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Mini Review Open Access

Rapid Microwave-Assisted Synthesis of Modified Pyrimidine and Purine Pyranonucleosides as Novel Cytotoxic, Antiviral Agents and Glycogen Phosphorylase B Inhibitors

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Abstract

Nucleosides take an important place in medicinal chemistry as the structural basis for the development of therapeutic agents. The chemistry of substituted base-modified nucleosides has been an interesting field of study over the last two decades owing to their biological properties. This mini-review summarizes recent efforts on the synthesis of *C*5- and *C*8-alkynyl base-modified pyranonucleoside analogues using Sonogashira cross-coupling reaction under microwave irradiation.

Keywords: Sonogashira reaction; Base-modified; Pyranonucleosides; Microwave irradiation; Cytotoxic/antiviral activity

Introduction

Several purine-and pyrimidine-substituted nucleosides exhibit activity in both solid tumors and hematological malignancies, behaving as antimetabolites, competing with physiological nucleosides, and consequently, interacting with a large number of intracellular targets to induce cytotoxicity [1]. Among them, alkynyl-modified uridines exhibited significant antiviral [2-4] and anticancer activities [4]. e.g., the internal aromatic-substituted alkyne *p*-tolylethynyl-2'-deoxyuridine showed high potency against MCF-7 (IC_{50} 0.9 ± 0.2 μM), comparable to 5-fluorouracil and Cisplatin [5] while 5- ethynyl-2'-deoxyuridine, was the most potent inhibitor against MCF-7 and MDA-MB-231 human breast cancer cells (IC_{50} 0.4 ± 0.3 and 4.4 ± 0.4 μM, respectively), the same compound also inhibited the replication of HSV-1, HSV-2 (herpes simplex virus type 1, 2) and VV (vaccinia virus) at concentrations of 0.1-1 μg/mL [6,7]. Little effort has been made towards the synthesis of *C*8-modified purine nucleosides, nevertheless, some interesting biological properties have been reported: e.g., selected 8-alkynyl adenosines were selective ligands for the A_3 adenosine receptor subtype behaving as adenosine antagonists [8], and various *C*8-modified 2'-deoxy adenosines induced delayed chain termination *in vitro* and showed moderate anti HIV-1 activity in cell culture [9]. Considering the progress made in this direction, the present mini review presents an update of recent developments on pyrimidine- and purine-modified pyranonucleosides that possess interesting biological properties. In particular, the molecular design, synthesis and biological activity of *C*5-alkynyl pyrimidines and *C*8-alkynyl purine pyranonucleosides is presented. Aiming at a more detailed structure-activity relationship studies, a variety of alkyne substituents R are reported, such as linear alkyl chains and arenes substituted with linear and branched alkyl groups.

Results and Discussion

In 2013, numerous novel *C*5-alkynyl uracil and cytosine glucopyranonucleosides were first synthesized and biologically evaluated [10]. Analogues **3a**,**b**-**9a**,**b**, **11a** and **12a** were prepared *via* their iodinated precursors **2a** and **2b** using Pd(0)-catalyzed Sonogashira cross-coupling reactions under microwave irradiation (Figure 1). When compared to conventional heating [11], the MW technology completed the synthesis much faster, while the yields of the products were slightly increased (by 3-13%). All the newly synthesized compounds were evaluated for their cytostatic activity against human cervix carcinoma (HeLa), human lymphocytes (CEM) as well as murine leukemia (L1210) cells. The 5-substituted uracil pyranonucleosides showed superior antiproliferative activity to their cytosine counterparts. Among the nucleosides tested, the phenylethynyl uracil pyranonucleoside derivative **5a**, effectively inhibited tumor cell proliferation (IC_{50} 5.2-6.2 μM) similar to that of 5-fluorouracil (IC_{50} 0.33-18 μM), whereas its cytosine congener showed no appreciable cytostatic action (IC_{50} 201→250 μM). The cyclization of **3a** and **4a** to the target bicyclic nucleosides **10a** and **11a** achieved through extended reaction time (irradiation for 8 min) and it was based on a *5-endo-dig* electrophilic cyclization *via* an *O*-hetero-annulation process. Kinetic studies also showed that 1-(β-*D*-glucopyranosyl)-5-ethynyluracil **9a** was the best glycogen phosphorylase b (GPb) inhibitor (Ki 4.7 μM). Crystallography revealed that inhibitors with a long *C*5-alkynyl group exploited interactions with the b-pocket of the active site and induced significant conformational changes of the 280s loop compared to GPb complex with compounds hosting a short *C*5-alkynyl group. The results highlight the importance in the length of the aliphatic groups used to enhance inhibitory potency for the exploitation of the hydrophobic b-pocket. The most active inhibitor also had a moderate effect on glycogenolysis at the cellular lever with an IC_{50} value of 291.4 μM.

