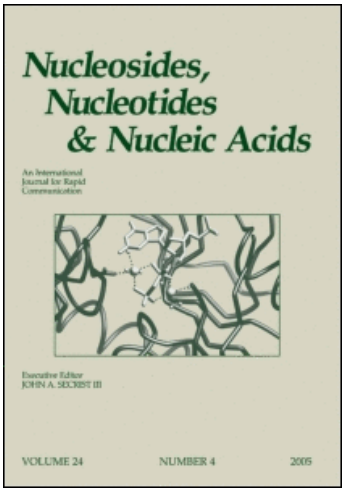

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Bicyclic Nucleoside Inhibitors of Varicella-Zoster Virus: Synthesis and Biological Evaluation of 2′,3′-Dideoxy-3′-fluoro and 2′-Deoxy-xylo Derivatives

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Bicyclic furano pyrimidine analogues have been shown to be potent and selective inhibitors of varicella-zoster virus (VZV). Our initial compounds bearing a C_8-C_{10} side chain showed *ca* 300-fold increase in activity against VZV compared with acyclovir (ACV) without appreciable cytotoxicity.[1] Since then, various modifications have been carried out on the side chain, the sugar moiety and the bicyclic core. These studies have led to the identification of the most potent and selective compound to date, the *p*-pentylphenyl derivative. With an EC_{50} less than 1 nM it is *ca* 10,000-fold

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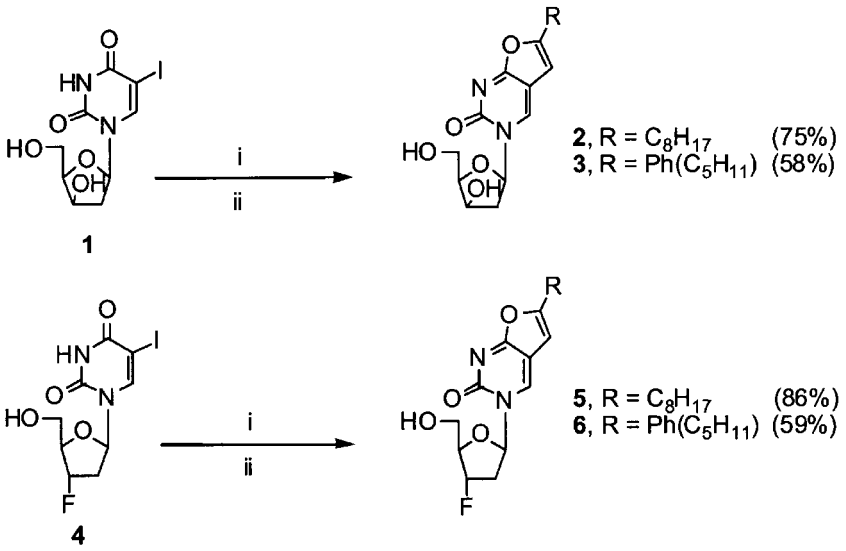

Figure 1.

more potent than ACV and has a selectivity index $> 1{,}000{,}000$.[2] More recently, we discovered that some 2′,3′-dideoxy furano pyrimidine nucleosides bearing alkyl side chains, whilst becoming inactive against VZV, showed a μM activity against human cytomegalovirus (HCMV).[3] In order to understand the structural requirements at the sugar moiety for anti-HCMV activity, thus drawing some initial SAR conclusions, we now report on the synthesis and biological evaluation of some novel 2′,3′-dideoxy-3′-fluoro and 2′-deoxy-xylo derivatives of the most active compounds, with octyl and *p*-pentylphenyl side chains respectively. The target structures (**2–6**) were prepared via the established procedure of palladium-catalyzed coupling of 5-iodo-2′-deoxy-xylo-uridine (**1**) and 5-iodo-2′,3′-dideoxy-3′-fluoro-uridine (**2**) with terminal alkynes, followed by heating at 80°C in the presence of copper iodide (Fig. 1). Both 5-iodo-2′-deoxy-xylo-uridine (**1**) and 5-iodo-2′,3′-dideoxy-3′-fluoro-uridine (**2**) were synthetically prepared from 2′-deoxyuridine following a known procedure.[4] The newly synthezised compounds did not show any relevant anti-HCMV activity, although some of them did retain low μM activity against VZV.

REFERENCES

1. McGuigan, C.; Yarnold, C.J.; Jones, G.; Velázquez, S.; Barucki, H.; Brancale, A.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. J. Med. Chem. **1999**, *42*, 4479–4484.
2. McGuigan, C.; Barucki, H.; Blewett; Carangio, A.; Erichsen, J.T.S.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. J. Med. Chem. **2000**, *43*, 4993–4997.

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3. McGuigan, C.; Pathirana, R.N.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. XV International Roundtable on Nucleosides, Nucleotides & Nucleic acids, 2002; 105 pp.
4. Janta-Lipinski, M.; Costisella, B.; Ochs, H.; Hübscher; Hafkemeyer, P.; Matthes, E. J. Med. Chem. **1998**, *41*, 2040–2046.

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