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Synthesis of some Mimics of Nucleoside Triphosphates

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The nucleoside analogues 9-[(1'β,4'β)-4'-(dihydroxyphosphonylmethoxy)cyclopent-2'-en-1'-yl]guanine and 1-[(1'β,4'β,5'β)-4'-(dihydroxyphosphonylmethoxy)-5'-fluorocyclopent-1'-yl]thymine were synthesised from cyclopentadiene monoepoxide and cyclopent-2-en-1-ol respectively. The phosphonates were converted into the corresponding diphosphoryl-phosphonates by formation of an activated derivative and subsequent condensation with pyrophosphate. These pseudo-triphosphates proved to have interesting biological properties. For example the diphosphoryl-phosphonate derivative of the fluorocyclopentylthymine was shown to be a potent inhibitor of HIV coded reverse transcriptase: the IC_{50} was of the same order of magnitude as that observed for AZT-triphosphate.

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SYNTHESIS AND ANTI-RSV ACTIVITIES OF NOVEL NUCREOSIDES : 6-SUBSTITUTED ANALOGS OF 2',3'-DIDEOXYPURINE NUCREOSIDES.

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Objective: Synthesis and evaluation of novel 2',3'-dideoxy-purine (ddP) nucleosides for anti-RSV activity. These compounds that show anti-RSV activity may have other retroviruses (i.e. HIV etc.) activity in vitro.
Methods: Six 6-substituted ddP, (that is 6-hidroxylamino-ddP, 2-amino-6-hydroxylamino-ddP, 6-hydrazino-ddP, 2-amino-6-hydrazino-ddP, 6-trimethylamino-ddP chloride, and 2-amino-6-trimethylamino-ddP chioride), were synthesized and tested for in vitro anti-RSV activity to supress the infectivity and cytopathic effect in Chick Embryo Fibrofast cells.
Results: The above compounds and their related Agents were tested. Several compounds were found to be potent and selective inhibitors RSV replication. The compounds and their corresponding ID_{50}'s and CD_{50}'s (in μg/ml) are: 6-NHOH-ddP, 8, 250 ; 2 NH_2-6 NHOH-ddP, 4, 250; 6-$NHNH_2$-ddP, 0.5, 500; 2-NH_2-6 $NHNH_2$-ddP, 0.5, 500; 6-$(CH_3)_3N^+$ ddP-Cl^-, 32, 500; 2 NH_2-6 $(CH_3)_3N^+$ ddP-Cl , 16, 500. As a control compounds, ddI and 6 trimethylaminopurine chloride (base only), gave 1.0, 250 and 500, 1000, respectivery.
Conclusion: This study showed that 6-hydroxylamino- and 6-hydrazino- derivatives of ddP were potent and selective inhibitors of RSV replication in vitro. These compounds should be further explored for anti-HIV activity in vitro.