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Mini-review

# Aryl furano pyrimidines: The most potent and selective anti-VZV agents reported to date

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Dedicated to Prof. Erik De Clercq on the occasion of reaching the status of Emeritus-Professor at the Katholieke Universiteit Leuven in September 2006.

**Abstract**

Bicyclic aryl furano pyrimidines represent the most potent anti-VZV agents reported to date. Lead compounds have $EC_{50}$ values in vitro as low as 0.1 nM and selectivity index values exceeding one million. They have an absolute requirement for VZV thymidine kinase (TK) and most likely act as their phosphate forms. Some structural modification, such as aryl substitution, is tolerated, while little sugar modification is acceptable. We herein summarise their biological profiles and structure activity relationships as discovered to date.


*Keywords:* Varicella zoster virus; Bicyclic nucleoside analogue; Shingles

## Contents



## 1. Introduction

Bicyclic nucleoside analogues (BCNAs) with a furanopyrimidine structure (**1**) have been known for over 20 years as unwanted by-products from the Pd-catalysed coupling of terminal alkynes with 5-iodo nucleosides, primarily deoxyuridine related (Robins and Barr, 1981, 1983; Crisp and Flynn, 1993). This by-product could be reduced by the use of dimethylformamide (DMF) as alternate reaction solvent (Robins et al., 1990), or could be enhanced by treatment of the (intended) 5-alkynyl nucleoside with copper(I) and triethylamine (Robins and Barr, 1983). Until our recent work, biological evaluation of the bicyclic by-products (**1**) (Fig. 1) had been limited to the parent compound (**1**, R = H) which was noted to be inactive as an antiviral against herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), cytomegalovirus (HCMV) and varicella zoster virus (VZV) (Kumar et al., 1991, 1996). Thus, it was surprising to us to note in 1999 the highly potent and specific anti-VZV activity of longer chain homologues of **1** (McGuigan et al., 1999). Activity peaked at R = C8(*n*-octyl), with a potency of 0.008–0.024 μM against VZV OKA and YS in vitro (Table 1). This compared to 1.9–2.1 μM for acyclovir in the same assay

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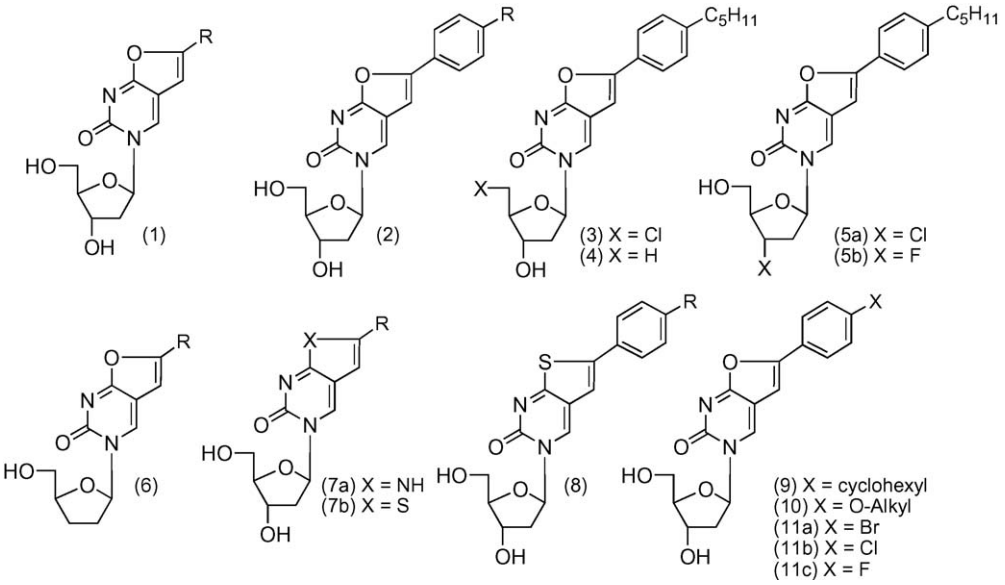


Fig. 1. Structures of BCNA nucleoside analogues.

(McGuigan et al., 1999). Thus, the lead octyl compound is ca. 300-times more potent than acyclovir vs. VZV. The whole family of agents of type **1** were all highly specific to VZV with no other detectable antiviral action, including the closely related herpes simplexvirus types 1 and 2 and Simian varicella virus (Sienaert et al., 2004). They were all rather non-cytotoxic ($CC_{50}$ values >50 μM).

