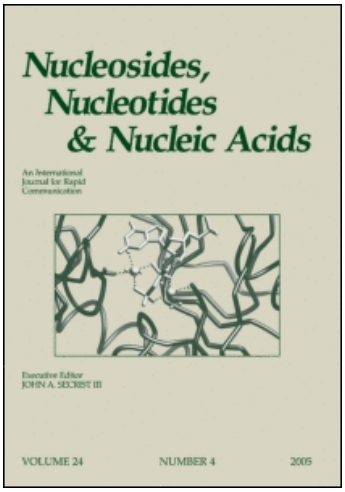

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 4'-C-HYDROXYMETHYL-2'-FLUORO-D-ARABINOFURANOSYLPURINE NUCLEOSIDES

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 4′-C-HYDROXYMETHYL-2′-FLUORO-D-ARABINOFURANOSYLPURINE NUCLEOSIDES

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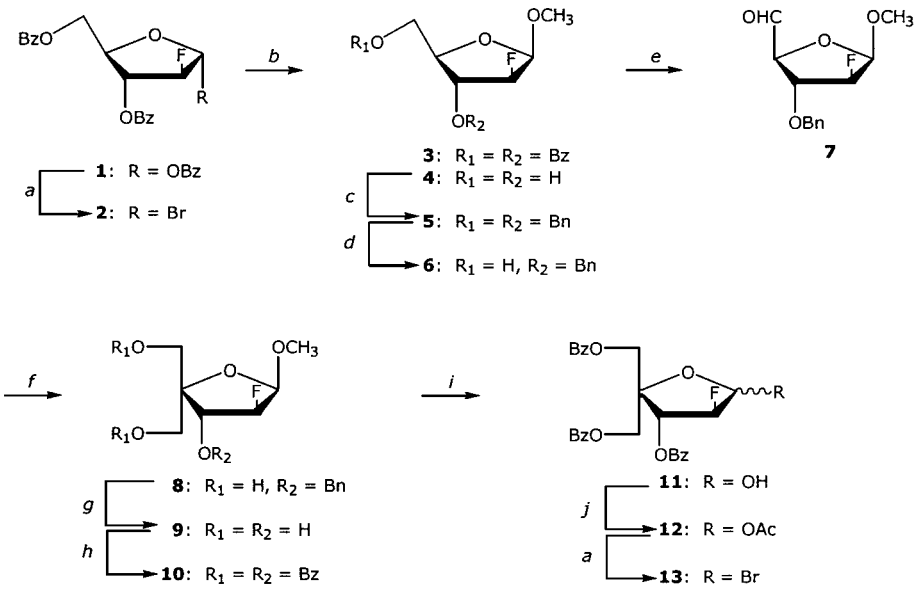
ABSTRACT

A series of 4′-C-hydroxymethyl-2′-fluoro-D-arabinofuranosylpurine nucleosides was prepared and evaluated for cytotoxicity in human tumor cell lines. A convenient synthesis of the carbohydrate precursor 4-C-hydroxymethyl-3,5-di-O-benzoyl-2-fluoro-α-D-arabinofuranosyl bromide (**13**) was developed. Coupling of **13** with the sodium salt of 2,6-dichloropurine led to five target purine nucleosides.

In recent years, synthesis of new nucleosides has gained a lot of attention because of their utility as anticancer and as antiviral agents. Lately, there has been interest in 4′-substituted nucleosides as potential anticancer agents (1–5). It has been shown that such a modification can be tolerated and that the structure either enhances or retains the biological activity (2,3,5). This suggests that metabolism to the triphosphate is likely occurring. Interest in the synthesis and anticancer activity of new nucleosides has continued in recent years in our laboratories. Fludarabine phosphate, which was developed in our laboratory (6), has been approved by FDA for the treatment of refractory lymphocytic leukemia. Clofarabine (2-chloro-2′-fluoroara-A), also developed in our laboratory (7), is currently in clinical trials.

*Corresponding author.



