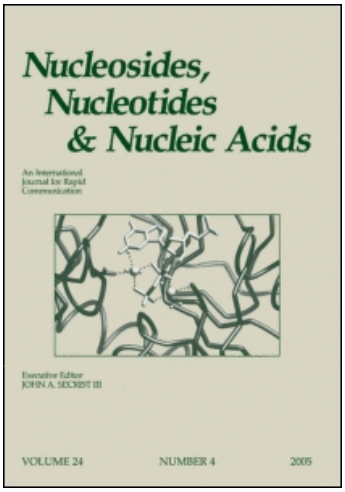

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Metabolic and Pharmacological Characteristics of the Bicyclic Nucleoside Analogues (BCNAs) as Highly Selective Inhibitors of Varicella-Zoster Virus (VZV)

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A unique class of bicyclic nucleoside analogues (BCNAs) was identified and found to display exquisite potency and selectivity as inhibitors of VZV replication in cell culture.[1] These compounds are characterized by the presence of a fused bicyclic pyrimidine ring, containing a bulky lipophilic aliphatic/aromatic moiety that is essential for antiviral activity. BCNAs are inactive against herpes simplex virus type 1 (HSV-1), type 2 (HSV-2), and simian varicella-zoster virus.

Previous studies have shown that VZV strains deficient in the virus-encoded thymidine kinase (TK) lose their sensitivity towards the BCNAs, suggesting a key role of this enzyme in the metabolic activation of the BCNAs. The BCNAs are selectively converted to their 5′-mono- and 5′-diphosphate derivatives by the VZV-encoded thymidine kinase (TK)/thymidylate (dTMP) kinase.[2] In contrast, BCNAs and BCNA 5′-monophosphates are not recognized by cytosolic TK-1, mitochondrial TK-2, HSV-1 TK and HSV-2 TK and by cytosolic dTMP kinase, respectively,

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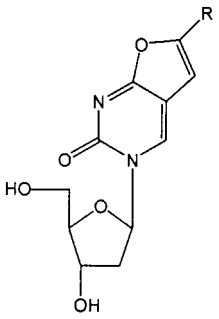

Cf 1368 ((3-(2′-deoxy-β-D-ribofuranosyl)-6-octyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one)) (R = octyl) represents the prototype of these BCNAs with an EC_{50} (50% effective concentration) of 0.008 μM against VZV.

Cf 1743 (R = *p*-pentylphenyl) is one of the most active BCNAs with an EC_{50} of 0.0003 μM

Figure 1. BCNA structure.

which explains their unprecedented selectivity for VZV. BCNA 5′-triphosphate formation from BCNA 5′-diphosphate by human erythrocyte NDP kinase could not be demonstrated in cell-free assays. Still, VZV DNA polymerase cannot be excluded as the final target and is currently under further investigation in our laboratory. TK-deficient (TK^-) HSV-1 replication in human osteosarcoma cells transduced with, and expressing the VZV TK gene, was not inhibited by the BCNAs, whereas (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU) strongly suppressed TK^- HSV-1 replication in these cells. This points to a selective VZV-directed action not only at the level of the VZV TK but also at the level of the eventual antiviral target.

In contrast with BVDU, the BCNAs are not converted by the human erythrocyte or *E.coli* thymidine phosphorylase (TPase) to their free base, and, in addition, the free base of the BCNAs is not inhibitory to human dihydropyrimidine dehydrogenase (DPD),[3] the enzyme that converts thymine and the anticancer drug 5-fluorouracil (5-FU) to their 5,6-dihydropyrimidine derivatives. Unlike BVDU, the BCNAs when administered together with 5-FU in mice, did not affect 5-FU plasma levels. Therefore, BCNAs may be expected not to affect 5-FU plasma levels in patients treated with 5-FU for cancer and concomitantly treated with the BCNAs for a concurrent VZV infection. The lack of substrate affinity of TPase for the BCNAs could be rationalized by computer-assisted modeling of Cf 1743 in the *E.coli* TPase active site using the coordinates of the enzyme/thymine complex.[4] Although the molecular mechanism of action of the BCNAs is currently unclear, we ascertained that, most likely, their anti-VZV activity is not based upon inhibition of VZV dTMP synthase by BCNA 5′-monophosphates.

The lack of interaction of the BCNAs with TPases and DPD, their very low cytotoxicity, high antiviral potency, good oral bioavailability (up to 40%, data not shown) as well as their easy synthesis make them very promising clinically useful anti-VZV drug candidates.

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