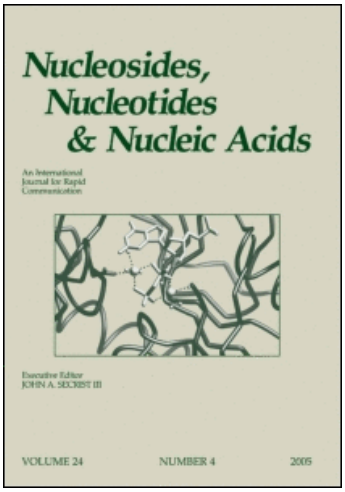


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# The Unabated Synthesis of New Nucleoside Analogues with Antiviral Potential: A Tribute to Morris J. Robins

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# THE UNABATED SYNTHESIS OF NEW NUCLEOSIDE ANALOGUES WITH ANTIVIRAL POTENTIAL: A TRIBUTE TO MORRIS J. ROBINS

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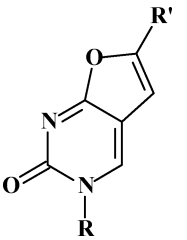


*The furo[2,3-*d*]pyrimidin-2(3*H*)-one is the key structural determinant in the exquisitely potent activity of its derivatives (R = 2-deoxyribosyl; R′ = p-pentylphenyl) against VZV (varicella-zoster virus) replication.*

## 1. INTRODUCTION

Referring to the 6-(alkyl-heteroaryl)furo[2,3-*d*]pyrimidin-2(3*H*)-one nucleoside, M.J. Robins concluded that "fortuitous combinations of structural features with the strongly hydrophobic *p*-alkylphenyl prodrugs resulted in unmatched potencies against VZV (varicella-zoster virus).[1] Such fortuitous combinations have, in fact, played a substantial part in the design and development of many nucleoside analogues as antiviral agents. Morris

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In honor of Morris J. Robins' 70th birthday.

I am much indebted to Mrs. C. Callebaut for her excellent editorial assistance and to Prof. G. Andrei and Prof. R. Snoeck for their expert help with the antiviral assays, and in particular the evaluation of activity against VZV and CMV, and to Prof. C. McGuigan (and his group at Cardiff) for the synthesis of Cf 1743. I am delighted and honored to dedicate this paper to my very good friend, colleague and top-notch chemist, Morris J. Robins, at the occasion of his seventieth birthday, as a grateful recognition for a collaboration that spanned almost 30 years.

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J. Robins has played a pioneering role in the design of many original nucleoside analogues and the synthetic approaches towards effective antiviral drugs.

Here, I review (some of) these strategies, pioneered by Morris Robins, with whom I was "fortunately" enough to collaborate on the biological (i.e., antiviral) side. This collaboration started in the early 1980s, now more than 25 years ago[2] and could be seen as emanating for an earlier collaboration I had started around 1976 with Phil Barr, Dick Walker, and Stan Jones (Chemistry Department, Birmingham University, UK) that had led to the discovery of (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU) as a potent and selective inhibitor of herpes simplex virus type 1 (HSV-1).[3] BVDU was then shown to be effective in vivo against VZV infections,[4] and has finally been licensed in several European countries for clinical use in the treatment of herpes zoster.[5]

I met with Morris Robins at several occasions, at several places, for example, in Edmonton (at the University of Alberta, Canada), Provo (at Brigham Young University, Utah, USA), in 1982 in Kyoto, Japan, at the International Symposium on Nucleic Acid Chemistry (24–26 November, 1982), in 1987 in Il Ciocco, Italy, at the NATO Advanced Study Institute/FEBS Advanced Course on Antiviral Drug Development: A Multidisciplinary Approach (10–23 May, 1987) and in 2002 in Leuven, Belgium, where Morris was an invited lecturer at the Fifteenth International Round Table on Nucleosides, Nucleotides and Nucleic Acids (10–14 September, 2002) (Figure 1).



