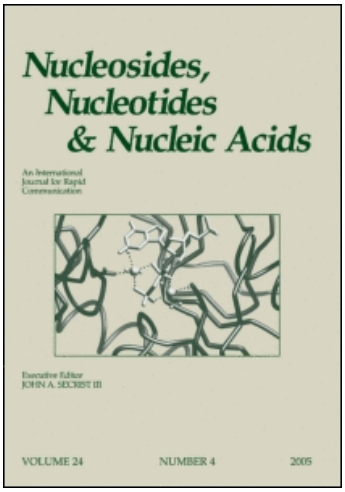

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SYNTHESES OF PYRIMIDINE ACYCLIC NUCLEOSIDE PHOSPHONATES AS POTENT INHIBITORS OF THYMIDINE PHOSPHORYLASE (PD-ECGF) FROM SD-LYMPHOMA

Karel Pomeisl, Ivan Votruba, Antonín Holý, and Radek Pohl □ *Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Prague, Czech Republic*

□ *In the present study, we synthesized a series of pyrimidine acyclic nucleoside phosphonates bearing a number of substituents in C-5 position of uracil moiety and in the N-1-side chain. In addition, we have investigated in particular the novel syntheses of fluorinated derivatives substituted in the N-1-side chain and uracil C-5 position because fluorine-containing substituents are often powerful modifiers of chemical and biological properties. The obtained compounds exhibit a considerable inhibitory potency of thymidine phosphorylase from SD-lymphoma. In contrast, the synthesized phosphonates are not efficient inhibitors of E. coli and human thymidine phosphorylase.*

Keywords Acyclic nucleoside phosphonates; thymidine phosphorylase; pyrimidines; FPMP derivatives; fluorination

INTRODUCTION

Acyclic nucleoside phosphonates (ANPs) exhibit various kinds of biological activities.[1] Among them ANPs are investigated as inhibitors of thymidine phosphorylase (TP).[2] This enzyme is identical to platelet-derived endothelial cell growth factor (PD-ECGF) which plays an important role in tumor angiogenesis. In this study, we have focused on the development of new inhibitors of TP based on the specifically base and side-chain modified and catabolically stable pyrimidine ANPs[2] (see Figure 1).

The study has been supported by the Grant Agency of the Czech Republic (grant #203/03/0089) as a part of research project Z 40550506 of the Institute of Organic Chemistry and Biochemistry, Centre of New Antivirals and Antineoplastics (1M0508)1M6138896301 supported by the Ministry of Education of the Czech Republic and the program of Gilead Sciences Research Centre. The financial support of the Descartes Prize HPAW-CT-2002-9001 of the European Union and of Gilead Sciences (Foster City, CA, USA) is gratefully acknowledged.

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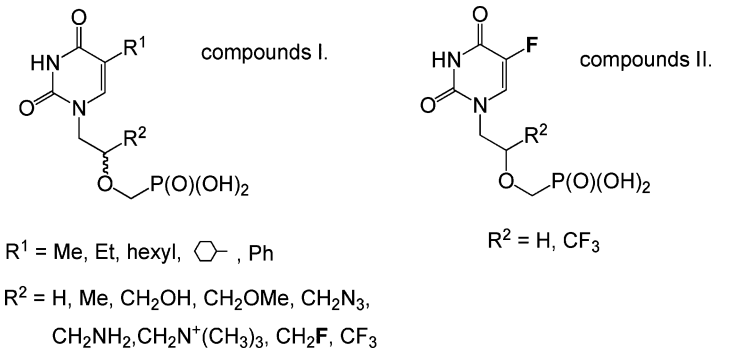
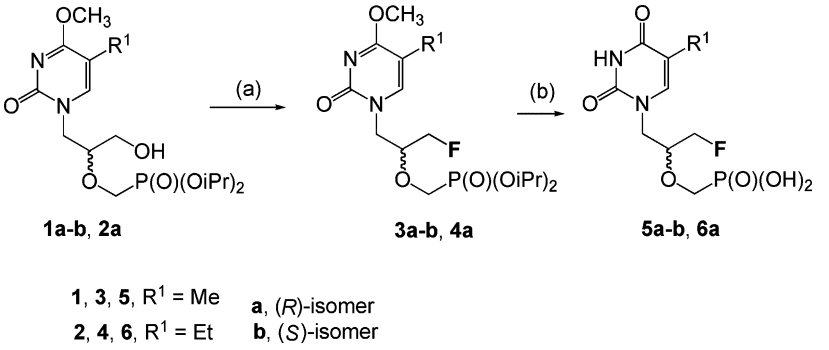


FIGURE 1 The examples of introduced groups R^1 and R^2 in pyrimidine ANPs under study.

