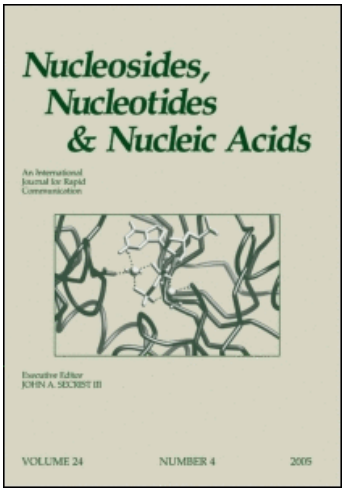

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SYNTHESIS AND *IN VITRO* ACTIVITY OF D- AND L-ENANTIOMERS OF 5-(TRIFLUOROMETHYL)URACIL NUCLEOSIDE DERIVATIVES

Raul Salvetti,[1] Massimo Pregnolato,[1,*] Annalisa Verri,[2] Federico Focher,[2] Silvio Spadari,[2] Arnaud Marchand,[3] Christophe Mathé,[3] and Gilles Gosselin[3]

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ABSTRACT

Recently, β-L-nucleoside analogues have emerged as a new class of sugar modified nucleosides with potential antiviral and/or antitumoral activity. As a part of our ongoing research on this topic, we decided to synthesize 5-CF_3-β-L-dUrd (**7**), the hitherto unknown L-enantiomer of Trifluridine, an antiherpetic drug approved by FDA but only used in topical applications due to concomitant cytotoxicity. 5-CF_3-β-L-dUrd (**7**) as well as some other related L-nucleoside derivatives were stereospecifically prepared and tested *in vitro* against viral (HSV-1 and HSV-2) and human thymidine kinases (TK).

Trifluridine (Viroptic^{TM}) is an antiherpetic drug approved by the FDA in 1980 for the clinical treatment of primary keratoconjunctivitis and epithelial keratitis (1). It is monophosphorylated by both cellular and HSV thymidine kinases, and upon further phosphorylation by cellular nucleotide kinases, it inhibits viral DNA replication by incorporation of its triphosphate form into DNA. On the other hand, interactions of Trifluridine and its phosphorylated metabolites with cellular enzymes, including human thymidine kinase, thymidylate synthase, and DNA

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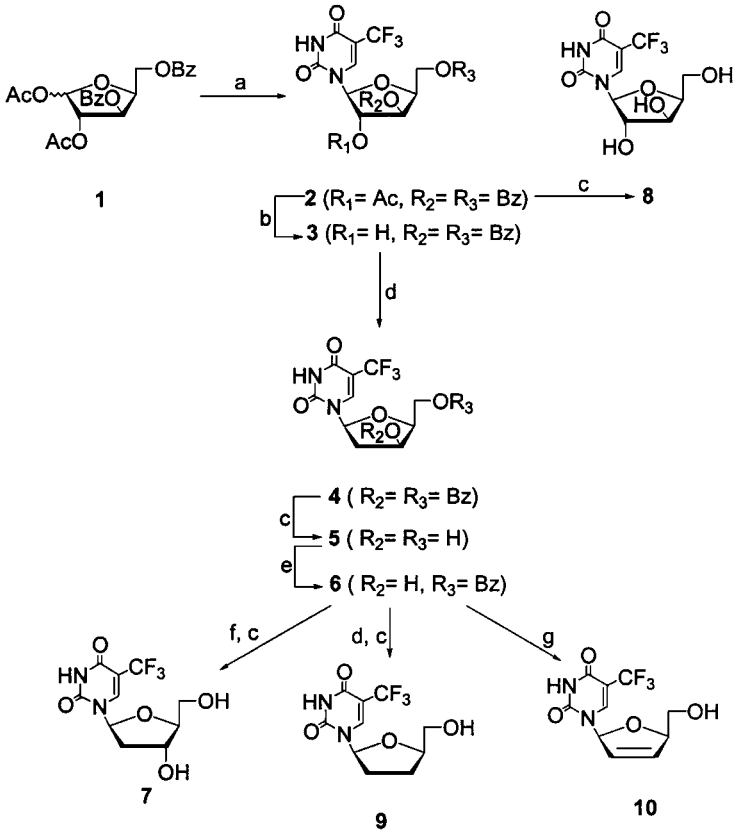
polymerases are responsible for cellular toxicity. In order to design compounds with reduced cytotoxic effects, we have carried out the synthesis of 5-CF_3-β-L-dUrd (**7**), the L-enantiomer of Trifluridine, as well as some other L-nucleoside derivatives modified at the 2′ and 3′ positions of the sugar moiety. Condensation of 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-L-xylofuranose (2) (**1**) with commercially available 5-(trifluoromethyl)uracil under Vorbrüggen conditions gave 1-(2-*O*-acetyl-3,5-di-*O*-benzoyl-β-L-*xylo*-furanosyl)-5-(trifluoromethyl)uracil (**2**) which was fully deacylated to give β-L-xylofuranosyl-5-(trifluoromethyl)uracil **8** (Scheme 1). On the other hand, regioselective 2′-*O*-deacylation of compound **2** afforded 1-(3,5-di-*O*-benzoyl-β-L-*xylo*-furanosyl)-5-(trifluoromethyl)uracil (**3**), which was converted *via* a radical reductive process (3) to compound **4**, and upon deprotection, gave 1-(2-deoxy-β-L-*threo*-pentofuranosyl)-5-(trifluoromethyl)uracil (**5**). Selective 5′-*O*-benzoylation of compound **5** provided the key-intermediate **6**.

