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Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

SYNTHESIS AND ANTIPROLIFERATIVE ACTIVITY OF SOME 4'-C-HYDROXYMETHYL- α - AND - β -D-ARABINO-PENTOFURANOSYL PYRIMIDINE NUCLEOSIDES

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Online publication date: 31 March 2001

To cite this Article Griffon, Jean-François, Montgomery, John A. and Secrist III, John A. (2001) 'SYNTHESIS AND ANTIPROLIFERATIVE ACTIVITY OF SOME 4'-C-HYDROXYMETHYL- α - AND - β -D-ARABINO-PENTOFURANOSYL PYRIMIDINE NUCLEOSIDES', *Nucleosides, Nucleotides and Nucleic Acids*, 20: 4, 649 – 652

To link to this Article: DOI: 10.1081/NCN-100002342

URL: <http://dx.doi.org/10.1081/NCN-100002342>

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**SYNTHESIS AND ANTIPROLIFERATIVE
ACTIVITY OF SOME 4'-C-HYDROXYMETHYL-
 α - AND - β -D-ARABINO-PENTOFURANOSYL
PYRIMIDINE NUCLEOSIDES**

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ABSTRACT

A suitably protected 4-C-hydroxymethyl-*arabino*-pentofuranose was prepared and condensed with the following nucleobases: uracil, 5-fluorouracil and thymine. The corresponding cytosine and 5-fluorocytosine derivatives have also been obtained respectively from the uracil and 5-fluorouracil nucleosides. Separation of the anomeric mixtures followed by deprotection afforded the target compounds that were found to be non-cytotoxic to CCRF-CEM leukemia cells.

In the search for new antineoplastic or antiviral agents, recent interest has been focused on 4' α -C-branched-chain sugar nucleosides: various 4' α -C-branched-chain 2'-deoxynucleosides, such as 4' α -C-methyl- (1–5), -fluoromethyl- (6), -cyano- (1,7) -ethynyl- (1,3,8) and -ethenyl (1) -2'-deoxycytidine have been reported to have potent antileukemic activity in vitro. Two 4' α -C-branched *arabino*-pentofuranonucleosides, 1-(4 α -C-methyl- (4,5) and -fluoromethyl (1) - β -D-*arabino*-pentofuranosyl)cytosine have also exhibited a significant cytotoxic effect on leukemia cells. Nevertheless, very few 4'-C-hydroxymethyl have been reported in the literature and the authors have limited their work to the synthesis of β -D-xylo-, ribo- and -2'-deoxyribo nucleosides (9,10). 4'-C-hydroxymethyl analogues of AZT, d4T, and

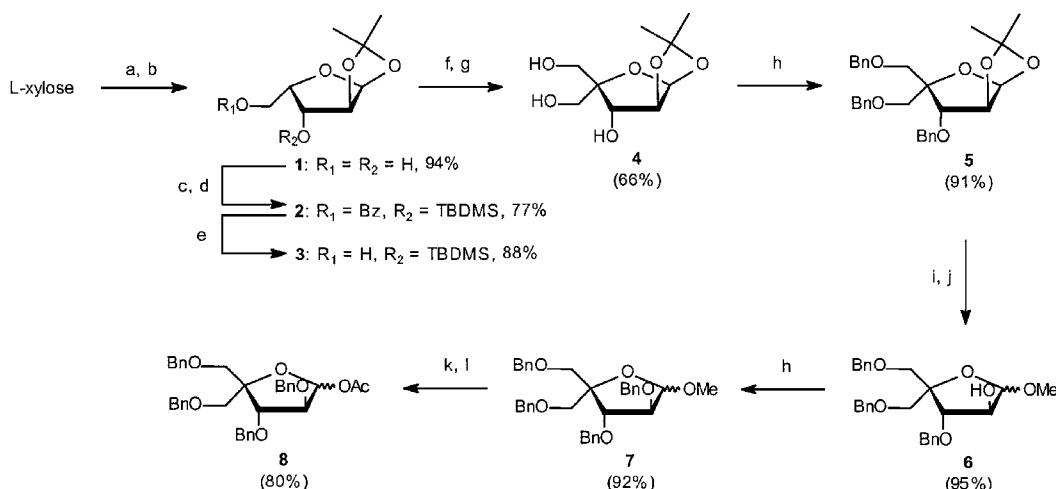
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ddT have also been reported (7,12). Based on these considerations, a series of 4'-C-hydroxymethyl- α - and - β -D-*arabino*-pentofuranosyl pyrimidine nucleosides has been prepared and evaluated as potential anticancer agents.