## 2. BICYCLIC (FURANOPYRIMIDINE) NUCLEOSIDE ANALOGUES (BCNAs)

The history of bicyclic (furanopyrimidine) nucleoside analogues BCNAs is going back to the early 1980s when Morris Robins and Phil Barr [the same "Barr" as the one who was the first to synthesize BVDU[3,5] described 6-*n*-butyl-3-methylfurano[2,3-*d*]pyrimidin-2(3*H*)-one as a by-product of 5-hexynyl-1-methyluracil following treatment of 5-iodo-1-methyluracil with hexyne in triethylamine at 50°C for 2 hours in the presence of catalytic quantities of $(Ph_3P)_2PdCl_2$ and CuI under a nitrogen atmosphere.[6,7] Treatment of 5-hexynyl-1-methyluracil with CuI in triethylamine/methanol at reflux gave the fluorescent by-product in 92% yield.[6,7] Apparently, the product cyclization was catalyzed by CuI, but could be reduced by using dimethylformamide (DMF).[8] The bicyclic by-product was also obtained during palladium-catalyzed coupling of terminal alkynes with 5-(trifluoromethanesulfonyloxy)pyrimidine nucleosides.[9]

Starting from 5-(1-fluoro-2-bromoethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (compound **6b**), (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (**1a**, 7.5% yield) and the bicyclic product **9** (50% yield) were obtained; the bicyclic compound **9** was likely formed by the nucleophilic displacement of the bromine group

(**1a**) by the negatively charged oxygen at C-4 of the pyrimidine ring.[10] However, the bicyclic compound **9** (referred to as compound **10** in Kumar et al.[11]) was reported to be inactive in vitro against HSV-1, HSV-2, VZV and CMV, and so were 5-(1-azidovinyl)- and 5-[2-(1-azirinyl)]-2′-deoxyuridine, the target compounds synthesized in this study.[11]

Various 5-substituted 2′-deoxyuridines, the most prominent being (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU) have been reported as potent and selective inhibitors of herpes simplex virus (HSV).[12–14] 5-Alkynyl-2′-deoxyuridines have also been studied as potential antiviral agents, the parent 5-ethynyl-2′-deoxyuridine being a potent, but rather cytotoxic agent so that its antiviral selectivity index was too low to further consider this compound as a potential antiviral drug.[13] Aiming at reducing the cytotoxicity by extending the 5-ethynyl side chain to longer alkynyls, the synthesis of such 5-alkynyl-2′-deoxyuridines was undertaken (see section 3). Unexpectedly, the furopyrimidine derivatives containing a long alkyl ($C_8$-$C_{10}$) side chain (Figure 2) exhibited a highly potent and selective activity against varicella-zoster virus (VZV).[15] This activity was further increased if this aliphatic side chain was interrupted by a phenyl moiety, thus leading to a series of bicyclic furopyrimidine nucleoside analogues (BCNAs) bearing an aryl side chain,[16] the prototype of this class of compounds being Cf 1743[17] (Figure 2).



## 5-ALKYNYL-2′-DEOXYURIDINES

With 5-ethynyl-2′-deoxyuridine as the lead compound, several 5-alkynyl-2′-deoxyuridines (dUrds), that is, 5-propynyl-, 5-butynyl-, 5-pentynyl-, 5-hexynyl-, 5′-heptynyl-dUrd, were synthesized, the cut off point for antiviral activity (i.e., HSV-1) being 5-alkynyl substitutions longer than 5-pentynyl[2] (Figure 3). Also in this work a minor quantity of the furano[2,3-*d*]pyrimidin-2-one (see section 2) was observed as a fluorescent spot on thin-layer chromatography. Although some of the 5-alkynyl dUrds, that is, 5-propynyl-dUrd, achieved reasonable potency and selectivity in their antiviral activity, including anti-HSV-1 activity but also anti-vaccinia virus (VV) activity, the compounds were not further pursued for their eventual antiviral potential.

