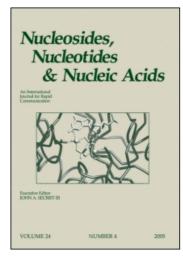
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Synthesis and Biological Evaluation of Pyrimidine Nucleosides Fused with 3',4'-Tetrahydrofuran Ring

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Synthesis and Biological Evaluation of Pyrimidine Nucleosides Fused with 3',4'-Tetrahydrofuran Ring

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ABSTRACT

Pyrimidine nucleosides fused with 3',4'-tetrahydrofuran ring were synthesized, starting from 1,2;5,6-di-O-isopropylidene-D-glucose and assayed for antiviral activities. Thymine analogue 1 and its corresponding 2'-deoxy analogue 3 exhibited high cytotoxicity instead of giving antiviral activities.

A number of 2',3'-dideoxy nucleosides have been discovered to possess significant antiviral activity against HIV-1 and other viruses. Since it has been suggested that proper conformation of the dideoxynucleosides is required for them to exhibit antiviral activity,^[1] bicyclic nucleoside analogues like the fused oxetanyl or cyclopropanyl derivatives of thymidine^[2,3] have been synthesized and reported

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Scheme 1.

to inhibit HIV replication. However, 3',4'-cyclopentane fused pyrimidine nucleosides did not show antiviral activity. Based on these findings, we report the synthesis of pyrimidine nucleosides fused with 3',4'-tetrahydrofuran ring starting from 1,2;5,6-di-O-isopropylidene-D-glucose as potential antiviral agents to obtain further information regarding the correlation between sugar ring conformation and antiviral activity.

1,2;5,6-Di-O-isopropylidene-D-glucose (4) was oxidized with PDC and Wittig reaction of the resulting ketone gave the olefin 5. Hydroboration-oxidation of 5 followed by benzylation of the resulting hydroxyl group yielded the benzyl ether 6. Selective removal of 5,6-O-isopropylidene of 6 using 75% acetic acid followed by oxidative cleavage of the diol with NaIO₄ afforded the aldehyde. Aldol reaction of the aldehyde using 37% aqueous formaldehyde and NaOH and then in situ Cannizzarro reaction produced diol 7 in good yield.

Mesylation of 7 followed by catalytic hydrogenolysis afforded 8, which underwent intramolecular cyclization in the presence of NaH and hydrolysis of the sulfonate using aqueous NaOH to give 9. Treatment of 9 with acetic anhydride gave the acetate which was hydrolyzed with 85% aqueous formic acid and then successively acetylated to give glycosyl donor 10. Condensation of 10 with silylated thymine and N⁴-benzoylcytosine gave the protected nucleosides 11a and 11b, respectively. Deacylation of 11a and 11b gave the desired nucleosides 1 and 2, respectively. Regioselective protection of primary hydroxyl group of 1 as a TBDPS ether followed by treatment with phenyl chlorothionoformate and then tributyltin hydride in the presence of AIBN furnished 2'-deoxy derivative 13. Deblocking of 5'-silyl group of 13 afforded the final 2'-deoxy analogue 3.

The final nucleosides 1, 2 and 3 were assayed for antiviral activities against HIV-1, VSV and HCMV, among which thymine analogue 1 and its corresponding 2'-deoxy analogue 3 exhibited high cytotoxicity without antiviral activities.

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