

This article was downloaded by:

On: 26 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



## Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

### SYNTHESIS AND IN VITRO EVALUATION OF NOVEL ANTI-VARICELLA-ZOSTER VIRUS (VZV) NUCLEOSIDES

Antonella Carangio<sup>a</sup>; Christopher McGuigan<sup>a</sup>; D. Cahard<sup>b</sup>; Graciela Andrei<sup>c</sup>; Robert Snoeck<sup>c</sup>; Erik De Clercq<sup>c</sup>; Jan Balzarini<sup>c</sup>

<sup>a</sup> Welsh School of Pharmacy, Cardiff University, Cardiff, United Kingdom <sup>b</sup> Université de Rouen, UFR des Sciences, Rouen, France <sup>c</sup> Rega Institute for Medical Research, Leuven, Belgium

Online publication date: 31 March 2001

**To cite this Article** Carangio, Antonella , McGuigan, Christopher , Cahard, D. , Andrei, Graciela , Snoeck, Robert , De Clercq, Erik and Balzarini, Jan(2001) 'SYNTHESIS AND IN VITRO EVALUATION OF NOVEL ANTI-VARICELLA-ZOSTER VIRUS (VZV) NUCLEOSIDES', *Nucleosides, Nucleotides and Nucleic Acids*, 20: 4, 653 – 656

**To link to this Article:** DOI: 10.1081/NCN-100002343

**URL:** <http://dx.doi.org/10.1081/NCN-100002343>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

## SYNTHESIS AND IN VITRO EVALUATION OF NOVEL ANTI-VARICELLA-ZOSTER VIRUS (VZV) NUCLEOSIDES

Antonella Carangio,<sup>1</sup> Christopher McGuigan,<sup>1,\*</sup> D. Cahard,<sup>2</sup>  
Graciela Andrei,<sup>3</sup> Robert Snoeck,<sup>3</sup> Erik De Clercq,<sup>3</sup>  
and Jan Balzarini<sup>3</sup>

<sup>1</sup>Welsh School of Pharmacy, Cardiff University, King Edward VII  
Avenue, Cardiff, CF10 3XF, United Kingdom

<sup>2</sup>Université de Rouen, UFR des Sciences, 76821 Mont Saint Aignan  
Cedex, Rouen, France

<sup>3</sup>Rega Institute for Medical Research, Minderbroedersstraat 10,  
Leuven B-3000, Belgium

### ABSTRACT

A series of alkyl-aryl, -phenoxy, and -thiophenoxy bicyclic furo pyrimidine nucleosides have been successfully synthesised by Pd-coupling of 5-iodo-2'-deoxyuridine (IDU) with terminal alkynes, followed by *in situ* copper-cyclisation. Synthesised compounds (**4a-i**) showed an anti-VZV activity at low  $\mu\text{M}$  concentration, comparable to that of current treatment acyclovir.

We have recently reported on the discovery of a new class of anti-VZV nucleosides with unusual bicyclic furo pyrimidine structures (1). Preliminary evaluation pointed out the structural requirement of a long alkyl side-chain on the base moiety for biological activity, with an optimal length of C8–C10 (1) (structure **1**, Fig. 1). Most recently, we observed that introduction of a phenyl group in the side chain of these compounds leads to further significant enhancement of antiviral potency (2) (structure **2**, Fig. 1). Following this extraordinary result, we sought to investigate SARs regarding the aromatic moiety in the lead structure **2** by synthesising a broad series of alkyl-aryl chain-modified analogues.

---

\*Corresponding author.

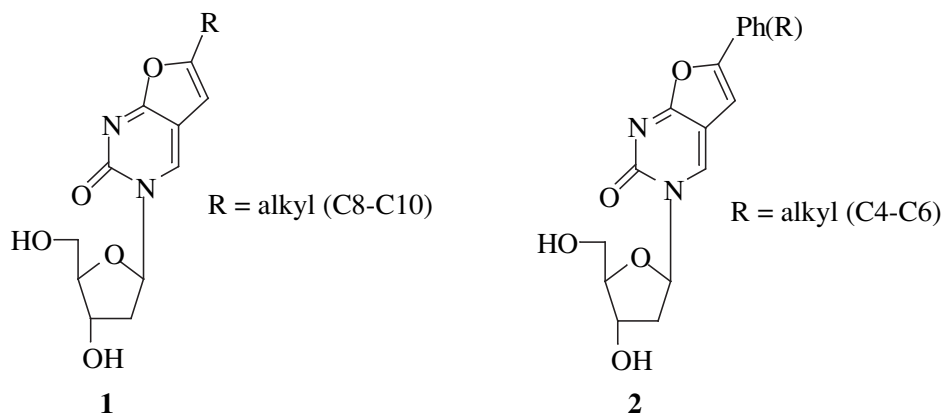


Figure 1.

