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Original article

Anticancer evaluation of some newly synthesized *N*-nicotinonitrile derivative

Ahmed H. Shamroukh [a, *], Mahmoud El-Shahat [a], Józef Drabowicz [b], Mamdouh M. Ali [c], Aymn E. Rashad [a, d], Hatem S. Ali [e]

[a] Photochemistry Department, National Research Center, Dokki, 12311 Cairo, Egypt
[b] Center of Molecular and Macromolecular Studies, Polish Academy of Science, Łódź, Poland
[c] Biochemistry Department, Division of Genetic Engineering and Biotechnology, National Research Center, Dokki, Cairo, Egypt
[d] Chemistry Department, Faculty of Science and Human Studies, Shaqra University, Hurraiymla, Saudi Arabia
[e] Department of Food Science and Nutrition, College of Food Science and Agriculture, King Saud University, Saudi Arabia

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ABSTRACT

Some novel *N*-nicotinonitrile derivatives **3**–**14** have been synthesized starting with compound **1**. The key step of this work is the coupling between compound **1** and activated sugars to afford the corresponding cyclic nucleosides **3**–**6**. Moreover, the cytotoxicity and *in vitro* anticancer evaluation of the prepared compounds have also been assessed against breast MCF-7 cancer, liver HepG2 cancer and lung A549 carcinoma cell lines with investigation the effect of the synthesized compounds on the expression of urokinase plasminogen activator (uPA). The results revealed that, although all the compounds showed no anticancer activity against A549 cells without showing any effect on the expression of uPA, the tested compounds exhibited remarkable cytotoxicity activity against MCF-7 and HepG2 cell lines. Among the tested compounds, compounds **11** and **12** revealed promising anticancer activity compared to the activity of the commonly used anticancer drug, doxorubicin with inhibiting the expression of uPA.

1. Introduction

Targeted therapies have a high specificity toward tumor cells, providing a broader therapeutic window with less toxicity. They are also often useful in combination with cytotoxic chemotherapy or radiation to produce additive or synergistic anticancer activity because their toxicity profiles often do not overlap with traditional cytotoxic chemotherapy. Thus, targeted therapies represent a new and promising approach to cancer therapy, one that is already leading to beneficial clinical effects. There are multiple types of targeted therapies available, including monoclonal antibodies, inhibitors of tyrosine kinases and antisense inhibitors of growth factor receptors [1].

Urokinase plasminogen activator (uPA) is a serine protease that functions in the conversion of the circulating plasminogen to the active, broad-spectrum, serine protease plasmin. uPA is secreted as an inactive single-chain proenzyme by many different cell types and exists in a soluble or cell-associated form by binding to a specific membrane uPA receptor (uPAR) [2,3]. The uPA is involved in many physiological functions and, along with members of the matrix metalloproteinases (MMPs) family; it has been implicated in cancer invasion and metastatization [4–6]. Besides the proteolytic function, upon binding to uPAR, uPA is involved in initiating versatile intracellular signal pathways that regulate cell proliferation, adhesion, and migration through its interaction with various integrins and vitronectin [7]. Urokinase is implicated in a large number of malignancies, e.g. cancers of breast, lung, bladder, cervix, kidney, stomach and brain [8,9]. Also, the expression of urokinase is associated with tumor growth, invasion and may be a useful prognostic factor for hepatocellular carcinoma [10]. The role of uPA in human cancer progression is further supported by clinical evidences demonstrating that high tissue levels of its components correlate with a poor prognosis in different types of cancer as breast, gastrointestinal cancers [11].

On the other hand, the chemistry of cyclic and acyclic nicotinonitrile nucleosides has attracted attention during the last few decades because of its interesting pharmacological activities as antiviral [12], antitumor [13], antibacterial [14,15], anticancer [16,17] and other biological activity [18–24]. In the same direction and in continuation of our previous work for the synthesis of different nucleosides [25–27], to find more potent and selective

* Corresponding author. Tel.: +20 (2)7617590; fax: +20 20337 0931.
E-mail address: ahshamroukh@yahoo.com (A.H. Shamroukh).

