

Synthesis and Biological Evaluation of 3'-C-Ethynyl and 3'-C-(1,4-disubstituted-1,2,3-triazolo) Double-Headed Pyranonucleosides

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Abstract: A novel series of 3'-C-ethynyl and 3'-C-(1,4-disubstituted-1,2,3-triazolo) double-headed pyranonucleosides has been designed and synthesized. Reaction of 3-keto glucoside **1** with ethynyl magnesium bromide gave the desired precursor 3-C-ethynyl-1,2:5,6-di-*O*-isopropylidene- α -D-allofuranose (**2**). Hydrolysis followed by acetylation led to the 1,2,4,6-tetra-*O*-acetyl-3-C-ethynyl- β -D-allopyranose (**3**). Compound **3** was condensed with silylated 5-fluorouracil, uracil, thymine, *N*⁴-benzoylcytosine and *N*⁶-benzoyladenine, respectively and deacetylated to afford the target 1-(3'-C-ethynyl- β -D-allopyranosyl)nucleosides **5a-c,f,g**. Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) reaction was utilized to couple the 3'-C-ethynyl pyranonucleoside derivatives with azidoethyl adenine, 5-fluorouracil and thymine, respectively to afford novel triazole double-headed nucleoside analogues **8a-h**. 3'-C-Ethynyl pyranonucleosides and the new double-headed analogues were evaluated for their antiviral and cytostatic activities. Although none of the compounds showed pronounced cytostatic activity and were devoid of a significant antiviral potential, the double-headed nucleoside derivatives **8a**, **8c** and **8e** showed a moderate cytostatic activity against human cervix carcinoma HeLa cells which may be the basis for the synthesis of analogous derivatives with improved cytostatic potential.

Keywords: Branched-chain nucleosides, C-ethynyl pyranonucleosides, click chemistry, double-headed nucleosides.

INTRODUCTION

Modified nucleosides have emerged as important therapeutic agents for the development of antiviral and anti-tumor drugs [1-4]. During the last decades, many modifications of the base and/or sugar moiety of natural nucleosides have been attempted, in order to discover novel derivatives endowed with potential biological properties.

Recently, considerable attention has been paid to furano-nucleosides containing an ethynyl group in their carbohydrate backbone as a result of their significant biological activity. Branched C-ethynyl nucleoside analogues showed antiviral properties against herpes simplex virus type-1 (HSV-1) and human immunodeficiency virus type-1 (HIV-1) [5-8], while 3'-C-ethynyl-branched nucleoside analogues have been reported to exhibit potent and broad spectrum anti-cancer activities [9-11]. Among them, the 1-(3'-C-ethynyl- β -D-ribo-pentofuranosyl)cytosine, a promising RNA-directed nucleoside anti-metabolite, is currently undergoing clinical trials [12,13].

Last decade, nucleosides bearing pyranosyl ring have been evaluated for their potential anticancer [14-16], antioxidant [17,18] and antibiotic [19] properties and as building blocks in nucleic acid synthesis [20]. In seeking to investigate novel biologically active agents, we recently reported that new classes of uncommon 3'-fluorinated and 3'-C-cyano pyranonucleosides proved to be efficient as tumor cell growth inhibitors and showed to have a promising potential in combating rotaviral infections [21-25]. Experimental evidence also disclosed that human poly(A)-specific ribonuclease [26] and glycogen phosphorylase [27] are among the molecular targets of these compounds.

With the above applications in mind and as an extension of our studies, we decided to synthesize novel pyranonucleosides in which the fluorine atom or the cyano group will be replaced by the biologically promising ethynyl group. Therefore, we report herein on the preparation and biological evaluation of 3'-C-ethynyl- β -D-allopyranonucleoside analogues, containing 5-fluorouracil, uracil, thymine, cytosine and adenine as base moieties. The presence of the triple bond of C-ethynyl-pyranonucleosides, provided an excellent opportunity to further synthesize a novel class of double-headed pyranonucleosides, *via* CuAAC reaction [28-31] with various purine or pyrimidine azides. Thus, in the present study, we also describe the utilization of 3'-C-ethynyl- β -D-

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