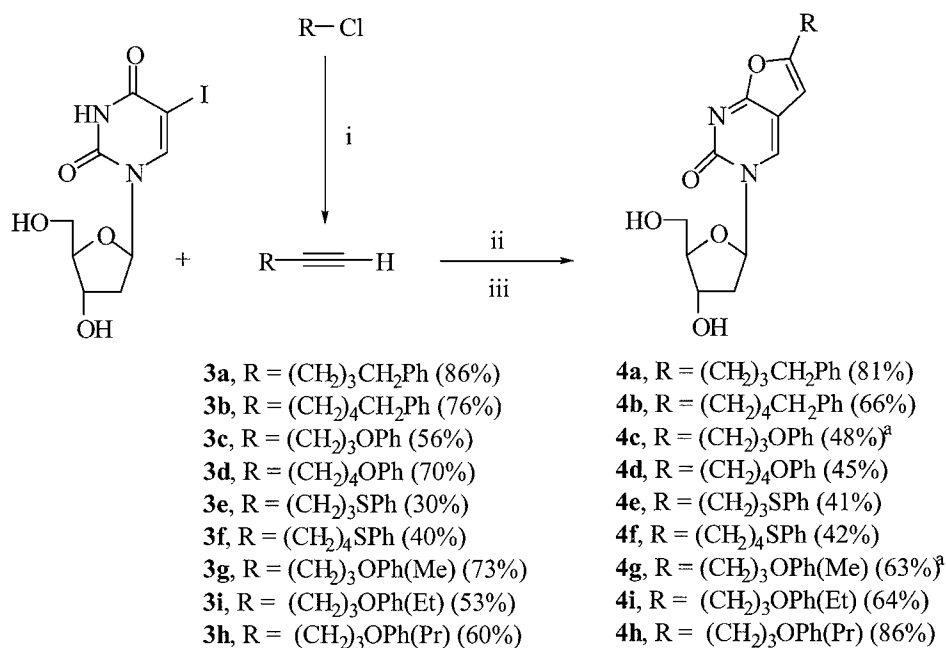
Effect of introduction of a heteroatom (O, S) on the antiviral activity was also investigated, through the synthesis and *in vitro* evaluation of phenoxy and thiophenoxy analogues.

**Chemistry.** Target structures have been synthesised in good yield following the previously reported procedure for this family of molecules (1). Thus, we treated 5-iodo-2'-deoxyuridine with the corresponding terminal alkynes in the presence of a catalytic amount of Pd(0). As previously observed (1), the resulting alkynyl-deoxyuridine may be easily cyclised *in situ*, by treatment with copper(I) and Et<sub>3</sub>N. The terminal alkynes (**3a-h**) used in the coupling step were synthesised in good yields from the appropriate halides, by treatment with lithium acetylide, ethylenediamine complex (3). The whole process is reported in Scheme 1.

Bearing in mind previous observation regarding derivatives with *p*-alkylaryl side-chains, where an alkyl chain of 4–6 carbon atoms was optimal for antiviral activity (2), we synthesised compounds **4a** and **4b**, with 4 and 5 methylene groups between the furo-system and the phenyl moiety. Following previous studies on derivatives bearing an oxygen along the alkyl side chain (4), we synthesised phenoxy-derivatives **4c** and **4d**. Since we previously observed that introduction of an oxygen atom in the side chain, whilst being extremely successful in enhancing water solubility, was detrimental for antiviral activity (4), we replace the oxygen by the more lipophilic sulphur (compounds **4e** and **4f**). Compounds **4g** (5), **4h** and **4i** have been synthesised in order to investigate the effect of a substitution on the phenyl ring, as well as increase the ClogP of the phenoxy-derivatives (Table 1).

