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Original article

Structure–activity relationships of 2′-modified-4′-selenoarabinofuranosyl-pyrimidines as anticancer agents

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ABSTRACT

Based on the potent anticancer activity of the D-arabino-configured cytosine nucleoside ara-C, novel 2′-substituted-4′-selenoarabinofuranosyl pyrimidines **3a**–**3u**, comprising azido, fluoro, and hydroxyl substituents at C-2′ were designed, synthesized, and evaluated for anticancer activity. The 2′-azido group was stereoselectively introduced by the Mitsunobu reaction using diphenylphosphoryl azide (DPPA), and the 2′-fluoro group was stereoselectively introduced through the double inversions of stereochemistry via the episelenium intermediate, which was formed by the participation of the selenium atom. Among the compounds tested, the 2′-fluoro derivative **3t** (X = NH_2, Y = H, R = F) was found to be the most potent anticancer agent and showed more potent anticancer activity than the control, ara-C in all tested human cancer cell lines (HCT116, A549, SNU638, T47D, and PC-3) except the leukemia cell lines (K562). The anticancer activity of the 2′-substituted-4′-selenonucleosides is in the following order: 2′-F > 2′-OH > 2′-N_3.

1. Introduction

DNA and RNA building blocks have long been regarded as valuable resources towards the development of therapeutically useful modified nucleosides. The major mechanism of action of these modified nucleosides for a variety of biological activities is to act as antimetabolites interfering with cellular or viral metabolism. Based on this mechanism, many anticancer or antiviral nucleosides have clinically been developed as antimetabolites [1].

Uridine (**1a**, X = OH) and cytidine (**1b**, X = NH_2) are essential RNA pyrimidine building blocks and have also been served as important templates for the development of new antiviral and anticancer agents. On the basis of the structure of these templates, modifications have largely been done on the 2′ or 3′ position and 2′-modified nucleosides generally showed better biological activities [2]. For example, 1-β-D-arabinofuranosyl cytosine (ara-C, **2**, X = NH_2, Y = O, R = OH) with an *arabino* configuration is one of the representative nucleosides and is being used clinically as an anticancer agent [3]. Its bioisosteric 2′-fluoro (Y = O, R = F) [4] and 2′-azido (Y = O, R = N_3) [5] analogues **2** also showed good antiviral or anticancer activities (Fig. 1).

On the basis of bioisosteric rationale, the corresponding 4′-methylene (carbocyclic) [6] and 4′-thionucleosides [7] **2** were also synthesized and reported to show various biological activities. Although they possessed better enzymatic and chemical stability than the corresponding 4′-oxonucleosides, only a few nucleosides showed attractive biological activity. Thus, the discovery of a new template to replace known modified nucleosides has highly been desirable.

Recently, the 4′-selenonucleoside has been reported as the next generation nucleoside for the development of new therapeutic agents as well as new biological tools [8]. Among these, the 4′-seleno analogue **3** (X = NH_2, Y = H, R = F) of 2′-fluoro-ara C showed potent anticancer activity in a panel of human tumor cell lines [8c]. Thus, based on these findings, it was of great interest to study the structure–activity relationship of the 4′-selenoarabinofuranosyl-pyrimidines **3** substituted with bioisosteric azido, fluoro, or hydroxyl group at the 2′ position as anticancer agents. The 2′-azido group was stereoselectively introduced by the Mitsunobu reaction using diphenylphosphoryl azide (DPPA) with inversion of

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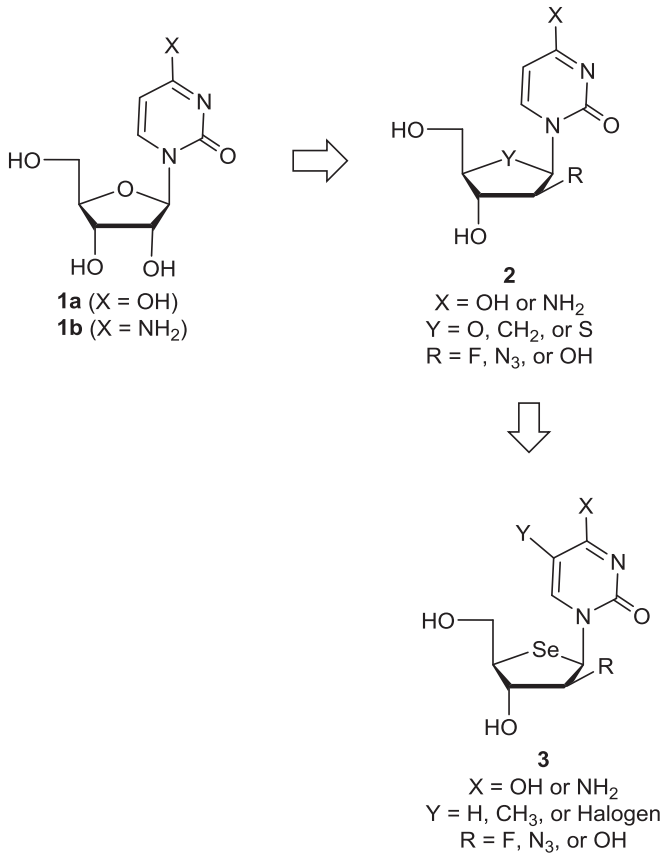


Fig. 1. The rationale for the design of the target nucleoside **3**.

configuration and the 2′-fluoro group was stereoselectively introduced by *N*,*N*-diethylaminosulfur trifluoride (DAST) reaction via an episelenium ion intermediate through double inversions of configuration. In this article, we report the full accounts of the structure–activity relationships of 2′-modified-4′-selenoarabibofuranosyl pyrimidines **3** as anticancer agents.

