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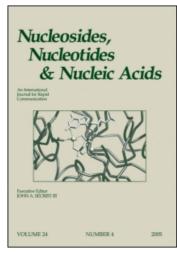
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#### Nucleosides, Nucleotides and Nucleic Acids

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## Bicyclic Nucleoside Inhibitors of Varicella-Zoster Virus: 5'-Chloro and 3'-Chloro Derivatives

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#### NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS Vol. 22, Nos. 5–8, pp. 931–933, 2003

# Bicyclic Nucleoside Inhibitors of Varicella-Zoster Virus: 5'-Chloro and 3'-Chloro Derivatives

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#### **ABSTRACT**

We have recently discovered bicyclic furopyrimidines as potent and selective inhibitors of VZV. In order to investigate the structural requirements for antiviral activity we have successfully synthesised some 3'-chloro and 5'-chloro derivatives. The compounds have been tested against VZV and CMV, but displayed no significant in vitro activity.

Key Words: Chloronucleoside; Varicella-Zoster Virus; Antiviral.

Bicyclic furano pyrimidines have been discovered to be potent and selective inhibitors of VZV. [1] The most potent compound reported to date is the p-pentylphenyl derivative with EC<sub>50</sub> values below 1 nanomolar against VZV and selectivity index values grater than 1,000,000. [2] We are interested in pursuing systematic variations in the structure of this class of molecules in order to investigate the structural requirements for optimal antiviral activity and to broaden the spectrum of action against other viruses.

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As part of the modifications carried out on the sugar moiety, we now report the synthesis and biological evaluation of some 3'-chloro and 5'-chloro derivatives. Target structures were synthesized by Pd(0)-catalysed coupling of the 1 and 2 with the appropriate alkynes, to afford the 5-alkynyl nucleosides which were subsequently cyclized in the presence of CuI as showed in Sch. 1.<sup>[1]</sup>

The synthesis of the nucleosides **1** and **2** was performed following published procedures, <sup>[3]</sup> starting from 5-iodo-2'-deoxyuridine.

Nucleosides 3–5 were evaluated for their ability to inhibit the replication of VZV in human embryonic lung (HEL) cells. Compounds 3 and 4 showed a decrease of antiviral activity of 10,000 compared to the corresponding 3'-OH derivatives. No significant activity was observed for compound 5 at concentration up to  $5\,\mu M$ .

The loss of activity for this 5'-chloro analogue may be further proof of a mechanism of action involving obligate 5'-phosphorylation. The reduced activity for the 3'-Cl derivatives 3-4 also indicates the importance of the 3'OH group for anti-VZV activity.

The newly synthesized compounds 3–5 were also tested against human cytomegalovirus but displayed no significant in vitro activity.

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