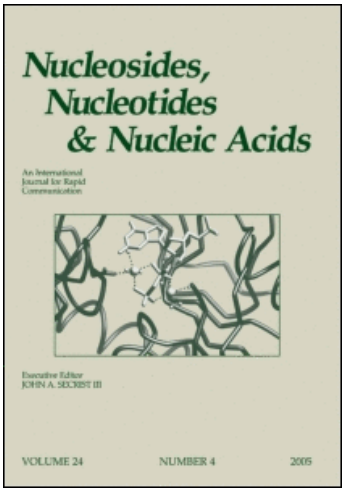

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5′-O-Ester Prodrugs of Potent and Selective Anti-HIV Agent—2′,3′-Dideoxy-3′-fluoro-2-thiothymidine (S^2FLT): Synthesis and Anti-HIV Activity

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ABSTRACT

Novel synthesis of 2′,3′-dideoxy-3′-fluoro-2-thiothymidine (SFLT) based on transformation of appropriately protected 1-β-D-*threo*-ribofuranosylthymine is presented. The synthesis and evaluation of SFLT 5′-O-ester prodrugs enzymatic hydrolysis, as well as their anti-HIV activity, is also described.

Key Words: S^2FLT; SFLT prodrugs; HIV-1 inhibitors.

INTRODUCTION

2′,3′-Dideoxy-3′-fluoro-2-thiothymidine (S^2FLT) is a potent and selective inhibitor of HIV[1] and its reverse transcriptase,[2] however its activity is lower than that of

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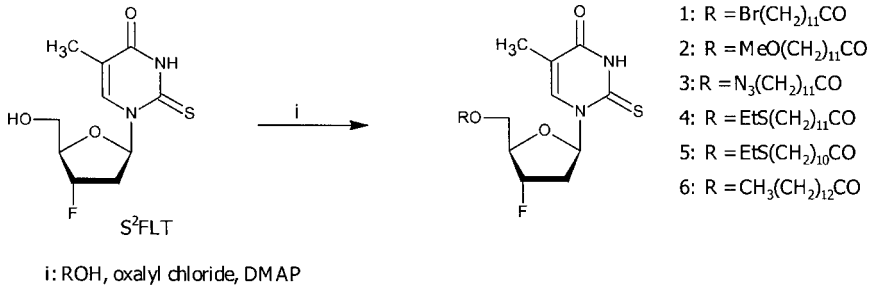
2′,3′-dideoxy-3′-fluoro-thymidine (FLT) which is the most potent anti-HIV agent, but with pronounced in vivo hematological toxicity. On the other hand it was previously shown that such FLT derivatives as 5′-O-myristic acid analogues exhibit enhanced anti-HIV activity, increased lipophylic properties and better selectivity index.[3] In addition such derivatives may act as bifunctional inhibitors of two important enzymes: HIV reverse transcriptase and myristoyl-CoA:protein N-myristoyltransferase (E.C. 2.3.1.97). To increase the antiviral activity and to improve selectivity we decided to synthesize 5′-O-ester prodrugs of S^2FLT.

SYNTHESIS

A new procedure, based on transformation of the known compound 1-(3-O-methanosulphonyl-5-O-trityl-2-deoxy-β-D-*threo*-ribofuranosyl)thymine in four steps, was applied to the synthesis of S^2FLT. Ethoxylation of position 2 of thymine ring of 1-(3-O-methanesulphonyl-5-O-trityl-2-deoxy-β-D-*threo*-ribofuranosyl)thymine with simultaneous inversion of *erythro*-3′-hydroxyl to *threo* configuration lead to 1-(5-O-trityl-2-deoxy-β-D-*threo*-pentofuranosyl)-2-O-ethylthymine.[4] The latter compound was easy transformed into 1-(5-O-trityl-2-deoxy-β-D-*threo*-pentofuranosyl)-2-thiothymine with the use of hydrogen sulfide in the presence of tetramethylguanidine. Fluorination of the 2-thio derivative with DAST gave 1-(5-O-trityl-2,3-dideoxy-3-fluoro-β-D-erythro-pentofuranosyl)-2-thiothymine. Deprotection of the tritylated compound with the use of 80% AcOH led to S^2FLT with spectral properties identical with those previously described.[1]



Scheme 1. Preparation of 5′-O-myristoilated analogues of S^2FLT.

S^2FLT was then esterified on its 5′-hydroxyl group using a variety of myristic acid analogues in the presence of oxalyl chloride and DMAP to afford the corresponding esters **1**–**6** (Sch. 1).

BIOLOGICAL REULTS

Preliminary tests of antiviral activity in vitro were carried out using the syncytia-inducing laboratory HIV-1 (cat#3) strain and MT-2 cells. Preliminary investigation

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Table 1. Half-life for in vitro enzymatic hydrolysis of 5′-O-myristoyl derivatives of S^2FLT.

Compound	Porcine liver esterase, $t_{1/2}$ (min)
1	25
2	2
3	10
4	10
5	10
6	> 60

of antiviral properties of the compounds **1**–**6** shows that 5′-O-myristoylated S^2FLT derivatives **2** and **3** are the most potent inhibitors of HIV-1 and exhibit ca. ten times higher anti-HIV-1 activity and higher therapeutic index than their mother nucleoside S^2FLT.

All derivatives are good substrates for porcine liver esterase with enzymatic hydrolysis half-life ($t_{1/2}$) 2–25 min (Table 1).

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