2. Results and discussion

2.1. Chemistry

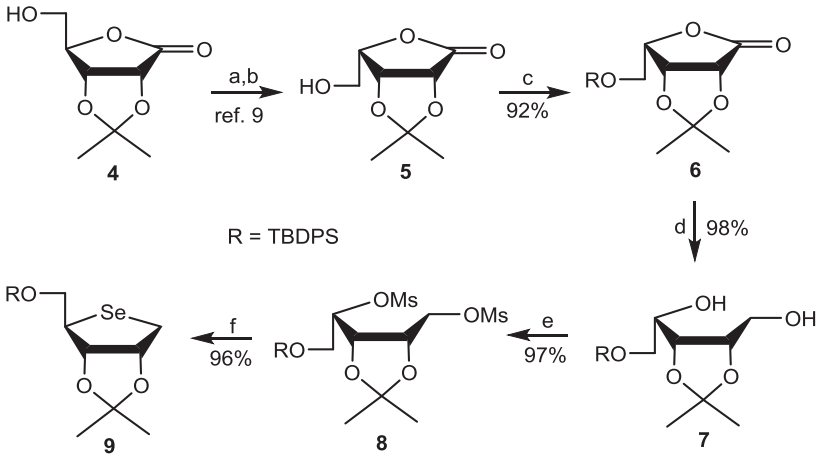
For the synthesis of the target nucleosides, the key intermediate 4-selenosugar **9** was first synthesized from D-ribose according to our previously reported procedure (Scheme 1) [8e]. Commercially available 2,3-*O*-isopropylidene-D-ribonolactone (**4**) was converted to known 2,3-*O*-isopropylidene-L-lyxonolactone (**5**) in two steps [9]. Protection of the hydroxyl group of **5** with TBDPS group gave **6** which was treated with $NaBH_4$ to give diol **7**. Treatment of **7** with MsCl followed by the treatment with the resulting dimesylate **8** with Na_2Se (prepared *in situ* with Se and $NaBH_4$), afforded the 4-selenosugar **9** [8e] in excellent yield.

The key intermediate **9** was first converted to the key precursors, 4′-selenoribofuranosyl pyrimidines **12a**–**12f** for the modification of the 2′-position, using a Pummerer type condensation reaction as a key step, as shown in Scheme 2 [8].

Oxidation of **9** with *m*-CPBA gave the glycosyl donor, 4-selenoxide **10** [8a,8e]. The Pummerer-type condensation of **10** with various pyrimidine bases such as uracil, thymine, and 5-halouracils in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and Et_3N yielded the β-anomers **11a**–**11f**, exclusively. The anomeric configurations of **11a**–**11f** were easily confirmed by the NOE experiment between 1′-H and 4′-H. Removal of the protecting groups of **11a**–**11f** with 50% TFA yielded the 4′-selenoribofuranosyl pyrimidines **12a**–**12f**.

For the synthesis of the 2′-azido-4′-selenoarabinofuranosyl pyrimidines **3a**–**3f**, the ribo analogues **12a**–**12f** were treated with $TIPDSCl_2$ to give the 3′,5′-*O*-TIPDS protected nucleosides **13a**–**13f**, respectively (Scheme 3).

To prevent the formation of *O*2,2′-anhydro nucleosides during the Mitsunobu reaction with diphenylphosphoryl azide (DPPA), the N-3 position of **13a**–**13f** was selectively protected with electron-withdrawing benzoyl group in the presence of the 2′-hydroxyl group to give **14a**–**14f**. Treatment of **14a**–**14f** with DPPA under the Mitsunobu conditions afforded the desired 2′-azidoarabinofuranosyl derivatives **15a**–**15f** with inversion of stereochemistry, respectively. The removal of TIPDS groups of **15a**–**15f** with $3HF{\cdot}Et_3N$ yielded **16a**–**16f**, which were treated with methanolic



Reagent and conditions: a) MsCl, TEA, MC, -20 °C to rt, 2 h; b) KOH, H_2O, rt, 15 h; c) TBDPSCl, Et_3N, DMAP, MC, rt, 3 h; d) $NaBH_4$, MeOH, 0 °C to rt, 3 h; e) MsCl, Et_3N, DMAP, MC, 0 °C, 30 min; f) Se, $NaBH_4$, MeOH, THF, 70 °C, 15 h.

Scheme 1.