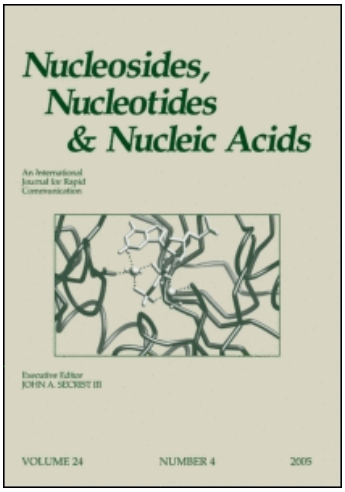


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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

G. Luoni[ab]; C. McGuigan[a]; G. Andrei[c]; R. Snoeck[c]; E. De Clercq[c]; J. Balzarini[c]
[a] Welsh School of Pharmacy, Cardiff University, Cardiff, UK [b] Welsh School of Pharmacy, Cardiff, UK [c] Rega Institute for Medical Research, Leuven, Belgium

Online publication date: 09 August 2003

To cite this Article Luoni, G. , McGuigan, C. , Andrei, G. , Snoeck, R. , De Clercq, E. and Balzarini, J.(2003) 'Bicyclic Nucleoside Inhibitors of Varicella-Zoster Virus: 5'-Chloro and 3'-Chloro Derivatives', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 931 — 933
To link to this Article: DOI: 10.1081/NCN-120022688
URL: http://dx.doi.org/10.1081/NCN-120022688

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

G. Luoni,[1,*] C. McGuigan,[1] G. Andrei,[2] R. Snoeck,[2] E. De Clercq,[2] and J. Balzarini[2]

[1]Welsh School of Pharmacy, Cardiff University, Cardiff, UK
[2]Rega Institute for Medical Research, Leuven, Belgium

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 succesfully synthesised some 3′-chloro and 5′-chloro derivatives. The compounds have been tested against VZV and CMV, but displayed no significant in vitro activity.

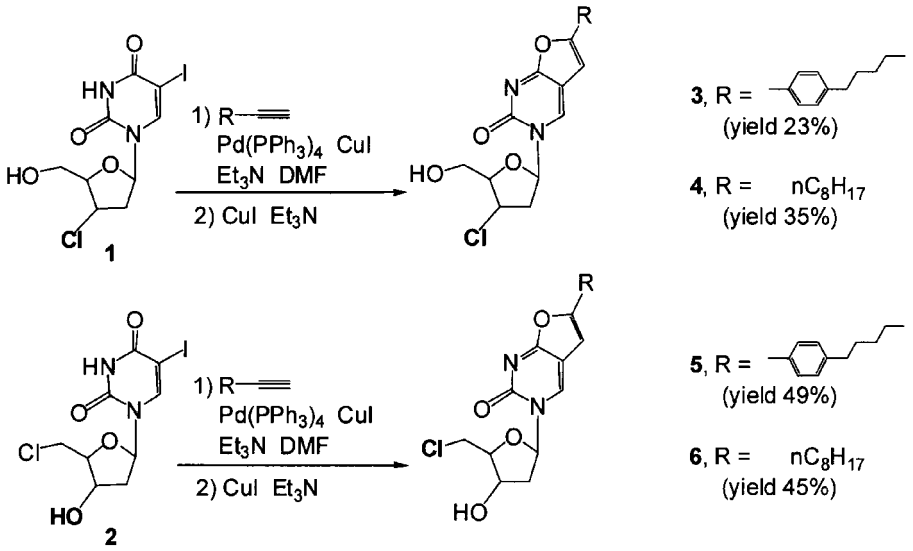
Key Words: Chloronucleoside; Varicella-Zoster Virus; Antiviral.

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_{50} 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.

*Correspondence: G. Luoni, Welsh School of Pharmacy, Redwood Building, King Edward VII Avenue, CF1 03XF Cardiff, UK; Fax: +44 2920 874537; E-mail: luonig@cf.ac.uk.

DOI: 10.1081/NCN-120022688
1525-7770 (Print); 1532-2335 (Online)

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016



Scheme 1.

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.[1]

The synthesis of the nucleosides **1** and **2** was performed following published procedures,[3] 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 μM.

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.

REFERENCES

1. McGuigan, C.; Yarnold, C.J.; Jones, G.; Velazquez, S.; Barucki, H.; Brancale, A.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. Potent and selective inhibition of varicella-zoster virus (VZV) by nucleoside analogues with an unusual bicyclic base. J. Med. Chem. **1999**, *42*, 4479–4484.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

2. McGuigan, C.; Baruki, H.; Blewett, S.; Carangio, A.; Erichsen, J.T.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. Highly potent ans selective inhibition of varicella-zoster virus by bicyclic furopyrimidine nucleosides bearing an aryl side chain. J. Med. Chem. **2000**, *43*, 4993–4997.
3. Verheyden, J.P.H.; Moffatt, J.G. Halo sugar nucleosides. III. Reactions for the chlorination and bromination of nucleoside hydroxyl groups. J. Org. Chem. **1972,** *37*, 2289–2299.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016