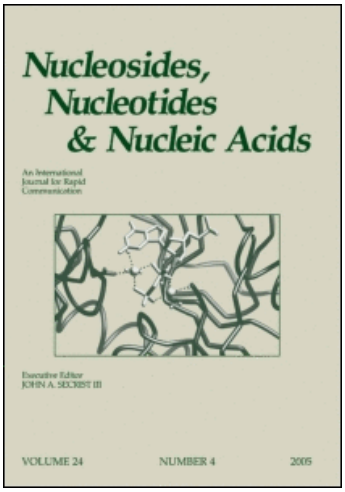

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Synthesis of Novel C-5 Substituted d4t Analogues Bearing Linker Arms as Potential Anti-HIV Agents

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SYNTHESIS OF NOVEL C-5 SUBSTITUTED d4T ANALOGUES BEARING LINKER ARMS AS POTENTIAL ANTI-HIV AGENTS

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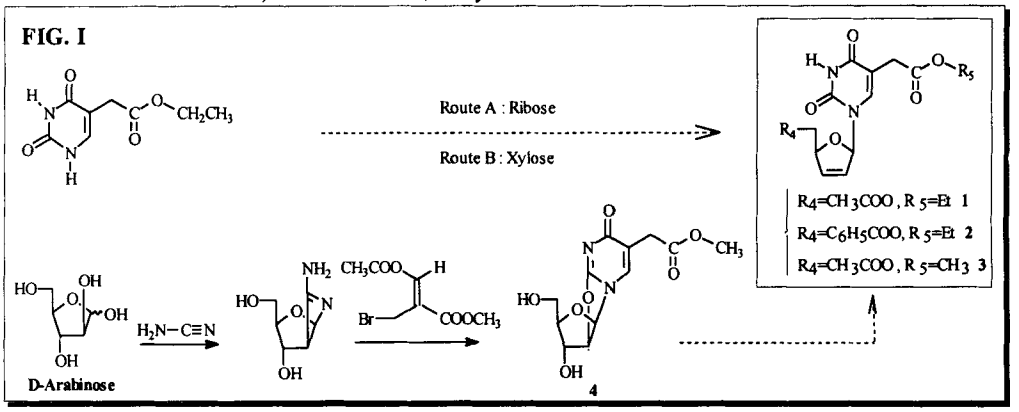
ABSTRACT

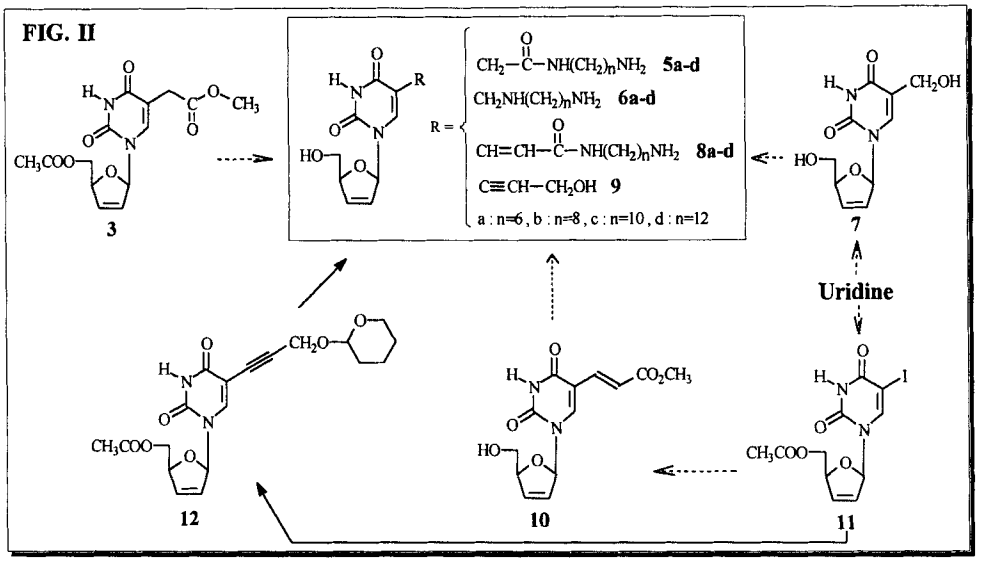
This work reports the synthesis of 2',3'-didehydro-2',3'-dideoxy-thymidine analogues bearing several kinds of amino-linker arms at the C-5 position of the pyrimidine moiety. C-5 is an attractive position since a flexible chain may permit the triphosphates to be generated. The β-D- and β-L-d4T analogues were synthesized following a multi-step reaction from D-ribose and D-xylose, from D- and L-arabinose (towards an oxazoline ring) or from uridine and then were reacted with alkylene diamines.

The 5-(alkoxycarbonylmethyl)-2',3'-didehydro-2',3'-dideoxy-nucleosides **1**, **2** and **3** were synthesized as useful intermediates in order to introduce a linker arm at the C-5 position through amide linkage **(Fig.I)**. We have investigated two procedures involving either a coupling reaction[1] and a subsequent olefination or a total synthesis[2] (starting from D- or L-arabinose) towards the 2,2'-cyclonucleoside **4**.

FIG. I



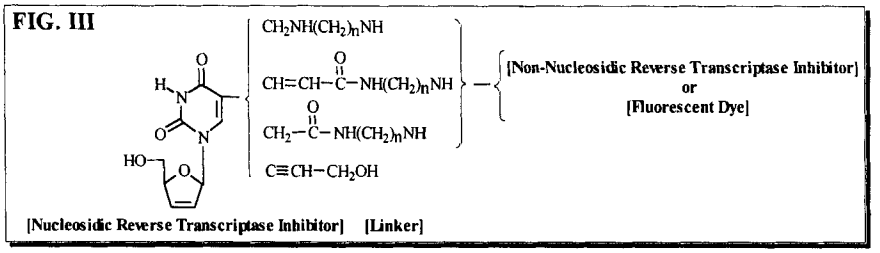
The unsaturated nucleoside **3** was reacted with alkylene diamine which derived from 1,6- 1,8- 1,10 and 1,12-alkyldiamines to afford the compounds **5a-d (Fig.II)**. Starting from uridine, the olefinic nucleosides **6a-d** were prepared towards the key intermediate 2',3'-didehydro-2',3'-dideoxy-5-hydroxymethyl-uridine **7**. Other functional groups have been substituted at the 5 position of pyrimidine including a range of alkenes (**8a-d**) and alkyne



(**9**) as a hydrophobic moiety. Based on the Heck reaction[3], the methyl ester of 5-(2-carboxyvinyl)-2',3'-didehydro-2',3'-dideoxy-nucleoside **10** has been prepared successfully from the 5-iodo derivative **11**. A similar strategy based on the Sonogashira[3] reaction gave the key component **12**.

CONCLUSION

The C-5 substituted-β-L-d4T analogues are devoid of any appreciable activity against HIV-1 in CEM-SS and MT-4 cells irrespectively of the chain length (*n*) of the methylene spacer (*n*=6-12). The antiviral evaluation of the β-D-analogues is in progress. These modified d4T-nucleosides will be attach either to a non-nucleosidic Reverse Transcriptase Inhibitor or to a label molecule **(Fig. III)**.



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