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## Nucleosides, Nucleotides and Nucleic Acids

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### BICYCLIC FURO PYRIMIDINE NUCLEOSIDES WITH ARYLOXYPHENYL AND HALOPHENYL SUBSTITUTED SIDE CHAINS AS POTENT AND SELECTIVE VARICELLA-ZOSTER VIRUS INHIBITORS

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**BICYCLIC FURO PYRIMIDINE NUCLEOSIDES  
WITH ARYLOXYPHENYL AND HALOPHENYL  
SUBSTITUTED SIDE CHAINS AS POTENT  
AND SELECTIVE VARICELLA-ZOSTER  
VIRUS INHIBITORS**

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**ABSTRACT**

The discovery of potent and selective inhibitors of VZV based on unusual bicyclic alkyl furo pyrimidine nucleosides has been recently reported. Modifications to the side-chain by addition of a phenyl group were found to further enhance the antiviral potency of these compounds. A series of alkoxyphenyl compounds (5a–5g) and two halophenyl derivatives (5h and 5i) were successfully synthesised and displayed anti-VZV activity at low  $\mu$ M concentrations.

We have recently reported the discovery of potent and selective inhibitors of Varicella Zoster Virus (VZV) based on unusual bicyclic alkyl furo pyrimidine deoxynucleosides (1). The alkyl side chain at the 6-position of the furo ring (**1**, Fig. 1), was found to be a prerequisite for anti-viral activity for these types of compounds, with an optimal chain length of C8–C10. The lead compounds displayed potencies ca. 300-fold greater than compounds currently used in treatment, such as acyclovir.

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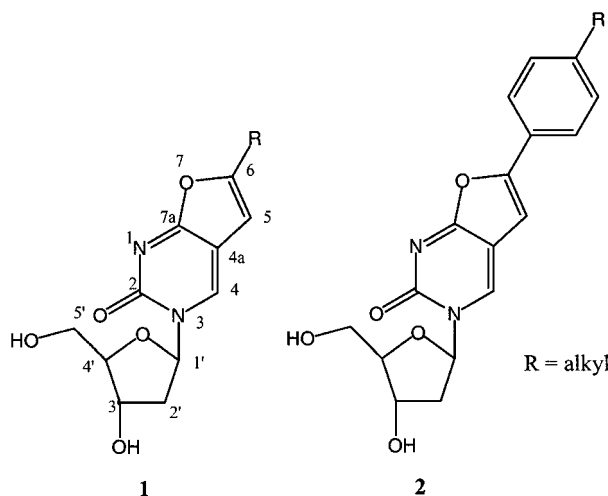


Figure 1.

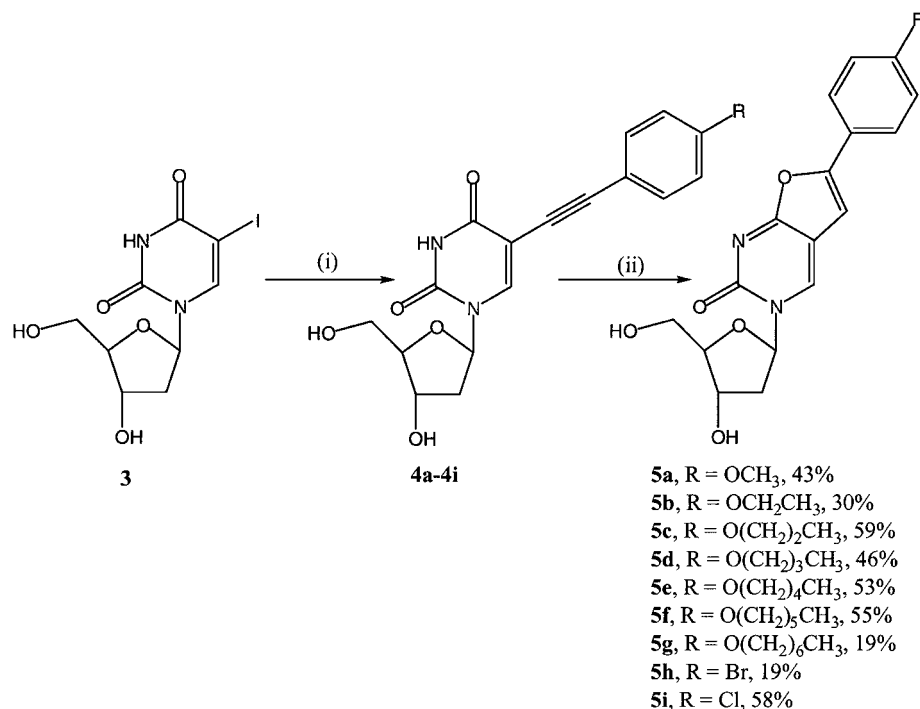
To investigate modifications to the required alkyl side-chain, extensive structure-activity relationship (SAR) studies are underway. A series of *p*-substituted alkyl phenyl substituted compounds were recently synthesised and found to have significantly enhanced potency (sub-nanomolar) with selectivity index values exceeding 500,000 for the most active compound in the series (**2**, Fig. 1) (2).