CHEMISTRY

The suitably protected 4-C-hydroxymethyl-*arabino*-pentofuranose **8** was prepared in 13 steps from L-xylose (Scheme 1). Selective benzylation of the primary hydroxyl group of the 1,2-*O*-isopropylidene intermediate **1**, followed by silylation of the 3-hydroxyl group, and debenzoylation gave **3**. Oxidation of the 5 position of **3** under Pfitzner-Moffatt conditions afforded a 5-aldehydo pentofuranose intermediate which was subsequently subjected to an aldol condensation-crossed Cannizzaro reaction sequence in the presence of formaldehyde in aqueous sodium hydroxide (10,12). The introduction of the C-4 linked hydroxymethyl in basic conditions also resulted in the deprotection of the 3-*O*-*t*-butyldimethylsilyl group (1), but without any epimerisation at the C-3 (13). The 3,5 and 6-hydroxyl groups of **4** were then benzylated to afford **5**. Cleavage of the 1,2-*O*-isopropylidene group followed by methylation of the anomeric hydroxyl led to the methyl glycoside **6**. The 2-hydroxyl group of **6** was benzylated to give the tetrabenzylated derivative **7**. Compound **8** was finally obtained after hydrolysis of the methyl glycoside **7** and acetylation of the anomeric hydroxyl.

Condensation of **8** respectively with silylated uracil, thymine or 5-fluorouracil afforded the fully corresponding benzylated nucleosides as α : β mixtures, separable by silica gel chromatography. Conversion of **9** α , β and **11** α , β into the corresponding cytosine and 5-fluorocytosine nucleosides **15** α , β and **16** α , β was carried



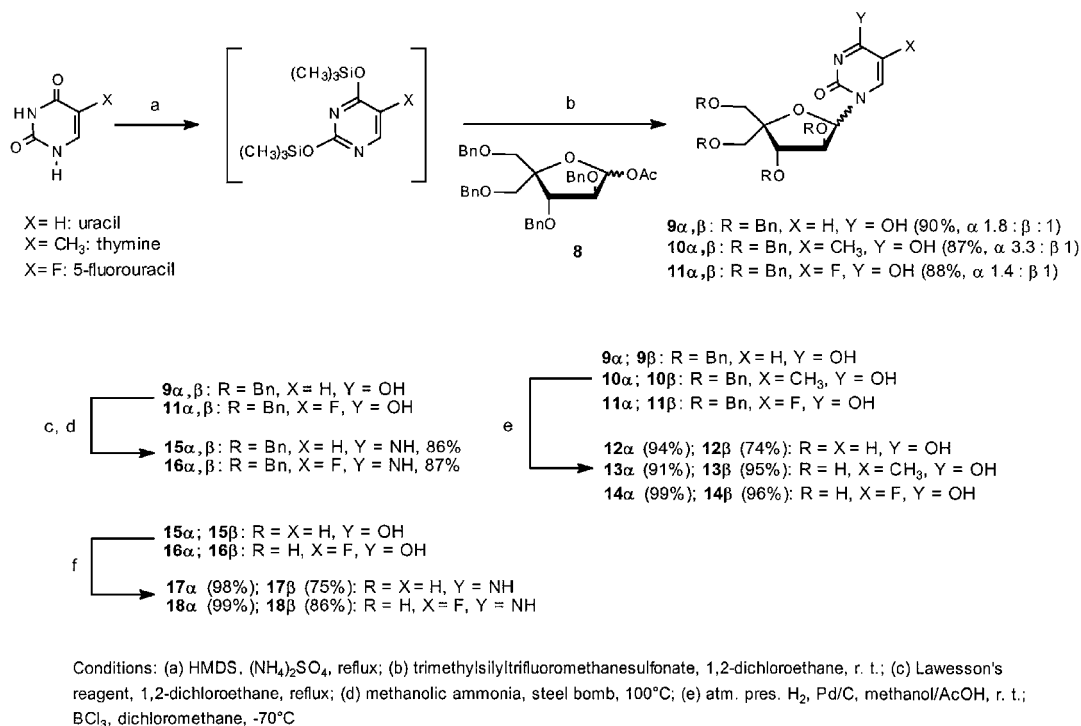
Conditions: (a) Me_2CO , H_2SO_4 , $CuSO_4$; (b) 0.2% HCl ; (c) C_6H_5COCl , pyridine, $0^\circ C$; (d) $TBDMSCl$, imidazole, pyridine, r. t.; (e) $MeONa$, $MeOH/toluene$; (f) $DMSO$, DCC , Cl_2CHCO_2H , benzene/pyridine, r. t.; (g) CH_2O , $NaOH$, $H_2O/dioxane$, r. t.; (h) $BnBr$, NaH , $Bu_4N^+I^-$, THF , r. t.; (i) 85% CH_3CO_2H , H_2SO_4 , r. t.; (j) $MeOH$, H_2SO_4 , r. t.; (k) 90% CF_3CO_2H , $5-15^\circ C$; (l) Ac_2O , pyridine, r. t.

Scheme 1.



