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Nucleosides, Nucleotides and Nucleic Acids

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SYNTHESIS OF 5'-THIOALKYL, SULFOXIDE AND SULFONE PYRIMIDINE NUCLEOSIDES

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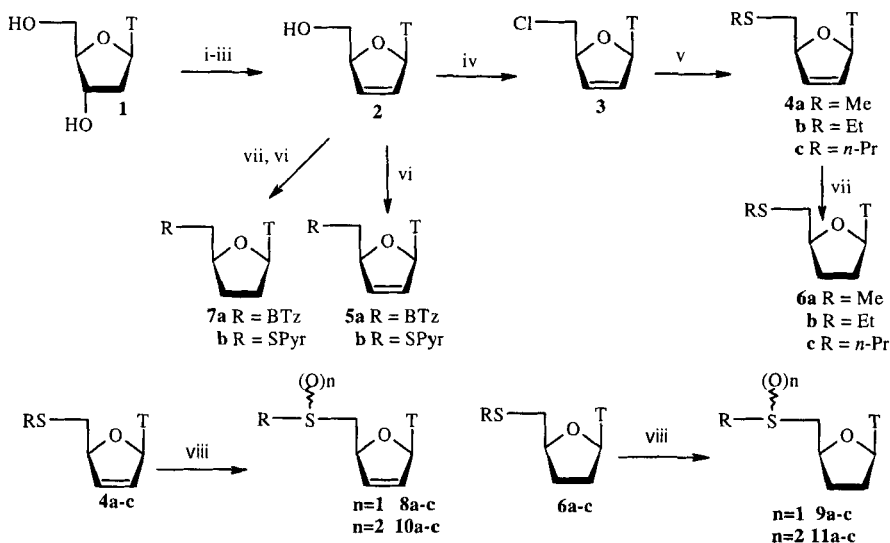
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ABSTRACT : The preparation of 5'-thioalkyl, sulfoxide and sulfone pyrimidine nucleosides is [4-11] is described. The key steps of this synthesis are the nucleophilic displacements of a chlorine by a thioalkyl sodium salt or the direct introduction of the thioalkyl group under Mitsunobu conditions.

The thymidine 5'-monophosphate (TMP) which is required for cell proliferation is biosynthesized *via* an alternate route which involves a reaction catalyzed by thymidine kinase (TK). In neoplastic tissue and proliferating cells, the activity of this enzyme is elevated to a high level that permits this enzyme to play a major role in TMP production *in vivo*. Evidence indicates a direct correlation between TK content in tumor tissue and tumor growth rate.¹⁻³ Several 5'-alkylthionucleosides have been synthesized and 5'-(ethylthio)-5'-deoxythymidine was found to be a noncompetitive inhibitor of the enzyme,⁴ and to exhibit anti-tumor activities. As part of our drug discovery program, we report herein the synthesis of these 3'-deoxy-2',3'-didehydro- and 3'-deoxy-5'-alkylthio thymidines.⁵ Some 5'-alkylsulfone and sulfoxide analogues are also described as the change in lipophilicity associated with the oxidation state of the S-atom, and body distribution are not straightforward to predict.⁶

Our synthetic strategy to the 5'-alkylthionucleosides utilized the known compound 2',3'-didehydro-3'-deoxythymidine⁷ **2**, D4T (Scheme 1). Chlorination of **2** by SOCl₂ yielded the key intermediate 5'-chloro analogue **3** which by treatment with an excess of sodium methylthioate, ethylthioate or *n*-propylthioate gave respectively the 5'-*S*-methyl-5'-thio-D4T **4a**, 5'-*S*-ethyl-5'-thio analogue **4b** and 5'-*S*-*n*-propyl-5'-thio analogue **4c**. The hydrogenation of **4a-c** yielded the 3'-deoxy-5'-alkylthio-thymidine **6a-c** respectively. D4T **2** was also directly reacted with thioheterocycles under

Mitsunobu conditions to yield **5a** and **5b**, respectively. The oxidation of compounds **4a-c** and **6a-c** with 0.5 eq of MMPP gave the diastereomeric sulfoxides **8a-c** and **9a-c** respectively, and sulfone derivatives **10a-c** and **11a-c** when treated with one equivalent MMPP.



Scheme 1. Reagents: (i) MsCl , CH_2Cl_2 , Et_3N ; (ii) NaOH 1 N, reflux; (iii) tBuOK , DMSO then toluene; (iv) SOCl_2 , HMPA; (v) RSH , NaH , THF; (vi) RSH , PPh_3 , DIAD, toluene or pyridine, reflux; (vii) H_2 Pd/C 40 psi; (viii) (for $n=1$) MMPP 0.5 eq, CH_2Cl_2 or (for $n=2$) MMPP 1 eq, CH_2Cl_2 .

In summary, the synthesis of 3'-deoxy-2',3'-didehydrothymidine derived 5'-alkylsulfides **4a-c**, **5a,b**, **6a-c**, **7a,b** and the sulfoxides **8a-c**, **9a-c** and sulfones **10a-c**, **11a-c** derivatives has been accomplished.⁸ The anti-tumoral activities of these compounds were evaluated on the inhibition of L1210 cells proliferation. However, these compounds did not show any significant activity ($\text{IC}_{50} > 100$ mM).

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