoside **13** has been treated with alkynes **29a-f**, **h** in the availability of $CuSO_4$ and sodium ascorbate in an equimolar solvent mixture of EtOH and H_2O to produce the compounds **30a-f**, **h**. Similarly, compound **27** and **28** have been reacted via similar reaction conditions with alkynes **29c**, **g-i** and **29c**, **h**, respectively, to afford the corresponding compounds **31c**, **g-i** and **32c**, **h**, respectively. Further, nucleosides **31c** and **31h** demonstrated significant cytotoxic effect on all four cancer cells such as melanoma (A375), colon (HT-29), breast (MCF-7) and lung (A549). Nucleosides **30b** and **30h** demonstrated remarkable antimicrobial activity with minimum inhibitory concentrations (MIC) against *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa.*

[21] [21]. Ruddarraju, R. R., Murugulla, A.C., Kotla, R., Tirumalasetty, M.C.B., Wudayagiri, R., Donthabakthuni, S., Maroju, R., Baburao, K., Parasa, L.S. Design, synthesis, anticancer, antimicrobial activities and molecular docking studies of theophylline containing acetylenes and theophylline containing 1,2,3-triazoles with variant nucleoside derivatives. Eur J Med Chem 2016, 123, 379-396.

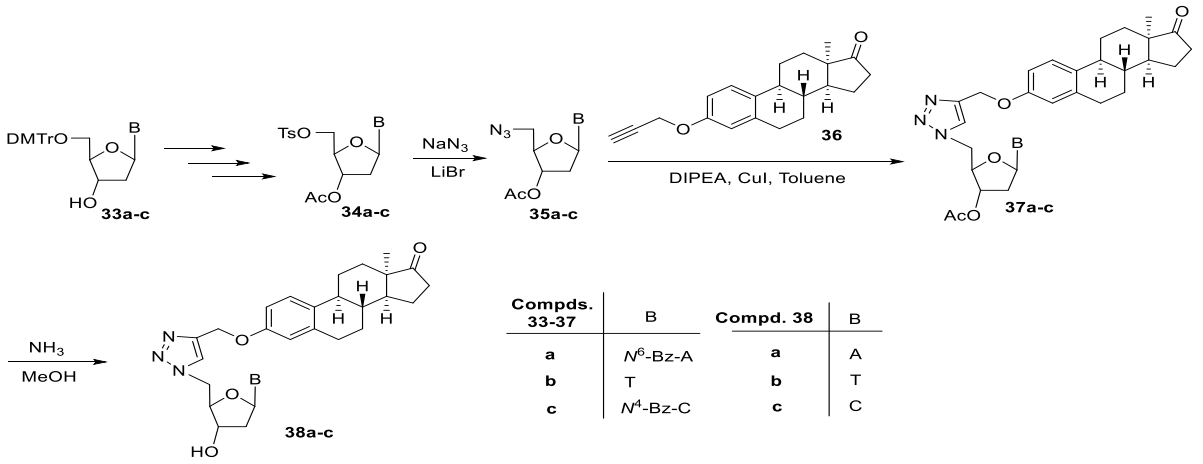




Scheme 5. Synthesis of triazolyl nucleosides **30a-f**, **h**, **31c**, **g-I**, **32c**, **h**.

Bodnar research group[22] prepared a triazolyl nucleosides using copper catalyzed azide-alkyne click chemistry (**Scheme 6**). Firstly, nucleosides 5'-*O*-DMTr-2'-deoxynucleosides **33a-c**, was acetylated by acetic anhydride at 3'-position followed by unmasking of DMTr from primary hydroxyl group and then masking with tosyl group through tosyl chloride in pyridine as a base to afford nucleosides **34a-c**. Further, azido nucleosides **35a-c** have been achieved by the reaction of tosylated nucleosides **34a-c** with sodium azide in the availability of lithium bromide. Click chemistry was achieved between the reaction between 5'-azido-2',5'-dideoxynucleosides **35a-c** and compound **36** in toluene or THF with CuI and DIPEA at 50 ºC. Further, deacylation of 37a-c was achieved in the presence of methanolic ammonia to afford the corresponding nucleosides **38a-c** (**Scheme 6**). Apart from this, all the prepared compounds demonstrated moderate to remarkable antiproliferative property against HeLa, A2780, and MCF-7 on human adherent cell lines.

[22] [22]. Bodnár, B., Mernyák, E., Wölfling, J., Schneider, G., Herman, B.E., Szécsi, M., Sinka, I., Zupkó, I., Kupihár, Z., Kovács, L. Synthesis and Biological Evaluation of Triazolyl 13α-Estrone–Nucleoside Bioconjugates. Molecules 2016, 21, 1212-1227.



Scheme 6. Synthesis of triazolyl nucleoside **38a-c**.

2. CONCLUSION

Recent studies demonstrated that triazolyl nucleosides have been enormous potential in the area of biochemistry and chemistry as possible drug candidates. Modified nucleosides containing triazole scaffolds have been exhibited a wide range of biological utility such as antimicrobial, antifungal, antiviral, anti-proliferative and antitumor activities. In this article, we discussed the synthesis

via click chemistry and biological application of C-5'-triazolyl nucleosides. The aim of this article is to give the recent development in the field of modified nucleosides containing triazole scaffold and their analogues and motivate further research to develop new biologically prominent triazolyl nucleosides.

3. ACKNOWLEDGEMENTS

All authors are thankful to their corresponding college/University for basic research facility.