4'-C-HYDROXYMETHYL PYRIMIDINE NUCLEOSIDES

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Scheme 2.

out *via* a treatment with Lawesson's reagent, which led to the 4-thioamide derivatives, followed by a treatment with methanolic ammonia at 100°C. Finally, benzyl ether protective groups were cleaved by catalytic hydrogenation or treatment with a boron trichloride solution to afford the target compounds **12–14α**, **12β–14β** and **17–18α**, **17–18β** (Scheme 2).

BIOLOGICAL EVALUATIONS

All the 4'-C-hydroxymethyl-*arabino*-pentofuranosyl pyrimidine nucleosides **12α**, **13α**, **14α**, **17α**, **18α** and **12β**, **13β**, **14β**, **17β**, **18β** were found to be non-cytotoxic to CCRF-CEM leukemia cell at the highest level tested (40 μg/ml).

ACKNOWLEDGMENT

The investigation was supported by the National Cancer Institute, National Institutes of Health (PO1-CA34200).



REFERENCES

1. Nomura, M.; Shuto, S.; Tanaka, M.; Sasaki, T.; Mori, S.; Shigeta, S.; Matsuda, A. Nucleosides and Nucleotides. 185. Synthesis and Biological Activities of 4' α -C-Branched-Chain Sugar Pyrimidine Nucleosides. *J. Med. Chem.*, **1999**, *42*, 2901–2908.
2. Shuto, S.; Kanazaki, M.; Ichikawa, S.; Minakawa, N.; Matsuda, A. Stereo- and Regioselective Introduction of 1- or 2-Hydroxyethyl Group via Intramolecular Radical Cyclization Reaction with a Novel Silicon-Containing Tether. An Efficient Synthesis of 4' α -Branched 2'-Deoxyadenosines. *J. Org. Chem.*, **1998**, *63*, 746–754.
3. Waga, T.; Nishizaki, T.; Miyakawa, I.; Ohrui, H.; Meguro, H. Synthesis of 4'-C-Methylnucleosides. *Biosci. Biotechnol. Biochem.*, **1993**, *57*, 1433–1438.
4. Waga, T.; Ohrui, H.; Meguro, H. Synthesis and Biological Evaluation of 4'-C-Methyl Nucleosides. *Nucleosides, Nucleotides*, **1996**, *15*, 287–304.
5. Yamaguchi, T.; Tomikawa, A.; Hirai, T.; Kawaguchi, T.; Ohrui, H.; Sayenoshi, M. Antileukemic Activities and Mechanism of Action of 2'-Deoxy-4'-methylcytidine and Related Nucleosides. *Nucleosides, Nucleotides*, **1997**, *16*, 1347–1350.
6. Kitano, K.; Miura, S. Synthesis of 4'-C-Fluoromethylnucleosides as Potential Anti-neoplastic Agents. *Tetrahedron*, **1997**, *53*, 13315–13322.
7. O-Yang, C.; Wu, H. Y.; Fraser-Smith, E. B.; Walker, K. A. M. Synthesis of 4'-Cyanothymidine and Analogs as Potent Inhibitors of HIV. *Tetrahedron Lett.*, **1992**, *33*, 37–40.
8. Kohgo, S.; Horie, H.; Ohrui, H. Synthesis of 4'-C-Ethynyl- β -D-arabino- and 4'-C-Ethynyl-2'-deoxy- β -D-ribo-pentofuranosyl Pyrimidines, and Their Biological Evaluation. *Biosci. Biotechnol. Biochem.*, **1999**, *63*, 1146–1149.
9. Leland, D. L.; Kotick, M. P. Studies on 4-C-(hydroxymethyl)pentofuranoses. Synthesis of 9-[4-C-(hydroxymethyl)- α -L-threo-pentofuranosyl]adenine. *Carbohydr. Res.*, **1974**, *38*, C9–C11.
10. Jones, G. H.; Taniguchi, M.; Tegg, D.; Moffatt, J. G. 4'-Substituted Nucleosides. 5. Hydroxymethylation of Nucleoside 5'-Aldehydes. *J. Org. Chem.*, **1979**, *44*, 1309–1317.
11. Hrebabecky, H.; Holy, A. Synthesis of 1-(3-Azido-2,3-dideoxy-4-C-hydroxymethyl- α -L-threo-pentofuranosyl)thymine, 1-(2,3-dideoxy-4-C-hydroxymethyl- α -L-glycero-pentofuranosyl)thymine and 1-(2,3-dideoxy-4-C-hydroxymethyl- α -L-glycero-pent-2-enofuranosyl)thymine. *Collec. Czech. Chem. Commun.*, **1993**, *58*, 409–420.
12. Schaffer, R.; Isbell, H. S. Structure of 5-Aldo-1,2-O-isopropylidene-D-xylo-pentofuranose. *J. Am. Chem. Soc.*, **1957**, *79*, 3864–3866.
13. Tidwell, T. T. Oxidation of Alcohols by Activated Dimethyl Sulfoxide and Related Reactions: An Update. *Synthesis*, **1990**, *10*, 857–870.



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