Subsequently, with a view to restricting the conformational freedom of the alkyl chain, we reported the preparation and evaluation of the corresponding phenyl systems (**2**) with a range of *p*-alkyl substituents (R = H–*n*-octyl) (McGuigan et al., 2000). These were noted to be highly potent against VZV, with the optimal compounds (R = pentyl–hexyl) displaying a ca. 50-fold boost over the optimal leads of type **1**. Thus, the *n*-pentyl compound in series (**2**), R = $C_5H_{11}$, shows an $EC_{50}$ in vitro of ca. 0.1–0.5 nM versus VZV and is non-toxic at 200 μM. In our view this represents the most potent agent reported to date against VZV and amongst the most potent of antivirals in any area. Thus, **2**, R = nPnt is ca. 10,000 times more potent than acyclovir versus VZV in vitro and ca. 10–50 times more potent than BVDU (E-5-(2-Bromovinyl)-2′-deoxyuridine) (McGuigan et al., 2000).

In 2001, we reviewed the data to date on analogues of **1** and **2** and the structure activity relationships (SARs) and mechanism of action as we then knew it (McGuigan et al., 2001). We now update this review with a particular emphasis on the aryl family (**2**).

Table 1
Anti-VZV activity and cytotoxicity of representative BCNA compounds

| | $EC_{50}$ (μM) | | MCC (μM) | $CC_{50}$ (μM) |
|---|---|---|---|---|
| | OKA | YS | | |
| **1**, R = $C_8H_{17}$ | 0.008 | 0.010 | >50 | >50 |
| **2**, R = $C_5H_{11}$ | 0.0003 | 0.0001 | >200 | >200 |
| **3** | >5 | – | 20 | >50 |
| **4** | >5 | >5 | 20 | 95 |
| **5a** | >20 | – | ≥20 | >200 |
| **5b** | >2 | >2 | 5 | 5.2 |
| **6**, R = $C_8H_{17}$ | >5 | >5 | 20 | 112 |
| **7a**, R = $C_8H_{17}$ | 0.15 | 0.38 | ≥20 | >50 |
| **7b**, R = $C_8H_{17}$ | 0.003 | 0.005 | 20 | 53 |
| **8**, R = $C_5H_{11}$ | 0.014 | 0.025 | 50 | >200 |
| **9** | 1.4 | 3.0 | ≥20 | >200 |
| **10**, R = $C_5H_{11}$ | 0.001 | 0.001 | 40 | >200 |
| **11a** | 0.29 | 0.2 | ≥5 | 96 |
| **11b** | 0.09 | 0.08 | 35 | >200 |
| **11c** | >50 | >50 | ≥200 | 171 |

## 2. Sugar modifications

In the parent alkyl family (**1**) we have previously noted little tolerance for structural modification in the deoxyribose sugar (McGuigan et al., 2000a). Thus, for a range of alkyl compounds we found that conversion to the ribo- and arabino-analogues lead to significant (ca. 150–3000-fold) loss of antiviral activity. The importance of the deoxy ribose structure has more recently been further probed by the replacement of the 3′- and 5′-hydroxyl groups in the aryl family (**2**) by other functionalities. Thus, the 5′-deoxy-5′-chloro compound (**3**) was prepared via the usual alkyne coupling and cyclisation on 2′,5′-dideoxy-5′-chloro-5-iodo-2′-deoxyuridine (Luoni et al., 2003). The product was found to be very poorly active against VZV in vitro ($EC_{50} \geq 5$ μM), with a more than 10,000-fold reduction in potency versus **2**, R = pentyl. This supports the notion of VZV TK-mediated phosphorylation as an essential step in activation of these agents (Sienaert et al., 2002; Balzarini and McGuigan, 2002). This conclusion was further supported by the preparation and evaluation of the 5′-deoxy parent compound (**4**) (Luoni et al., 2004) which was again poorly active/inactive. On the basis of the essential requirement for VZV TK, the requirement for a free 5′-hydroxyl group is to be anticipated. However, the 3′-hydroxyl group is less obviously essential. Thus, it was of interest to test the corresponding 3′-chloro (**5a**) species. Again this was poorly active or inactive (Luoni et al., 2004). Similarly, we found that the 3′-fluoro