Further modifications which contain an alkyl and/or a substituted aromatic moiety at the 6-position are being investigated. These include a series of compounds (**5a–5g**) in which an oxygen tethers an alkyl chain to the phenyl ring at the 6-position. It was previously observed that the introduction of an oxygen atom in the alkyl side chain of the parent compounds enhanced water solubility but was detrimental for antiviral activity (3). It is anticipated that the alkoxyphenyl series will be more water soluble than the previously reported alkylphenyl series. Previously, a small series of  $\omega$ -substituted compounds were synthesised and the  $\omega$ -chloro nonyl compound in particular was observed to be potent and selective (4). The other halogen atoms were also found to be acceptable. The synthesis of *p*-halo substituted phenyl derivatives is currently being undertaken and the results for the chloro- and bromo- derivatives (**5h**, **5i**) are discussed herein.

## Chemistry

The synthetic route for the target compounds involved Pd catalysed coupling of 5-iodo-2'-deoxyuridine (**3**) with the corresponding terminal alkyne to give intermediate 5-(2-alkoxyphenyl) ethynyl-2'-deoxyuridines (**4a–4i**, Scheme 1). As previously noted (1), these intermediates were cyclised in situ using copper (1) catalysis (5). Target structures (**5a–5i**) were characterised by H-1 and C-13 NMR, high resolution mass spectrometry and microanalysis (6).





Scheme 1.

Table 1.

CPD	$\text{EC}_{50}(\mu\text{M})^a$ VZV OKA	$\text{EC}_{50}(\mu\text{M})$ VZV YS	$\text{EC}_{50}(\mu\text{M})$ TK <sup>-</sup> 07/1	$\text{EC}_{50}(\mu\text{M})$ TK <sup>-</sup> YS-R	$\text{MCC}(\mu\text{M})^b$	$\text{CC}_{50}(\mu\text{M})^c$	$\text{ClogP}^d$
5a	<0.5	<0.5	>50	>50	>50	n.d.	0.27
5b	<0.5	<0.5	>50	>50	>50	n.d.	0.80
5c	<0.5	<0.5	>50	>50	>50	n.d.	1.33
5d	<0.5	<0.5	>50	>50	>50	n.d.	1.86
5e	<0.5	<0.5	>50	>50	>50	n.d.	2.39
5f	<0.5	<0.5	>50	>50	>50	n.d.	2.92
5g	<0.5	<0.5	>50	>50	>50	n.d.	3.45
5h	0.1	0.1	>50	>50	200	n.d.	1.07
5i	0.5	0.5	>50	>50	50	n.d.	1.22
ACV	2.9	1.0	74	125	>200	>200	-2.30

a)  $\text{EC}_{50}$ , effective concentration ( $\mu\text{M}$ ), the concentration required to reduce virus plaque formation after 5 days in HEL cell cultures by 50% compared to untreated controls; b) MCC, minimal cytotoxic concentration ( $\mu\text{M}$ ), the compound concentration required to cause a microscopically visible alteration of normal cell morphology; c)  $\text{CC}_{50}$ , 50% cytotoxic concentration ( $\mu\text{M}$ ), required concentration to reduce the cell number by 50% after 5 days in the absence of virus; d)  $\text{ClogP}$  is the calculated logarithm of the octanol-water partition coefficient P. n.d., not determined.



Compounds **5a–5i** were evaluated for their ability to inhibit the replication of VZV according to previously described methods (7). Data are shown in Table 1 for the activity of **5a–5i** versus two strains of thymidine kinase-competent VZV and also two strains of thymidine kinase-deficient (TK<sup>−</sup>) VZV, with data also included for the reference anti-herpetic agent acyclovir.

Preliminary data shows that the compounds are more active than ACV. No cytotoxicity is detectable at the concentration required for antiviral activity. The absence of antiviral activity against thymidine kinase-deficient VZV strains indicates the requirement for thymidine kinase mediated phosphorylation for antiviral action as was previously observed for this family of compounds (8).

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- 3-(2'-deoxy- $\beta$ -D-ribofuranosyl)-6-(4-n-chlorophenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one (**5i**). <sup>1</sup>H-NMR (d<sub>6</sub>-DMSO; 300MHz); 8.91 (1H, s, H-4), 7.88 (2H, H<sub>a</sub>) – 7.57 (2H, H<sub>b</sub>) (AB system, <sup>3</sup>J = 7.89Hz, <sup>4</sup>J = 2.3Hz), 7.37 (1H, s, H-5), 6.19 (1H, dd, <sup>3</sup>J = 6.17Hz, H1'), 5.35 (1H, d, <sup>3</sup>J = 4.1Hz, 3'-OH), 5.24 (1H, t, <sup>3</sup>J = 5.12Hz, 5'-OH), 4.26 (1H, m, H-3'), 3.95 (1H, m, H-4), 3.70 (2H, m, H-5'), 2.41 and 2.13 (2H, m, 2-H'a and 2-H'b). MS (ES<sup>+</sup>) m/e 385 (MNa<sup>+</sup>, 100%), 269 (baseNa<sup>+</sup>, 10%). Accurate mass: C<sub>17</sub>H<sub>15</sub>N<sub>2</sub>O<sub>5</sub>ClNa requires: 385.0567; found: 385.0575. Found: C, 56.02%; H, 4.39%; N, 7.67%. C<sub>17</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>5</sub> requires: C, 56.29%; H, 4.17%, N, 7.72%.
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