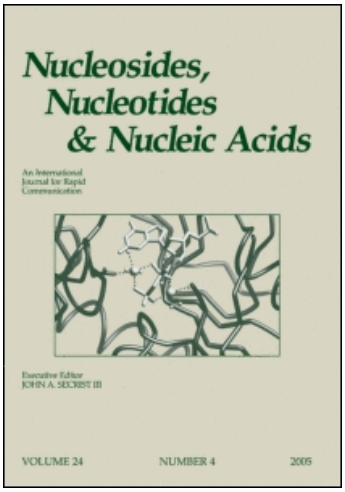

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Synthesis and Antitumor Properties of Some Neutral Triesters of 5-Fluoro-2'-deoxyuridine-5'-monophosphate and 3',5'-Cyclic Monophosphate

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SYNTHESIS AND ANTITUMOR PROPERTIES OF SOME NEUTRAL TRIESTERS OF 5-FLUORO-2'-DEOXYURIDINE-5'-MONOPHOSPHATE AND 3',5'-CYCLIC MONOPHOSPHATE

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Abstract: Several new prodrugs of 5-fluoro-2'-deoxyuridine 5'-monophosphate and 3',5'-cyclic monophosphate were synthesized and their antitumor activities were evaluated *in vitro*.

5-Fluoro-2'-deoxyuridine (FdUrd) is a clinically useful antitumor agent. It is converted intracellularly into 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUrdMP), which is a mechanism-based inhibitor of thymidylate synthetase.[1]

With the aim to overcome the phosphorylation step of FdUrd, we synthesized several new neutral 5'-monophosphate and 3',5'-cyclic monophosphate derivatives of this compound (Fig. 1). In this regard, two kinds of bioreversible protective groups were used: the DTE [2] and the SATE [3] groups, which are liberated following a reductase- and an esterase-dependent activation process, respectively.

The *in vitro* antitumor activities of the newly synthesized compounds **1-4** were determined by measuring their inhibitory effects on the proliferation of several murine and human proliferating cells, including thymidine kinase deficient (TK^-) cell lines (Table 1).

	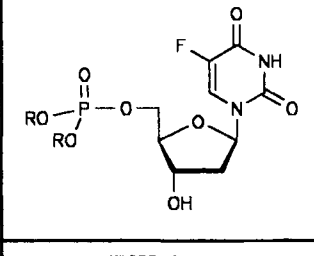	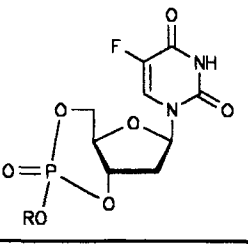
R=H	FdUrdMP	FdUrdcMP
R=HO$(CH_2)_2SS(CH_2)_2$-	Bis(DTE)FdUrdMP (1)	(DTE)FdUrdcMP (3)
R=$CH_3COS(CH_2)_2$-	Bis(SATE)FdUrdMP (2)	(SATE)FdUrdcMP (4)

FIGURE 1

TABLE 1

	CC_{50} (M)				
	FM3A/0	FM3A/TK-	CEM/0	CEM/TK-	Molt4F/Cl8
FUra	$7.8\ 10^{-7}$	$3.5\ 10^{-7}$	$5.2\ 10^{-6}$	$4.2\ 10^{-6}$	$2.4\ 10^{-5}$
FdUrd	$8.1\ 10^{-9}$	$1.5\ 10^{-6}$	$1.0\ 10^{-8}$	$3.9\ 10^{-6}$	$9.3\ 10^{-6}$
FdUrdMP	$5.6\ 10^{-9}$	$1.8\ 10^{-6}$	$1.2\ 10^{-8}$	$4.8\ 10^{-6}$	$1.3\ 10^{-5}$
Bis(DTE)FdUrdMP	$3.5\ 10^{-8}$	$2.3\ 10^{-6}$	$1.9\ 10^{-8}$	$9.4\ 10^{-6}$	$2.5\ 10^{-5}$
Bis(SATE)FdUrdMP	$3.9\ 10^{-8}$	$1.8\ 10^{-6}$	$1.6\ 10^{-8}$	$5.4\ 10^{-6}$	$1.4\ 10^{-5}$
FdUrdcMP	$2.3\ 10^{-7}$	$1.4\ 10^{-5}$	$2.9\ 10^{-7}$	$6.8\ 10^{-5}$	$9.8\ 10^{-5}$
(DTE)FdUrdcMP	$4.6\ 10^{-8}$	$7.9\ 10^{-6}$	$2.0\ 10^{-7}$	$3.6\ 10^{-5}$	$3.0\ 10^{-5}$
(SATE)FdUrdcMP	$5.7\ 10^{-8}$	$4.4\ 10^{-6}$	$2.6\ 10^{-7}$	$2.0\ 10^{-5}$	$6.6\ 10^{-6}$

50 % inhibitory effects (CC_{50}) on the proliferation of murine mammary carcinoma cells (FM3A, FM3A/TK-) and human T-lymphocyte cells (CEM/0, CEM/TK-, Molt4F/Cl8)

From the data presented in Table 1, it appears that:

i) As expected, FdUrd is clearly much less active in TK^- cells than in TK^+ cells. In all cells, FdUrdMP behaves as FdUrd, which means that this 5'-mononucleotide must be hydrolyzed extracellularly. Compared to FdUrd and FdUrdMP, FdUrdcMP shows a decreased inhibitory effect on all the cell lines.

ii) The newly synthesized phosphotriesters **1** and **2**, as compared to the parent compounds FdUrd and FdUrdMP, do not show an increased activity against the TK^- cells. These results are not in accordance with the functioning of these phosphotriesters as intracellular delivery forms of the 5'-monophosphate (FdUrdMP).

iii) The reduced activities of the cyclic phosphotriesters **3** and **4** suggest that either these compounds do not readily enter into the cells or they are not converted easily to FdUrdMP or FdUrd intracellularly.

Further work is currently in progress in our laboratory in order to explain why the nucleotide prodrug approach seems unsuccessful in the 5-fluorouracil series.

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