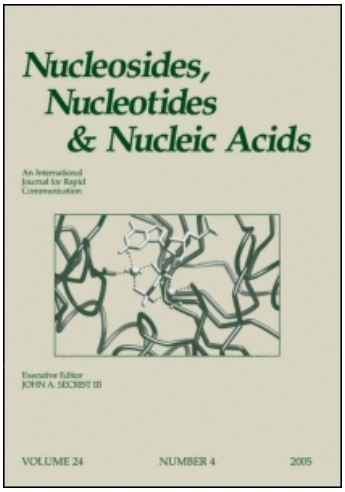

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8-Substituted Purine Ribosides: Synthesis and Biological Activity

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8-SUBSTITUTED PURINE RIBOSIDES: SYNTHESIS AND BIOLOGICAL ACTIVITY

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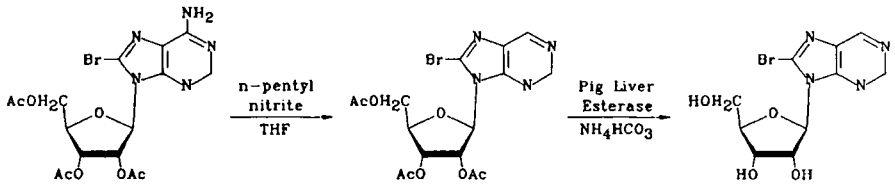
Summary: The syntheses of a series of 8-substituted purine ribofuranosides are described. Reductive deamination of 8-bromoadenosine triacetate (1) provides the key intermediate (2) for subsequent displacement reactions. Four compounds show significant activity in two cell culture screens.

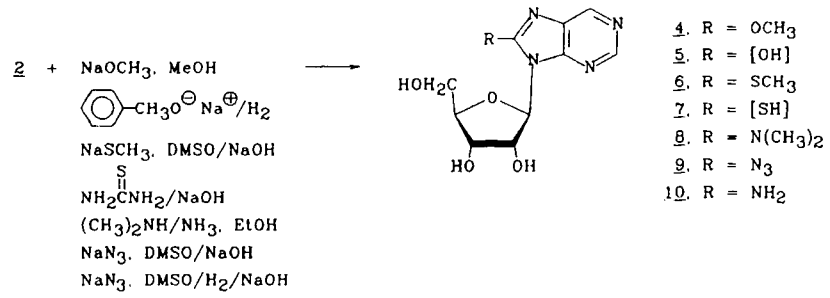
As a part of our program to design biologically active nucleosides with altered metabolism, we previously prepared 8-amino-6-fluoro-β-D-ribofuranosylpurine.[1,2] This cytotoxic compound is a substrate for adenosine kinase and adenosine deaminase, and the monophosphate is a substrate for AMP-deaminase. The products formed by the action of the deaminases, 8-aminoinosine and 8-amino-IMP, are not significant contributors to the cytotoxicity of the compound. To reduce the loss of potency caused by the two deaminases, we prepared and tested a series of 8-substituted purine ribosides with hydrogen in the 6-position.

8-Bromoadenosine[3] was acetylated[4] and deaminated[5] to give the crystalline intermediate 2 that was used in subsequent displacement reactions.[6,7]

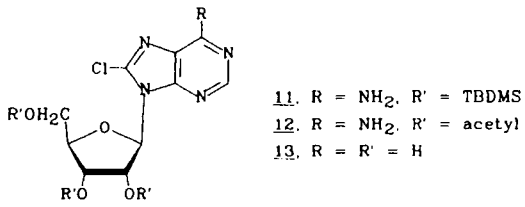


1 2 3

Treatment of 2 with $NaOCH_3$ in MeOH gave 4 in one step. Treatment of 2 with sodium in benzyl alcohol gave 8-benzyloxypurine riboside that was hydrogenated at atmospheric pressure to give 5. Reaction of 2 with $NaSCH_3$ in DMSO gave 8-methylthiopurine riboside triacetate. The protecting groups were removed with NaOH (3 eq.) in 1:1 MeCN:H_2O to give 6. Reaction of 2 with thiourea in EtOH followed by similar deprotection gave pure 8-thiopurine riboside (7). Treatment of 2 with dimethylamine in EtOH followed by deprotection gave 8. For compounds 4→8, the yield from 2 averaged 45%.



The most rapid displacement reaction in the series was observed when **2** was treated with NaN_3 in DMSO. The resulting triacetate was deprotected to give **9** in 35% yield. When **2** was treated with NaN_3, DMSO followed by hydrogenolysis and deprotection, a good yield of **10** was obtained.



Of the entire series, the 8-halo compounds were the most difficult to make. The 8-bromo (**3**) and 8-chloro (**13**) were prepared successfully, but all attempts to obtain the 8-fluoro so far have failed. In the case of the 8-bromo, conventional methods for deprotection of **2** resulted in bromine displacement or incomplete deacetylation. Treatment of **2** with pig liver esterase[3] gave **3** in 39% yield. A variety of reaction conditions failed to produce the 8-chloro compound cleanly from the 8-bromo. Consequently, we elected to explore an alternate route. Compound **11** was prepared,[8] and the TBDMS groups were replaced with acetyl groups using standard conditions.[4] We were able to prepare **13** from **12** by a route identical to that used for **3**.

Results from H.Ep.-2 and L1210 cell culture screens show some interesting structure-activity relationships. Compounds **4**, **5**, **7**, and **8** show little or no cytotoxicity. But compounds **9**, **10**, **3**, and **13** exhibit high cytotoxicities in both cell lines. We can presume that these four are substrates for adenosine kinase and are phosphorylated to the triphosphate level. We examined **10** for phosphorylation in L1210 cells and found conversion in large amount to a triphosphate.

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