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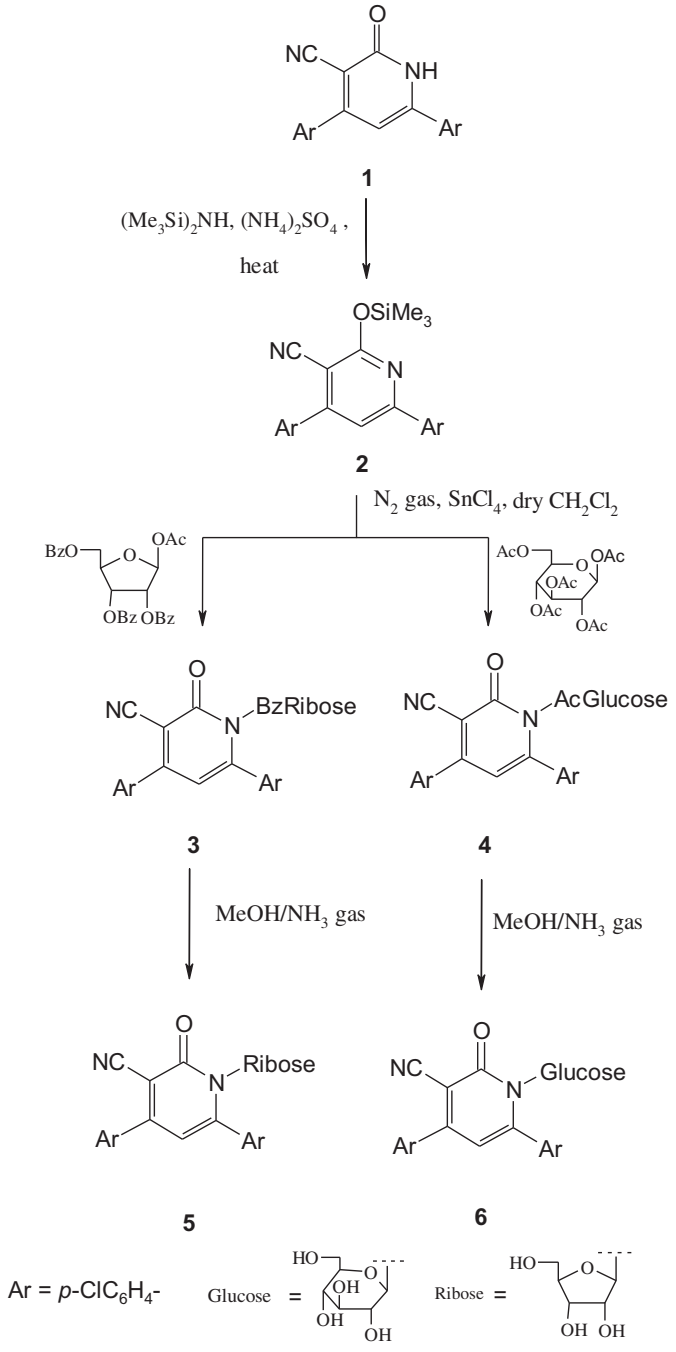
anticancer compounds, we synthesized a series of cyclic nucleosides of pyridine derivatives.