## 4. 8-SUBSTITUTED DERIVATIVES OF 9-[(2-HYDROXYETHOXY)METHYL]GUANINE (ACYCLOVIR)

Starting from BVDU and related 5-substituted dUrds various acyclic versions were derived, which, however, failed to exhibit any activity against HSV-1[18] (6-substituted derivatives such as the HEPT –1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine˝ analogues would later be

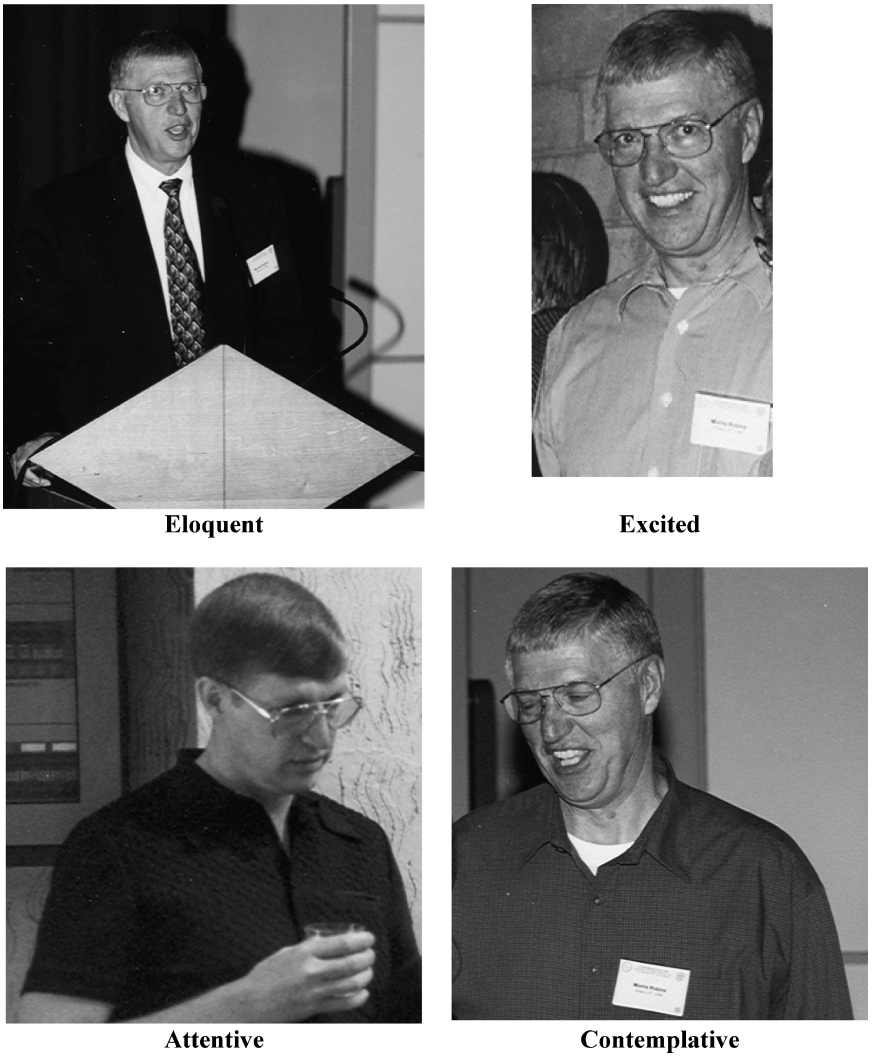



**FIGURE 1** Pictures taken of Morris J. Robins at the Fifteenth International Round Table on Nucleosides, Nucleotides, and Nucleic Acids in Leuven, Belgium, on 10–14 September 2002.

identified as specific inhibitors of HIV-1, thus representing the first NNRTIs (non-nucleoside reverse transcriptase inhibitors) ever described.[19,20]

However, with acyclovir as the starting compound, several 8-substituted derivatives, that is, 8-methyl-, 8-amino-, 8-bromo-, and 8-iodoacyclovir were obtained, which approached acyclovir in potency (Figure 4), and which were considered as worthy of further investigation.[18] Some of these compounds may have shown a therapeutic profile equal or superior to acyclovir, but this possibility was not further examined.

