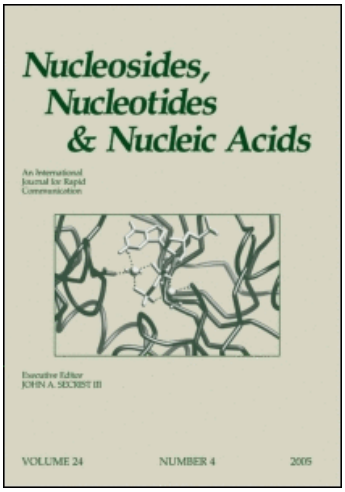

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Approaches to New Dideoxynucleosides

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APPROACHES TO NEW DIDEOXYNUCLEOSIDES

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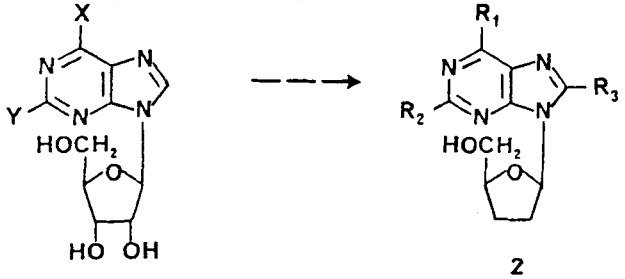
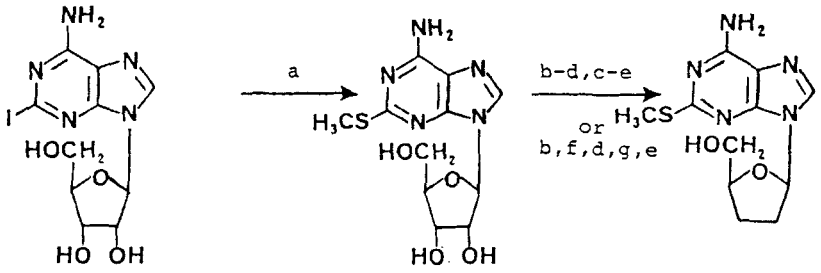
Abstract. The syntheses of novel analogues of purine dideoxynucleosides of anti-HIV potential are described. The synthetic approach involved strategic modification of both the carbohydrate and base components of natural and synthetic ribonucleosides.

Discovery of the anti-HIV activity of dideoxynucleosides has stimulated considerable interest both in the synthesis of new compounds of this family and in the development of efficient methodologies for their preparation.[1-8] The impetus for most of this work is the expectation that some of these compounds may have anti-HIV activity and/or would be useful as biological probes in the study of both viral and mammalian enzymes. In a program in our laboratory directed at the synthesis of novel dideoxynucleosides with potential anti-HIV activity, we have synthesized a number of novel analogues of purine dideoxynucleosides involving modifications in both the carbohydrate and base moieties.

The major class of compounds investigated can be represented by the generalized structure shown in **2**. They were synthesized through multi-step syntheses starting from either guanosine or adenosine (**1**). Key synthetic

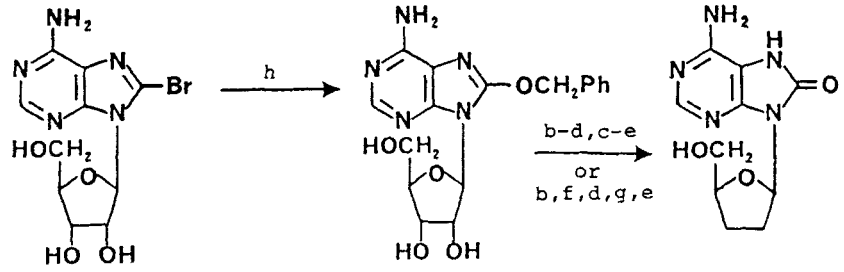


1 **2**



(a) $(CH_3S)_2$, CH_3CN, hν; (b) TBDMSiCl, DMAP, $(Et)_3N$, DMF, CH_2Cl_2; (c) $(Im)_2CS$, DMF; (d) Bu_3SnH, AIBN, toluene, Δ; (e) Et_4NF, CH_3CN; (f) CS_2, NaOH, CH_3I, DMSO; (g) H_2, Pd/C, C_2H_5OH.

Scheme 1



(b-g as above), (h) $PhCH_2ONa$, DMF, Δ.

Scheme 2

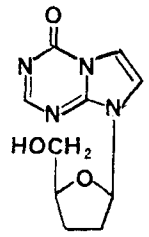
methodologies used were selective silylation, radical dideoxygenation, metal-mediated, photochemical and thermal functionalizations, and metal-catalyzed hydrogenolysis.[9-11] The syntheses can be illustrated with two cases, 2-thiomethyl-2',3'-dideoxyadenosine (Scheme 1) and 8-hydroxy-2',3'-dideoxyadenosine (Scheme 2).

8-Hydroxy-2',3'-dideoxyadenosine, which shows some anti-HIV activity, is very stable to glycosidic bond hydrolysis unlike many other dideoxynucleosides.[12] Spectral data, particularly its high-field ^{13}C NMR and FTIR, suggest that this molecule exists almost exclusively in the

lactam (urea) form and that its preferred conformation is syn (chemical shift difference C2'- C3'= 1 ppm).

Most of the base-modified dideoxyadenosines **2** were either poor substrates for adenosine deaminase (e.g. 8-hydroxy analogue) or were totally resistant to deamination by this enzyme (e.g. 2-iodo, 2-cyano, 2-thiomethyl, 2-ethyl). The 2-substituted dideoxyadenosine analogues were also examined for inhibitor activity against this enzyme and were found to be competitive inhibitors (K_i = 10^{-4} to 10^{-5}).

Approaches to the synthesis of isosteres of 2',3'-dideoxyinosine involving ring modification (C and N interchange) at the 3, 5 and 7 positions are also being investigated. A representative example is shown in structure **3**. The base isostere for the glycosylation reaction was synthesized from 5-azacytosine by reaction with chloroacetaldehyde.[13,14] Differentiation of the structures of the two nucleosides obtained on glycosylation was made through correlation with UV and high-field NMR (NOESY) data.



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