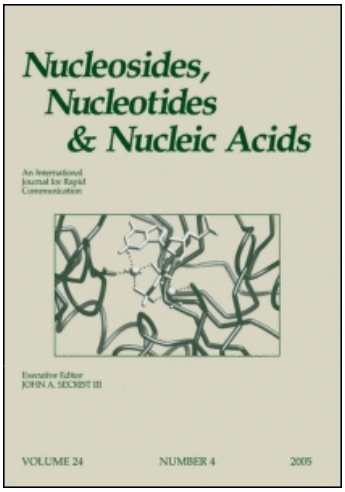

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Synthesis of a Nucleoside Bioconjugate System as a Potential Anti-HIV Agent

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SYNTHESIS OF A NUCLEOSIDE BIOCONJUGATE SYSTEM AS A POTENTIAL ANTI-HIV AGENT

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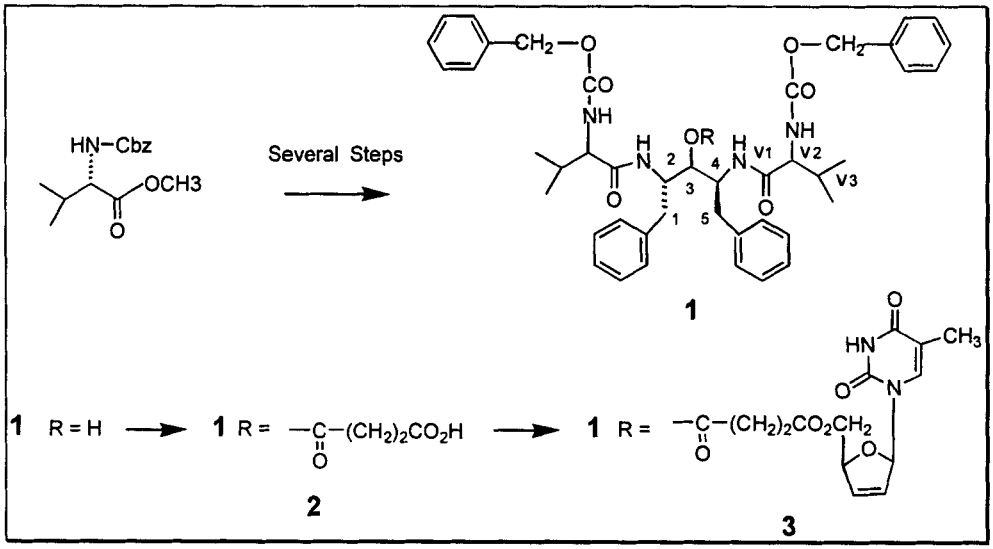
ABSTRACT: Synthesis and anti-HIV data for a bioconjugate molecule incorporating a HIV protease inhibitor (A74704) and a HIV RT inhibitor (d4T) are presented.

Current antiviral therapy for the human immunodeficiency virus (HIV) is based largely on the inhibition of two viral enzymes that play essential roles in the replication of HIV, i.e., HIV reverse transcriptase (HIV RT) and HIV protease (HIV PR).[1] More recent approaches to therapy have involved combinations of antiviral agents.[2] These findings led us to the synthesis and *in vitro* anti-HIV evaluation of a bioconjugate molecule **3** consisting of a HIV RT inhibitor and a HIV protease inhibitor.

Compound **3** was constructed by combining the known disubstituted methanol analog **1** (Abbot, A74704) as the HIV PR inhibitor,[3] and d4T [1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine] as the HIV RT inhibitor.[4] Compound **1** was obtained following a described multi-step procedure.[5] d4T was synthesized as previously reported.[6] As a first linker, succinic acid was selected. Esterification of **1** with succinic anhydride/ DMAP in CH_2Cl_2 provided, after work-up, a 64% yield of the ester **2**. Reaction of the carboxyl functionality of **2** with the 5'-CH_2OH group of d4T (DCC, catalytic DMAP) afforded the desired succinylic diester **3** in 40% yield. The structure and stereochemistry of the target compound was established by FAB mass spectral data and extensive NMR studies. Assignment of the signals in the ^1H NMR spectra of compound **1** and the target bioconjugate molecule **3** was aided by COSY and HMQC experiments.

One criterion that a successful bioconjugate molecule must satisfy is that of its cellular conversion to the pharmacologically active species. However, compound **3** exhibited resistance to hydrolysis with porcine lipase, while only marginal hydrolysis (< 20%) was achieved rabbit liver esterase. Consistent with this was the inactivity of **3** against HIV-1 (IIIB) and HIV-2 (ROD) at subtoxic concentrations in acutely infected MT-4 cells or in chronically infected HUT-78 IIIB cells.



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