This article was downloaded by: [University of Newcastle, Australia] On: 27 December 2014, At: 01:45 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: <u>http://www.tandfonline.com/loi/lncn20</u>

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

Antonella Carangio ^a , Christopher McGuigan ^b , D. Cahard ^c , Graciela Andrei ^d , Robert Snoeck ^d , Erik De Clercq ^d & Jan Balzarini ^d

 $^{\rm a}$ Welsh School of Pharmacy, Cardiff University , King Edward VII Avenue, Cardiff, CF10 3XF, United Kingdom

^b Welsh School of Pharmacy, Cardiff University, King Edward VII Avenue, Cardiff, CF10 3XF, United Kingdom

^c Université de Rouen, UFR des Sciences , 76821, Mont Saint Aignan Cedex, Rouen, France

^d Rega Institute for Medical Research, Minderbroedersstraat 10, Leuven, B-3000, Belgium

Published online: 07 Feb 2007.

To cite this article: Antonella Carangio , Christopher McGuigan , D. Cahard , Graciela Andrei , Robert Snoeck , Erik De Clercq & Jan Balzarini (2001) SYNTHESIS AND IN VITRO EVALUATION OF NOVEL ANTI-VARICELLA-ZOSTER VIRUS (VZV) NUCLEOSIDES, Nucleosides, Nucleotides and Nucleic Acids, 20:4-7, 653-656, DOI: <u>10.1081/NCN-100002343</u>

To link to this article: http://dx.doi.org/10.1081/NCN-100002343

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 20(4-7), 653-656 (2001)

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

Antonella Carangio,¹ Christopher McGuigan,^{1,*} D. Cahard,² Graciela Andrei,³ Robert Snoeck,³ Erik De Clercq,³ and Jan Balzarini³

 ¹Welsh School of Pharmacy, Cardiff University, King Edward VII Avenue, Cardiff, CF10 3XF, United Kingdom
²Université de Rouen, UFR des Sciences, 76821 Mont Saint Aignan Cedex, Rouen, France
³Rega 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 μ 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.

ORDER		REPRINTS
-------	--	----------

654

CARANGIO ET AL.



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 Et₃N. The terminal alkynes (**3a-h**) used in the coupling step were synthesised in good yields from the appropriate halides, by treatment with lithium acetylide, ethylene-diamine 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

Copyright © Marcel Dekker, Inc. All rights reserved

ORDER		REPRINTS
-------	--	----------

ANTI-VARICELLA-ZOSTER VIRUS NUCLEOSIDES



i) lithium acetylide, EDA complex, DMSO/Et₂O 7/3, r.t., 17 h. ii) Pd(PPh₃)₄, CuI, DIPEA, DMF, r.t., 17h. iii) CuI, MeOH/TEA (7/3), reflux, 4-6 h.

Sc	heme	? 1 .

			Table 1.				
Cpd	$\frac{EC_{50}{}^{a}\left(\mu M\right)}{TK^{+}~YS}$	$EC_{50}^{a} (\mu M)$ TK ⁺ OKA	EC ₅₀ ^a (μM) TK ^{-d} 07/1	$\frac{EC_{50}{}^{a}\left(\mu M\right)}{TK^{-}{}^{d}} \frac{YS}{R}$	MCC ^b (µM)	CC ₅₀ ^c (μM)	ClogP ^e
4a	N.D. ^f	N.D. ^f	N.D. ^f	N.D. ^f	N.D. ^f	N.D. ^f	1.76
4b	N.D. ^f	N.D. ^f	N.D. ^f	N.D. ^f	N.D. ^f	$N.D.^{f}$	2.29
4c	92	77	>200	>200	>200	>200	0.65
4d	13	25	>200	>200	≥ 200	>200	1.18
4e	0.67	0.90	>50	>50	200	>200	1.29
4f	N.D. ^f	N.D. ^f	N.D. ^f	N.D. ^f	N.D. ^f	$N.D.^{f}$	1.82
4g	11	5	>50	>50	200	>200	1.15
4h	10.8	8.4	>50	>50	200	165	1.68
4i	2.8	3.2	>20	>20	≥ 50	>200	2.21
ACV	1.0	2.9	74	125	>200	>200	_

^aEC₅₀, effective concentration (μ M), required to reduce virus plaque formation by 50%. ^bMCC, minimal cytotoxic concentration (μ M), required to alter microscopically detectable cell morphology.

^cCC₅₀, 50% cytotoxic concentration, required to inhibit Hel cell growth by 50%.

^dTK; thymidine kinase-deficient.

eValues calculated using ClogP version 1.0.0.. Biobyte, P.O. Box 517, Claremont, CA 91711, USA. ^fN.D., not determined: data awaited (Sept. 2000). Marcel Dekker, Inc.



Copyright @ Marcel Dekker, Inc. All rights reserved

ORDER		REPRINTS
-------	--	----------

of thymidine kinase-deficient VZV, with data also included for the reference antiherpetic 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**). ¹H-nmr (d₆-DMSO; 300 MHz): 9.00 (1H, s, H-4), 7.07 (2H, d, ³J = 7.9 Hz., *m*-Ph), 6.80 (2H, d, ³J = 7.9 Hz., *o*-Ph), 6.49 (1H, s, H-5), 6.17 (1H, dd, ³J = 5.6 Hz, H-1'), 5.30 (1H, d, ³J = 4.1 Hz, 3'-OH), 5.13 (1H, t, ³J = 4.9 Hz, 5'-OH), 4.23 (1H, m, H-3'), 3.98 (2H, t, ³J = 5.9, OCH₂), 3.91 (1H, m, H-4'), 3.63 (2H, m, H-5'), 2.82 (2H, t, ³J = 6.9 Hz, α -CH₂), 2.38 and 2.16 (2H, m, H-2'), 1.38 (2H, m, CH₂). ¹³C-nmr (d₆-DMSO; 75 MHz): 19.2 (CH₃) 24.6, 26.65 (2 × CH₂) 41.5 (C-2'), 61.1 (C-5'), 66.6 (OCH₂), 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⁺) m/e 423 (MNa⁺, 100%), 307 (baseNa⁺, 10%). Accurate mass: C₂₁H₂₄N₂O₆Na 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>U.S. Copyright Office</u> for information on Fair Use limitations of U.S. copyright law. Please refer to The Association of American Publishers' (AAP) website for guidelines on <u>Fair Use in the Classroom</u>.

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 <u>Website</u> <u>User Agreement</u> for more details.

Order now!

Reprints of this article can also be ordered at http://www.dekker.com/servlet/product/DOI/101081NCN100002343