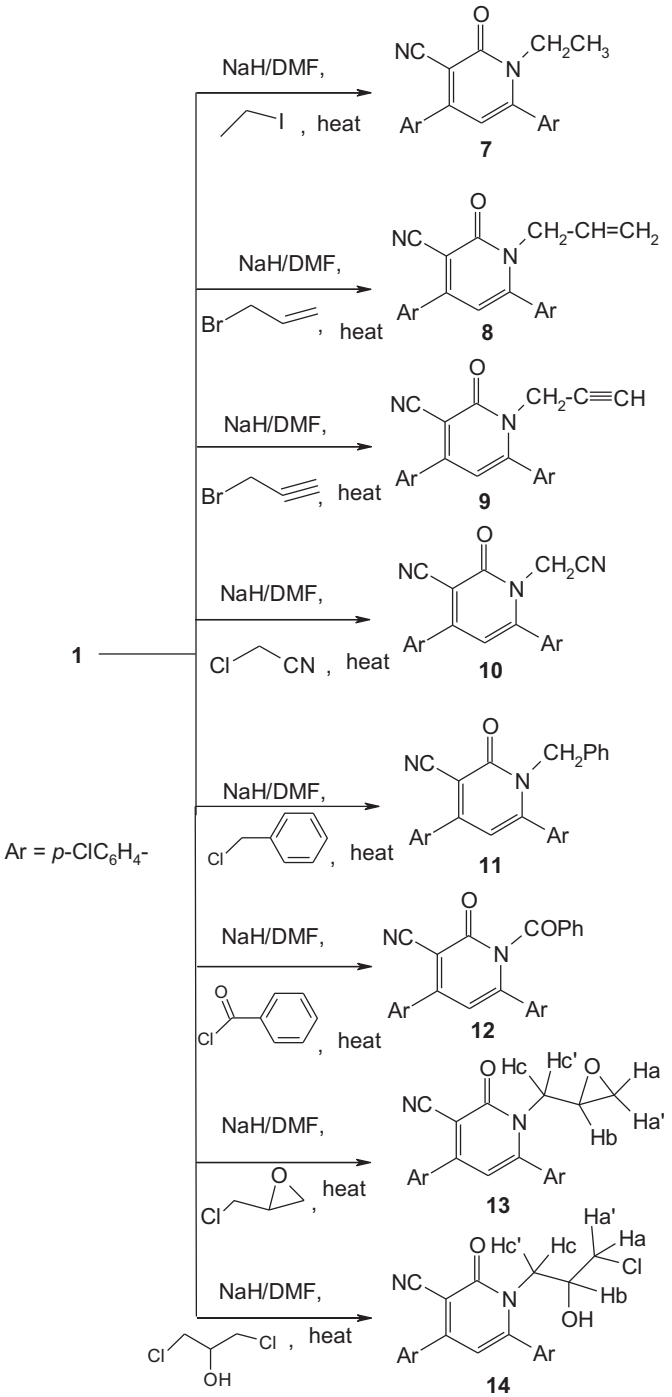
2. Results and discussion

2.1. Chemistry

Heating of 4,6-bis-(4-chloro-phenyl)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (**1**) [26] with hexamethyldisilazane (HMDS) in the presence of ammonium sulfate gave the silyloxypyridine derivative **2**, which was subsequently treated with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of $SnCl_4$ according to the method of Niedballa and Vorbrüggen [28] to afford the corresponding *N*-riboside **3** (Scheme 1). The ^{1}H NMR spectrum of compound **3** showed a doublet at δ 6.05 ppm ($J_{1',2'}$ = 4.30 Hz) assigned to the anomeric proton indicating the β-configuration [27,29] and the other sugar protons resonate at δ 3.37–3.55 (m, 1H, 4′-H); 4.43–4.76 (m, 4H, 2′-H, 3′-H, 5′-H_2). Similarly, when the silyloxypyridine derivative **2** was treated with β-D-glycopyranose pentaacetate in the presence of $SnCl_4$, it afforded the corresponding *N*-glycoside **4**. The ^{1}H NMR spectrum of compound **4** showed a doublet at 5.26 ppm ($J_{1',2'}$ = 10.40 Hz) assigned to the anomeric proton of the glucose moiety with a diaxial orientation of H-1′ and H-2′ indicating the β-configuration. The other protons of the glucopyranose ring resonate at 3.91–4.09 (m, 2H, 6′-H2); 4.26–4.69



Scheme 1. Synthesis of compounds **2**–**6**.



Scheme 2. Synthesis of compounds **7**–**14**.