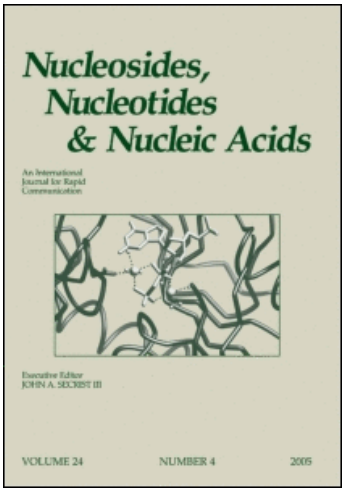


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of 5'-Thioalkyl, Sulfoxide and Sulfone Pyrimidine Nucleosides

L. A. Agrofoglio[a]; F. Girard[a]; F. Fleury[a]; S. Léonce[b]
[a] associé au CNRS, Faculté des Sciences, I. C. O. A., Orléans, France [b] Institut de Recherche Servier, Suresnes, France

To cite this Article Agrofoglio, L. A. , Girard, F. , Fleury, F. and Léonce, S.(1999) 'Synthesis of 5'-Thioalkyl, Sulfoxide and Sulfone Pyrimidine Nucleosides', Nucleosides, Nucleotides and Nucleic Acids, 18: 4, 599 — 600
To link to this Article: DOI: 10.1080/15257779908041508
URL: http://dx.doi.org/10.1080/15257779908041508

NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 599–600 (1999)

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

L. A. Agrofoglio,[†]* F. Girard,[†] F. Fleury,[†] S. Léonce,[‡]

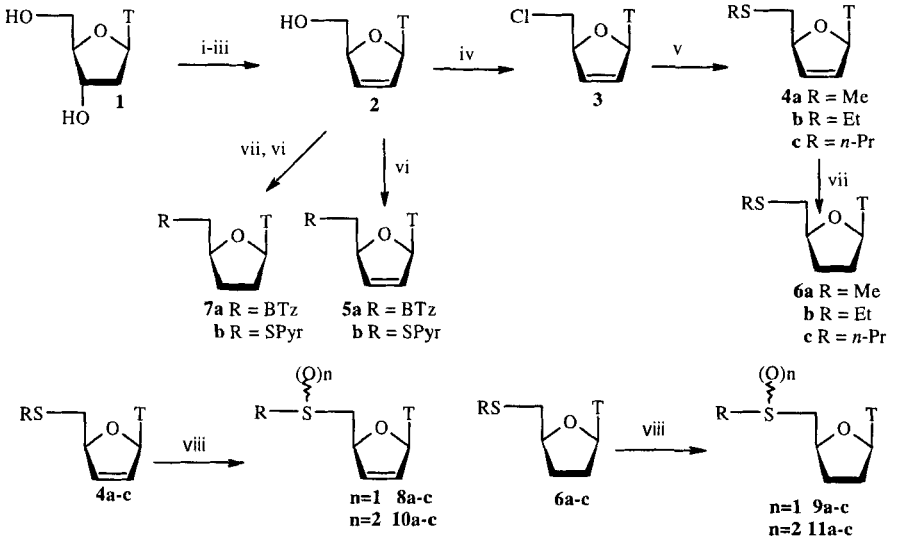
[†]) I.C.O.A., associé au CNRS, Faculté des Sciences, 45067 Orléans-France.
[‡]) Institut de Recherche Servier, 11 rue des Moulineaux, 92150 Suresnes-France.

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'-deoxythymidine[7] **2**, D4T (Scheme 1). Chlorination of **2** by $SOCl_2$ 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 (IC_{50} > 100 mM).

Acknowledgments: This research was supported by grant from the Fondation pour la Recherche Médicale.

References :

1. Attardi, B.; Attardi, G. *Proc. Natl. Acad. Sci. USA* **1972**, *69*, 2874-2878.
2. Taylor, A. T.; Stafford, M. A.; Jones, O. W. *J. Biol. Chem.* **1972**, *247*, 1930-1935.
3. Herzfeld, A.; Raper, S. M.; Gore, I. *Pediatr. Res.* **1980**, *14*, 1304-1310.
4. (a) Hampton, A.; Chawla, R. R.; Kappler, F. *J. Med. Chem.* **1982**, *25*, 644-649.
   (b) Hampton, A.; Kappler, F.; Chawla, R. R. *J. Med. Chem.* **1979**, *22*, 621-631.
5. Girard, F.; Léonce, S.; Agrofoglio, L. A. *Tetrahedron Lett.* **1997**, *38*, 7535-7538.
6. (a) Testa, B. in « The Metabolism of Drugs and Other Xenobiotics, Biochemistry of Redox Reactions », Academic Press, London, **1995**; pp. 434-437.
   (b) Caron, G.; Gaillard, P.; Carrupt, P.-A.; Testa, B. *Helv. Chim. Acta* **1997**, *80*, 449-462.
7. Horwitz, J. P.; Chua, J.; Da Rooge, M. A.; Noel, M.; Klundt, I. L. *J. Org. Chem.* **1966**, *31*, 205-211.
8. All compounds were fully characterized by NMR, UV, MS and elemental analysis.