

# Synthesis and Antiviral Activities of Enantiomerically Pure Carbocyclic Pyrimidine Nucleosides

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**BACKGROUND:** Since the discovery of abacavir with potent anti-HIV activity, considerable effort has been devoted to the synthesis and evaluation of carbocyclic nucleosides. In contrast to carbocyclic purine nucleosides, carbocyclic pyrimidine nucleosides, especially chiral analogs, have not been researched extensively. Previously, we reported the synthesis and biological activity of racemic carbocyclic nucleosides. These racemic nucleosides showed low levels of anti-HIV activity. Accordingly, it would be interesting to know if the enantiomers of these nucleosides possess a different antiviral profile.

**METHODS:** The synthesis of enantiomerically pure carbocyclic pyrimidine nucleosides was based on the formation of chiral p-allylpalladium complexes. From chiral bicyclic lactams, two chiral cyclopentenyl ditosylimides were prepared. Under Trost conditions, the ditosylimides were converted to p-allylpalladium complexes, which were coupled with pyrimidines to yield the desired chiral carbocyclic nucleosides. These nucleosides were evaluated for anti-HIV and anti-HBV activities, and for cytotoxicity in PBM, CEM, and Vero cells.

**RESULTS:** Four enantiomers of carbocyclic cytosine and 5-fluorocytosine nucleosides were synthesized and evaluated for their antiviral activity. Among the four enantiomers, the two L-nucleosides demonstrated low levels of anti-HIV activity, while the two D-counterparts were inactive. These enantiomers did not show significant anti-HBV activity, and cytotoxicity (up to 100 mM) in PBM, CEM, and Vero cells.

**CONCLUSION:** 1) The antiviral assays showed that only the L-carbocyclic nucleosides possessed low levels of anti-HIV activity. 2) All the synthesized carbocyclic nucleosides showed no cytotoxicity in various cell lines. 3) An efficient and versatile method for synthesis of enantiomerically pure carbocyclic nucleosides was successfully developed. 4) The synthetic method provides more possibilities for the synthesis of other chiral carbocyclic nucleoside analogs.