**Antiviral Activity.** The target bicyclic compounds **4a-i** were evaluated for their ability to inhibit the replication of VZV *in vitro*, according to previously described methodology (6). Data are shown in Table 1 for the activity of these compounds *versus* two strains of thymidine kinase-competent, and also two strains





<sup>a</sup> Yield of the cyclisation step

i) lithium acetylide, EDA complex, DMSO/Et<sub>2</sub>O 7/3, r.t., 17 h.

ii) Pd(PPh<sub>3</sub>)<sub>4</sub>, CuI, DIPEA, DMF, r.t., 17h.

iii) CuI, MeOH/TEA (7/3), reflux, 4-6 h.

Scheme 1.

Table 1.

Cpd	EC <sub>50</sub> <sup>a</sup> (μM) TK <sup>+</sup> YS	EC <sub>50</sub> <sup>a</sup> (μM) TK <sup>+</sup> OKA	EC <sub>50</sub> <sup>a</sup> (μM) TK <sup>-d</sup> 07/1	EC <sub>50</sub> <sup>a</sup> (μM) TK <sup>-d</sup> YS/R	MCC <sup>b</sup> (μM)	CC <sub>50</sub> <sup>c</sup> (μM)	ClogP <sup>e</sup>
<b>4a</b>	N.D. <sup>f</sup>	N.D. <sup>f</sup>	N.D. <sup>f</sup>	N.D. <sup>f</sup>	N.D. <sup>f</sup>	N.D. <sup>f</sup>	1.76
<b>4b</b>	N.D. <sup>f</sup>	N.D. <sup>f</sup>	N.D. <sup>f</sup>	N.D. <sup>f</sup>	N.D. <sup>f</sup>	N.D. <sup>f</sup>	2.29
<b>4c</b>	92	77	>200	>200	>200	>200	0.65
<b>4d</b>	13	25	>200	>200	≥200	>200	1.18
<b>4e</b>	0.67	0.90	>50	>50	200	>200	1.29
<b>4f</b>	N.D. <sup>f</sup>	N.D. <sup>f</sup>	N.D. <sup>f</sup>	N.D. <sup>f</sup>	N.D. <sup>f</sup>	N.D. <sup>f</sup>	1.82
<b>4g</b>	11	5	>50	>50	200	>200	1.15
<b>4h</b>	10.8	8.4	>50	>50	200	165	1.68
<b>4i</b>	2.8	3.2	>20	>20	≥50	>200	2.21
ACV	1.0	2.9	74	125	>200	>200	—

<sup>a</sup>EC<sub>50</sub>, effective concentration (μM), required to reduce virus plaque formation by 50%.

<sup>b</sup>MCC, minimal cytotoxic concentration (μM), required to alter microscopically detectable cell morphology.

<sup>c</sup>CC<sub>50</sub>, 50% cytotoxic concentration, required to inhibit Hel cell growth by 50%.

<sup>d</sup>TK; thymidine kinase-deficient.

<sup>e</sup>Values calculated using ClogP version 1.0.0.. Biobyte, P.O. Box 517, Claremont, CA 91711, USA.

<sup>f</sup>N.D., not determined: data awaited (Sept. 2000).



of thymidine kinase-deficient VZV, with data also included for the reference anti-herpetic agent acyclovir (ACV).

A preliminary evaluation shows that target nucleosides retain an anti-VZV activity comparable to that of acyclovir, although their antiviral activity is considerably less pronounced than that of our previously reported analogues (1,2). No cytotoxicity is detectable *in vitro* at the concentration required for antiviral activity.

The clear absence of antiviral activity against thymidine kinase-deficient VZV strains remains a constant characteristic of this family of compounds (7), and strongly suggests the absolute requirement for a thymidine kinase-mediated phosphorylation for antiviral activity.

