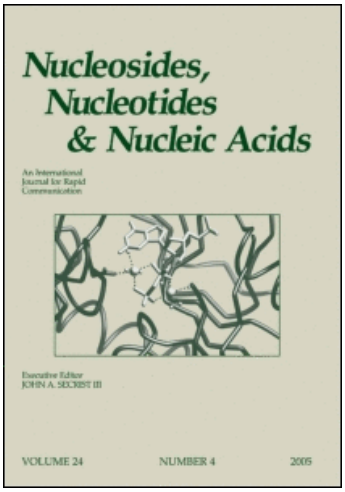

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1-(2,3-Dideoxy-3-Fluoro-β-D-Ribofuranosyl)Tine (FDDT). Improved Preparation and Evaluation as a Potential Anti-Aids Agent

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1-(2,3-DIDEOXY-3-FLUORO-β-D-RIBOFURANOSYL)THYMINE (FDDT). IMPROVED PREPARATION AND EVALUATION AS A POTENTIAL ANTI-AIDS AGENT

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SUMMARY: 3'-Deoxy-3'-fluorothymidine was prepared and evaluated as a potential anti-AIDS agent.

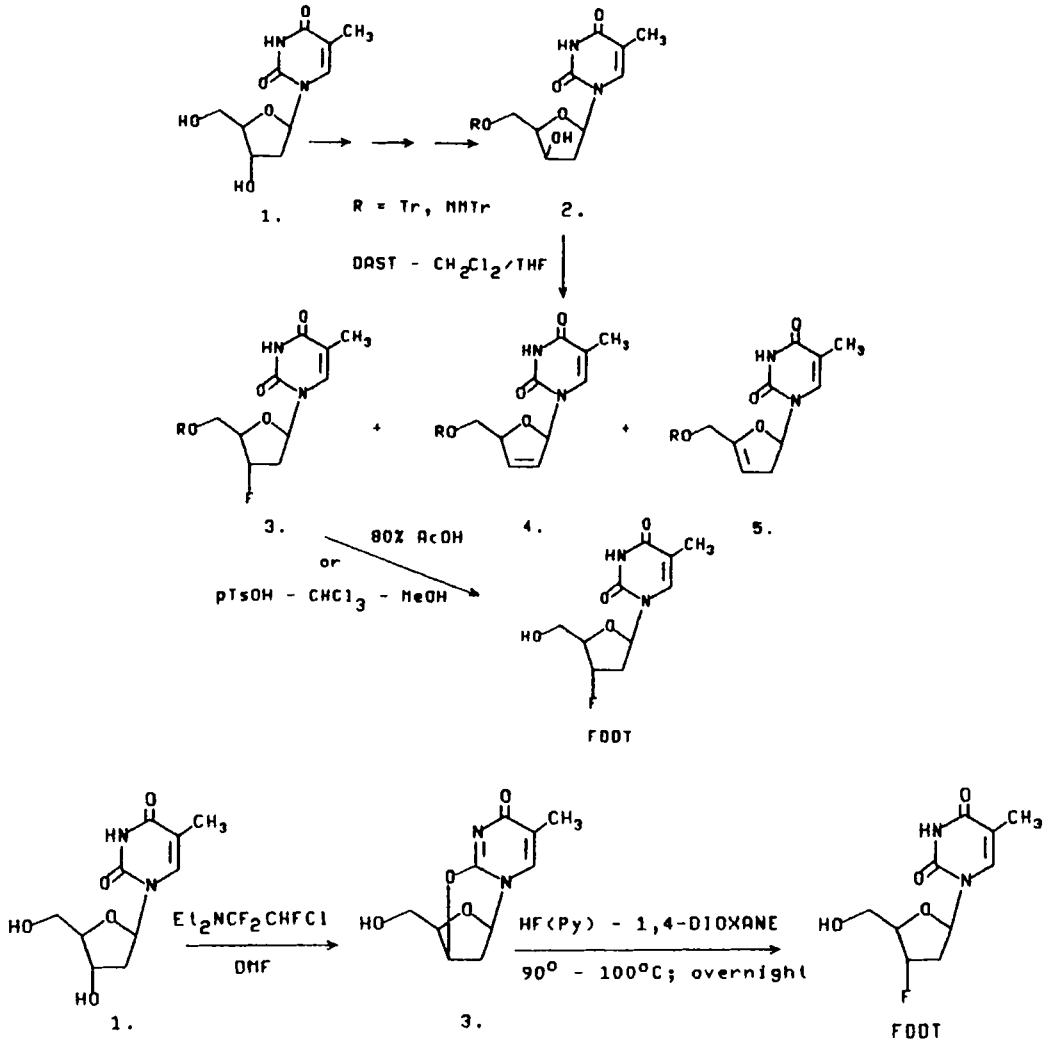
1-(2,3-Dideoxy-3-fluoro-β-D-ribofuranosyl)thymine (FDDT)[1] is, like AZT, a 3'-deoxy-3'-substituted thymidine (1) analog. Here we report two alternative synthetic approaches to FDDT.

For a large scale preparation 5'-protected-3'-threo-thymidine[2] (2) was treated with DAST.

Subsequent deprotection gave FDDT with up to 56% overall yield (5'-Tr protection). The protected elimination products (4) and (5) were also isolated and characterized.

In a small scale study 2,3'-anhydrothymidine (3) was opened with an excess of HF(Py) at 90 - 100°C (bath) to give FDDT with 30 - 40% yield.

FDDT was evaluated in HIV1 infected CEM cells and was found to be a potent inhibitor of viral replication (ED_{50} = 0.007 μM - 0.1 μM). FDDT toxicity in vitro was comparable to AZT in the cellular systems studied. Recently several groups[3,4,5,6] evaluated FDDT against HIV1 in vitro.



FDDT-TP, the nucleotide believed to be responsible for the anti-HIV1 activity of FDDT, was prepared and evaluated as an inhibitor HIV1 RT. The Ki value of FDDT-TP for DNA template was 84 μM and for RNA template was 0.26 μM.

In vivo toxicity was evaluated in the mouse model in a four week study. Death of experimental animals was observed at all investigated doses (oral administration , 100 - 1000 mg/kg/day).

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