Recently, *C*5-aryl ethynyl uracil glucopyranonucleosides **13**,**15** and *C*5-arylethyl uracil pyranonucleosides **17a**,**e**,**i**,**j**,**k** were also prepared [12] and evaluated for their cytostatic and antiviral activities. The protected analogues **12a**,**e**,**i**,**j** (Figure 2) showed better cytostatic activity against human lymphocyte CEM tumor cells (IC_{50} 18-42 μM) compared to their unprotected counterparts **13a**,**e**,**i**,**j** which did not enhance growth inhibition of CEM cells (IC_{50} >250 μM), while derivatives **17a**,**e**,**i**,**j**,**k** were devoid of significant cytostatic activity (IC_{50} 94-250 μM). Their antiviral activities were measured against a large

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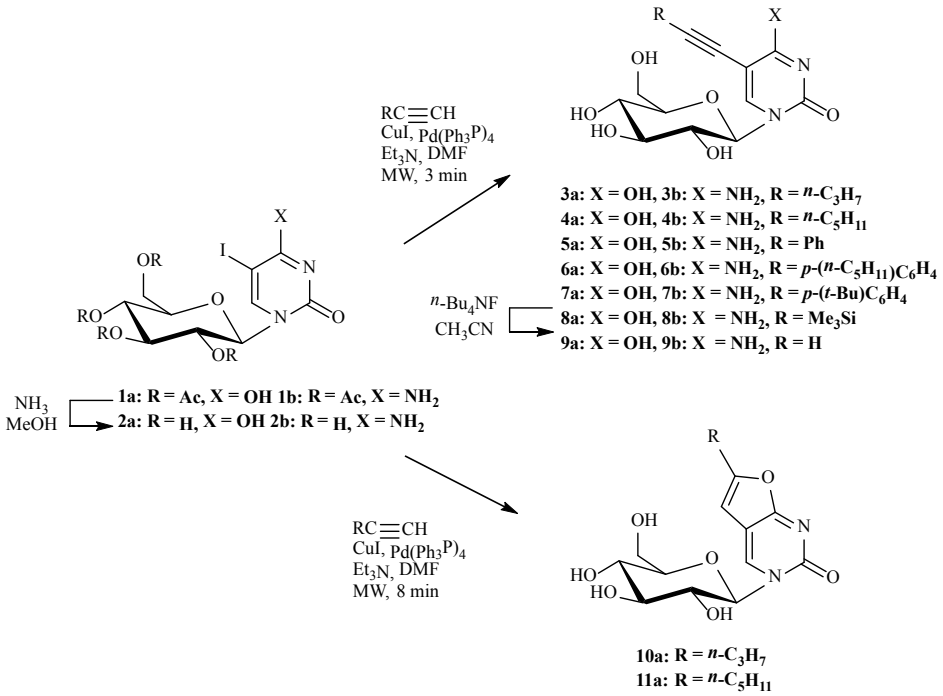

Figure 1: Synthesis of *C*5-alkynyl pyrimidine glucopyranonucleosides.

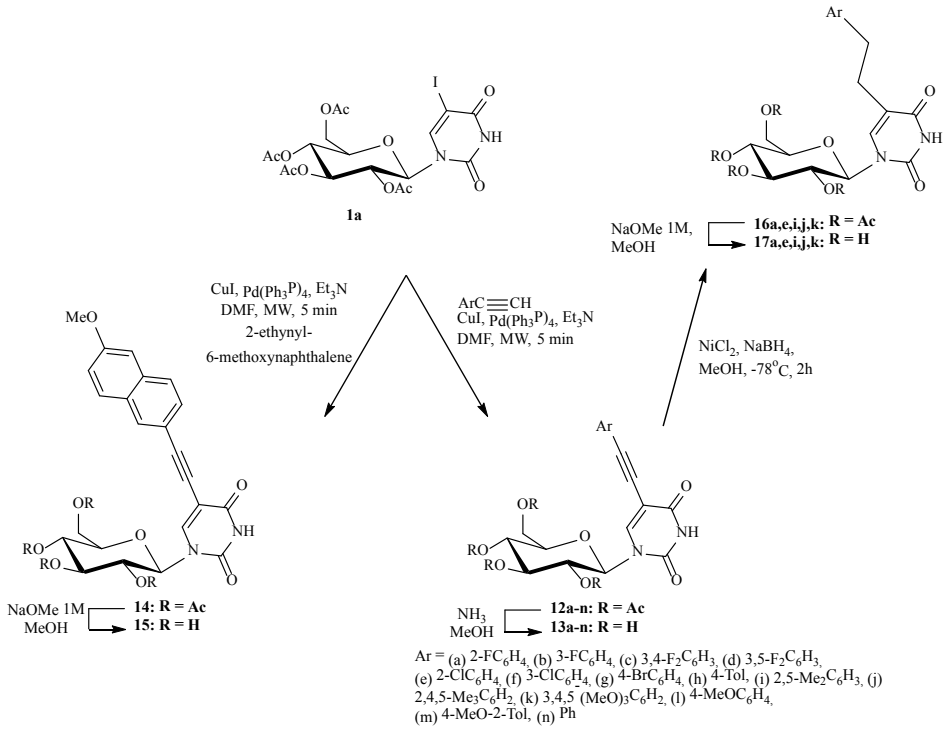

Figure 2: Synthesis of *C*5-arylalkynyl uracil glucopyranonucleosides and of 1-(*β*-*D*-glucopyranosyl)- 5-[arylethyl]uracil.