## REFERENCES

- a). 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.
- a). McGuigan, C.; Barucki, H.; Carangio, A.; Blewett, S.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J., *J. Med. Chem.*, **2000**, submitted.
- a). Nyström, J.E., McCanna, T.D., Helquist, P., Amouroux, R., *Synthesis*, **1988**, *1*, 56.
- a). Brancale, A., Srinivasan, S., McGuigan, C., Andrei, G., Snoeck, R., De Clercq, E., and Balzarini, J., *Antiv. Chem & Chemother.*, in press, **2000**.
- 5-. **3[4-hydroxy-5-(hydroxymethyl)tetrahydrofuro-2-furanyl]-6-(3-*p*-methyl-phenoxypropyl)-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one (4g).** <sup>1</sup>H-nmr (d<sub>6</sub>-DMSO; 300 MHz): 9.00 (1H, s, H-4), 7.07 (2H, d, <sup>3</sup>J = 7.9 Hz, *m*-Ph), 6.80 (2H, d, <sup>3</sup>J = 7.9 Hz, *o*-Ph), 6.49 (1H, s, H-5), 6.17 (1H, dd, <sup>3</sup>J = 5.6 Hz, H-1'), 5.30 (1H, d, <sup>3</sup>J = 4.1 Hz, 3'-OH), 5.13 (1H, t, <sup>3</sup>J = 4.9 Hz, 5'-OH), 4.23 (1H, m, H-3'), 3.98 (2H, t, <sup>3</sup>J = 5.9, OCH<sub>2</sub>), 3.91 (1H, m, H-4'), 3.63 (2H, m, H-5'), 2.82 (2H, t, <sup>3</sup>J = 6.9 Hz, α-CH<sub>2</sub>), 2.38 and 2.16 (2H, m, H-2'), 1.38 (2H, m, CH<sub>2</sub>). <sup>13</sup>C-nmr (d<sub>6</sub>-DMSO; 75 MHz): 19.2 (CH<sub>3</sub>) 24.6, 26.65 (2 × CH<sub>2</sub>) 41.5 (C-2'), 61.1 (C-5'), 66.6 (OCH<sub>2</sub>), 70.0 (C-3'), 87.7 (C-4'), 88.4 (C-1'), 100.4 (C-5), 106.7 (C-4a), 114.6 (*o*-Ph), 129.5 (*p*-Ph), 130.1 (*m*-Ph), 137.2 (C-4), 154.1 (*ipso*-Ph), 156.7 (C-6), 157.9 (C-2), 171.5 (C-7a). MS (ES<sup>+</sup>) *m/e* 423 (MNa<sup>+</sup>, 100%), 307 (baseNa<sup>+</sup>, 10%). Accurate mass: C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub>Na requires: 423.1532. Found: 423.1534.
- 6-. De Clercq, E.; Holy, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P.C.; *Nature*, **1986**, *324*, 464–467.  
McGuigan, C., Brancale, A., Barucki, H., Srinivasan, S., Jones, G., Pathirana, R., Blewett, S., Alvarez, R., Yarnold, C.J., Carangio, A., Velázquez, S., Andrei, G., De Clercq, E. and Balzarini, J., *Drugs of the Future*, **2000**, *25*, in press.



## **Request Permission or Order Reprints Instantly!**

Interested in copying and sharing this article? In most cases, U.S. Copyright Law requires that you get permission from the article's rightsholder before using copyrighted content.

All information and materials found in this article, including but not limited to text, trademarks, patents, logos, graphics and images (the "Materials"), are the copyrighted works and other forms of intellectual property of Marcel Dekker, Inc., or its licensors. All rights not expressly granted are reserved.

Get permission to lawfully reproduce and distribute the Materials or order reprints quickly and painlessly. Simply click on the "Request Permission/Reprints Here" link below and follow the instructions. Visit the [U.S. Copyright Office](#) for information on Fair Use limitations of U.S. copyright law. Please refer to The Association of American Publishers' (AAP) website for guidelines on [Fair Use in the Classroom](#).

The Materials are for your personal use only and cannot be reformatted, reposted, resold or distributed by electronic means or otherwise without permission from Marcel Dekker, Inc. Marcel Dekker, Inc. grants you the limited right to display the Materials only on your personal computer or personal wireless device, and to copy and download single copies of such Materials provided that any copyright, trademark or other notice appearing on such Materials is also retained by, displayed, copied or downloaded as part of the Materials and is not removed or obscured, and provided you do not edit, modify, alter or enhance the Materials. Please refer to our [Website User Agreement](#) for more details.

**[Order now!](#)**

Reprints of this article can also be ordered at

<http://www.dekker.com/servlet/product/DOI/101081NCN100002343>