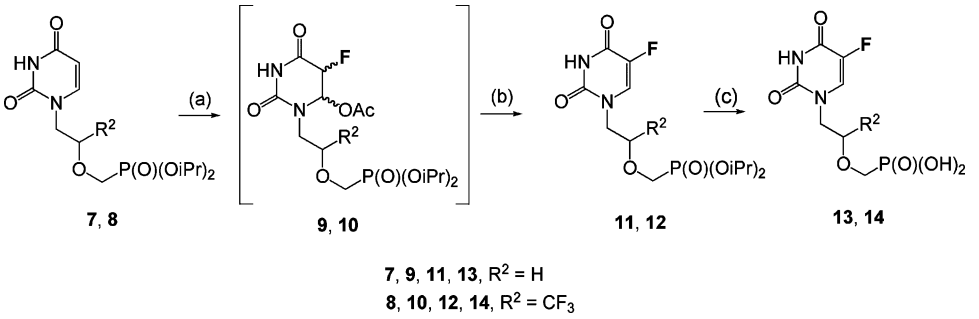
RESULTS AND DISCUSSION

All synthesized side-chain modified thymine and 5-alkyluracil ANPs designed as multisubstrate inhibitors and bearing various groups in side chain possess considerable in vitro inhibitory potency toward TP from SD-lymphoma.[3–5] The most efficient chiral fluoroderivatives **5** and **6** (FPMP compounds) in this series (e.g., **6a**, $v_i/v_0 = 0.02$ [ref. 4]) were obtained by our improved procedure[3,4] using nucleophilic fluorination of easily available compounds **1** and **2** with perfluorobutanesulfonyl fluoride in the presence of DBU followed by deprotection of **3** and **4** with bromotrimethylsilane (see Scheme 1).

The inhibitory effect of our ANPs decreases with substitution at the side chain of the (phosphonomethoxy)alkyl groups[4] in the order: $R^2 = -CH_2F > -CH_2OCH_3 > -CH_2N_3 > -CF_3 > -CH_2N^+(CH_3)_3 > -CH_2OH > -CH_2NH_2 \gg H$, R^1 = Me, Et (see Figure 1). The effect of the substitution of the uracil ring at position 5 with various alkyl (e.g., R^1 = hexyl, cyclohexyl) and aryl (R^1 = Ph) substituents is only marginal.[6]



SCHEME 1 a) $CF_3(CF_2)_3SO_2F$, DBU, toluene, rt->90°C; b) $(CH_3)_3SiBr$, CH_3CN, rt.



SCHEME 2 a) 5–10% F_2/N_2, 99% AcOH; b) Et_3N, EtOH, reflux; c) $(CH_3)_3SiBr$, CH_3CN, rt.

In addition, we have investigated in particular the novel syntheses of two derivatives of 5-fluorouracil **13** and **14** to compare their potential inhibitory effect because fluorine-containing substituents are often powerful modifiers of chemical and biological properties (see Scheme 2).

However, the inhibitory potency of these compounds obtained by using the direct fluorination of the uracil moiety[7] of the easily available phosphonates **7** and **8** with F_2 in acetic acid solution, is lower than the newly synthesized C-5 alkyl and side-chain modified compounds. Probably this result is due to small fluorine atom or its unfavourable electron-drawing effect. The reaction course may be assumed to include the primary addition of hardly formed CH_3COOF to 5,6-double bound of base[8] to form intermediate adducts **9** and **10**, which are completely and clearly converted to **11** and **12** by treatment with triethylamine.

The synthesized pyrimidine ANPs are not efficient inhibitors of *E. coli* and human TP. These differences in the recognition of active sites of rat T-cell lymphoma by ANPs, compared with human and *E. coli* TP, could result from some mutation or post-translation modification of the enzyme.

Despite their in vitro activity, some of the presented compounds possess at a concentration of 10 μmol/L, a significant cytostatic activity in tissue cultures estimated in mouse lymphocytic leukemia L1210 cells (ATCC CCL 219), CCRF-CEM T lymphoblastoid cells (human acute lymphoblastic leukemia, ATCC CCL 119), human promyelocytic leukemia HL-60 cells (ATCC CCL 240) and human cervix carcinoma HeLa S3 cells (ATCC CCL 2.2).

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