number of DNA and RNA viruses including herpes simplex virus type 1,2 (HSV-1,2), vaccinia virus (VV), adeno-virus 2 (Ad-2) and human coronavirus 229E (HCoV-229E). Only analogue **17i** exhibited the best anti-VV activity (EC_{50} 10 μM): 10- and 25-more active than the reference drugs Ganciclovir (CMV) (EC_{50} 100 μM) and Acyclovir (ACV) (EC_{50} 250 μM), respectively, on HEL cell culture. Novel *C*5-arylalkynyl uracil pyranonucleosides bearing 3′-*C*-trifluoromethyl-D-allose as sugar moiety were recently synthesized *via* microwave-

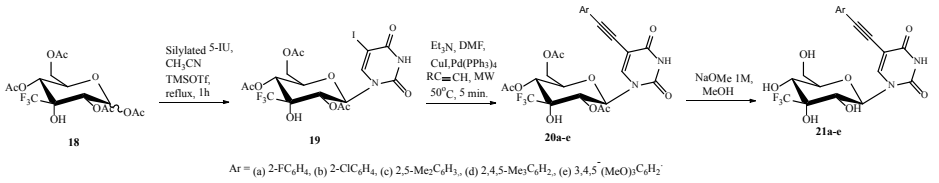

Figure 3: Synthesis of 1-(3′-*C*-trifluoromethyl-*β*-*D*-glucopyranosyl)-5-[arylethynyl]uracil.

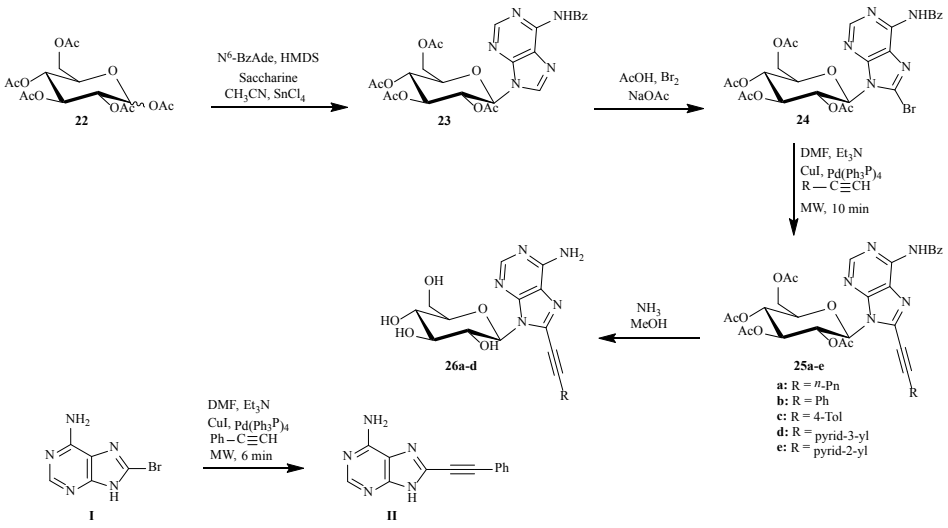

Figure 4: Synthesis of *C*8-alkynyl adenine glucopyranonucleosides and 8-phenylethynyl-adenine.

assisted Sonogashira coupling and were biologically evaluated [12]. The protected nucleosides **20c**,**d** proved to be cytotoxic against human lymphocyte (CEM) cells (IC_{50} 19-20 μM) similarly to 5-fluorouracil (IC_{50} 0.33-18 μM), contrary to their unprotected analogues **21c**,**d** which proved to be inactive (IC_{50} >178 μM) (Figure 3).

Finally, the synthesis of the first purine glucopyranonucleosides *C*8-alkynyl adenines **25**, **26** and 8-phenyl-ethynyl-adenine (**II**) itself were also reported (Figure 4) [13] using the Sonogashira cross-coupling reaction. The cytostatic potential of compounds **25e** (IC_{50} 2.9-5.9 μM) and **II** (IC_{50} 3.0-10.0 μM) was an order of magnitude lower than 5-fluorouracil (IC_{50} 0.33-0.54 μM) on murine leukemia (L1210), and human cervix carcinoma (HeLa) cells, while the same compounds (IC_{50} 1.2-4.2 μM) were more active than 5-fluorouracil (IC_{50} 18 μM) on human lymphocyte (CEM) cells.

Conclusion

In the present review, we focused our attention on the relatively new literature data, concerning the *C*5- and *C*8-alkynyl base-modified glucopyranonucleosides, as well as 8-phenylethynyl-adenine itself, *via* Sonogashira coupling conditions under microwave irradiation. With chemists becoming increasingly interested in biology, the demand for novel bioactive compounds with improved therapeutic potential is becoming high. Moreover, extensive structure-activity relationship studies of the novel pyranonucleoside analogues concerning different substituents in the aromatic ring as well as more detailed investigations on the molecular drug targets are envisaged.

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