From **6**, inversion of configuration at C-3′ *via* a Mitsunobu reaction (4), and subsequent debenzoylation with methanolic ammonia gave the target molecule



Scheme 1. *Reagents and conditions*: (a) silylated 5-CF_3-uracil/TMSOTf/dichloroethane, r.t.; (b) H_2N-NH_2.H_2O/AcOH/pyridine, r.t.; (c) NH_3/MeOH, r.t.; (d) DMAP/PhO(C=S)Cl/CH_3CN, r.t.; then, $(Me_3Si)_3SiH$/AIBN/dioxane, reflux; (e) BzCl/pyridine, 0°C; (f) DEAD/benzoic acid/THF, 0°C; (g) MsCl/TBAF/THF, r.t.; then, MeONa/MeOH, r.t.

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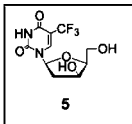
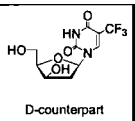
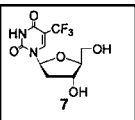
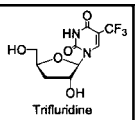
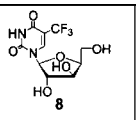
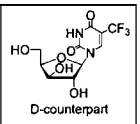
Table 1.

	 5	 D-counterpart	 7	 Trifluridine	 8	 D-counterpart
HSV-1TK IC_{50} (μM)	45	24	**0.5**	0.25	13	32
HSV-2TK IC_{50} (μM)	119	56	**14.5**	2	115	164

5-CF_3-β-L-dUrd (**7**). Starting from the same key-intermediate **6**, other modifications on 2′ and 3′ positions provided the corresponding 2′,3′-dideoxynucleoside **9** and the 2′,3′-unsaturated derivative **10**.

The potential inhibitory effects of compounds **5**, **7** and **8** *versus* their D-nucleoside counterparts toward the thymidine kinases (5) of HSV-1 and HSV-2 have been evaluated. The IC_{50} values are reported in Table 1. All the nucleosides (D and L) show higher affinity for HSV-1 TK with respect to HSV-2 TK. Furthermore, 5-CF_3-β-L-dUrd (**7**) and commercially available Trifluridine show the best inhibitory properties toward both viral enzymes. Regarding HSV-2 TK, Trifluridine shows an IC_{50} value of 2 μM while 5-CF_3-β-L-dUrd shows a higher value (14.5 μM). On the other hand, against HSV-1 TK 5-CF_3-β-L-dUrd (**7**) has an IC_{50} value of 0.5 μM which is comparable to the IC_{50} value (0.25 μM) found for Trifluridine. This last result seems promising in term of potential antiherpetic activity for 5-CF_3-β-L-dUrd (**7**).

In order to investigate the potential antiherpetic activity of 7 and to study its cellular effects of 5-CF_3-β-L-dUrd (**7**), we have evaluated its inhibition of cellular TK. Trifluridine shows an IC_{50} value of 2 μM while its L-enantiomer is not able to inhibit cellular TK up to a concentration of 200 μM. This result appears very interesting in terms of a lack of cellular toxicity for 5-CF_3-β-L-dUrd (**7**). Based on these results, the antiherpetic evaluation of 5-CF_3-β-L-dUrd (**7**) in cell cultures is warranted, and work on this topic is currently in progress in our laboratories.

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