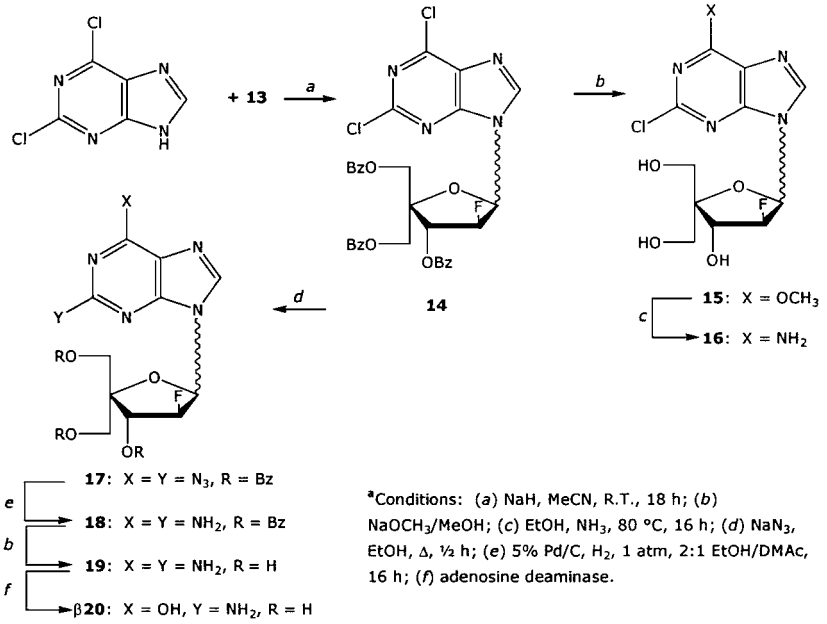
[a]Conditions: (a) HBr/HOAc; (b) $NaOCH_3$/MeOH, 0°C then R.T.; (c) BnCl/KOH, THF; (d) 10% Pd/C, H_2, 50 psi, 1:1 MeOH/HOAc, pyridine; (e) PCC, 4A sieve, CH_2Cl_2; (f) 37% HCHO, NaOH, THF/H_2O; (g) 10% Pd/C, H_2, 50 psi, 1:1 MeOH/HOAc; (h) BzCl/pyridine; (i) TFA/H_2O, 55°C; (j) Ac_2O/pyridine.

Scheme 1.

Based upon its structure, with a 2′-fluorine in the *arabino* configuration, we initiated a program to systematically examine other carbohydrate modifications, especially at the 4′-position.

Initially, we focused our attention on the synthesis of the 4′-C-hydroxymethyl analogue of clofarabine and related compounds. Very few 4′-C-hydroxymethyl nucleosides have been reported in the literature, and most of the work has been limited to the synthesis of ribonucleosides and 2′-deoxynucleosides (8,9). No 4′-C-hydroxymethyl-arabino or 2′-fluoroarabinonucleosides have been reported in the literature. Towards that goal, we developed a route to a 4-C-hydroxymethyl-2-fluoroarabinofuranose derivative and utilized it in the synthesis of certain purine nucleosides containing that carbohydrate moiety.

Our route (Scheme 1) to this series was accomplished by preparing the 4-C-hydroxymethyl derivative **13** of α-bromo sugar **2** (10). Compound **2** was converted to **3** by the careful addition of $NaOCH_3$ in MeOH at 0°C. When bromo displacement was complete, more $NaOCH_3$ was added with the reaction continuing at room temperature to provide deprotected **4**. Benzylation of **4** to **5** followed by the selective removal of the primary benzyl ether (11) gave alcohol **6**. A molecular sieve catalyzed pyridinium chlorochromate oxidation (12) of **6** to aldehyde **7** followed by



Scheme 2.

reaction with formaldehyde in base (8) led to diol **8**. The remaining benzyl group was removed, and the product **9** was benzoylated to give **10**. Acid hydrolysis of the methyl group of **10** provided **11** as an anomeric mixture (2α:1β), which was acetylated yielding **12** (3α:1β) (13). Reaction of **12** with excess HBr in acetic acid gave the target 4-C-hydroxymethyl bromo sugar **13** (6α:1β) suitable for subsequent coupling reactions.

Our route (Scheme 2) to the purine nucleosides began with the coupling of 2,6-dichloropurine and **13** using the sodium salt glycosylation procedure (14) to give an 82% total yield of 9-isomers **14**. Treatment of **14** with $NaOCH_3$/MeOH removed the benzoyl groups and replaced the 6-Cl with $-OCH_3$ to give **15**. Preparative TLC resolved **15**β and **15**α, which were reacted separately with ethanolic ammonia at 80°C to provide **16**β and **16**α. Conversion of **14** to **17** was done with NaN_3 in refluxing EtOH. When the reaction was cooled, **17**β crystallized and **17**α remained in solution. After isolation, the separate anomers were hydrogenated to give intermediates **18**β and **18**α. Deprotection with $NaOCH_3$/MeOH led to **19**β and **19**α. Deamination of **19**β occurred slowly with adenosine deaminase to produce guanosine analogue **20**β. Under the same conditions, **19**α failed to deaminate.

The 4′-C-hydroxymethyl nucleosides (**16**α, **16**β, **19**α, **19**β, **20**β) were examined *in vitro* against a spectrum of human tumor systems. Only clofarabine analogue (**16**β) showed slight cytotoxicity (IC_{50} ~13 μM) in CCRF-CEM leukemia cells.

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