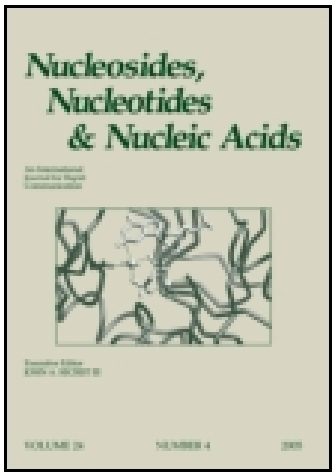

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Synthesis of Unusual Bicyclic Nucleosides Bearing an Unsaturated Side-Chain, as Potential Inhibitors of Varicella-Zoster Virus (VZV)

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We have previously reported a novel class of unusual bicyclic furano pyrimidine nucleosides bearing *p*-alkyl phenyl side-chains[1] that showed an outstanding potency and highly selective activity against varicella-zoster virus (VZV). The *p*-pentyl phenyl analogue displayed an EC_{50} value of 0.3 nM against the TK^+ strain of VZV, representing an inhibitory activity 10,000 times more potent than that of acyclovir (ACV).

In an effort to further explore the structure-activity relationship in this series, we decided to introduce a more rigid side chain by inclusion of an alkene unsaturation

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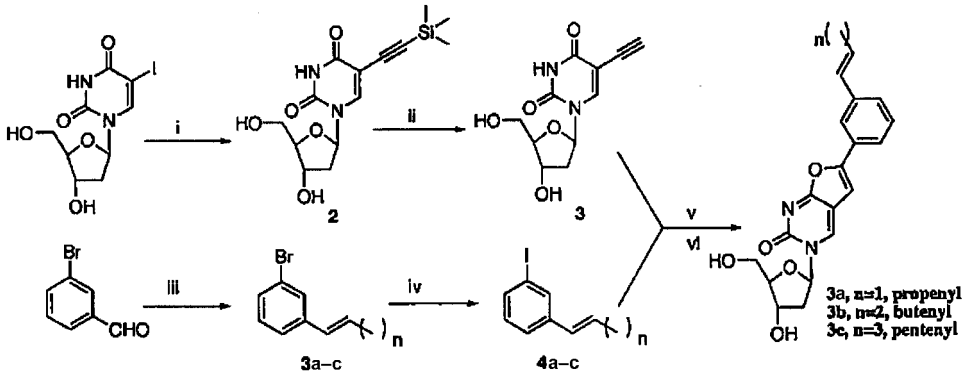
to the α-phenyl unit. The substitution of the side-chain on the phenyl group at the *meta* position **1a–c** was carried out to probe the shape and size of the presumed lipophilic pocket of the target enzyme.

As previously reported by Robins and Barr,[2] the target molecules were synthesized by the Pd(0) -catalyzed coupling of the alkenylphenyl iodide (**5a–c**) with 5-ethynyl-2′-deoxyuridine[3] to yield 5-alkenylphenyl nucleosides which were finally cyclized in presence of CuI (**1a–c**). Compound **3** was prepared from the coupling of 5-iodo-2′-deoxyuridine with trimethylsilylacetylene, followed by desilylation. Alkenylphenyl iodide was the product of a two step reaction involving an Aldol-Grob[3] reaction on the bromobenzaldehyde and a reverse halogen exchange.[4]



i) HC≡C-Si(Me)$_3$, DIPEA, Pd(PPh$_3$)$_4$, CuI, DMF; ii) 10% NH$_3$/H$_2$O, MeOH; iii) CH$_3$-(CH$_2$)n-CO-(CH$_2$)n-CH$_3$, BF$_3$.Et$_2$O, Hexane, r.t; iv) KI, CuI, HMPA; v) DIPEA, Pd(PPh$_3$)$_4$, CuI, DMF; vi) CuI, Et$_3$N, 80°C.

The target bicyclic compounds were evaluated for their ability to inhibit the replication of VZV in human embryonic lung (HEL) fibroblasts. The results showed a severe reduction of activity by more than 40,000-fold compared to the *p*-pentyl phenyl nucleoside. Thus, it is noticed the lipophilic pocket does not tolerate any alkenyl extension at the *meta* position of the aromatic system.

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