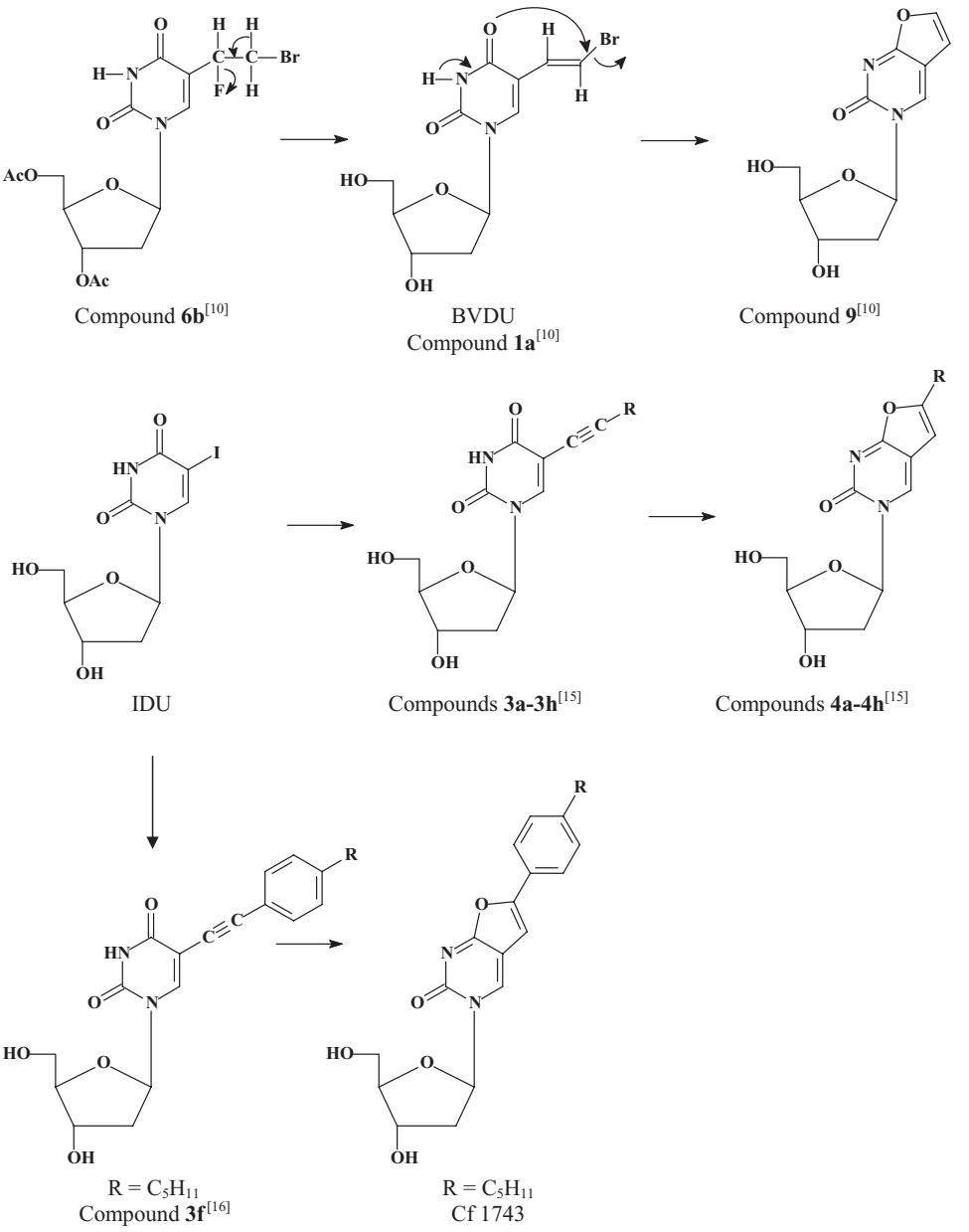
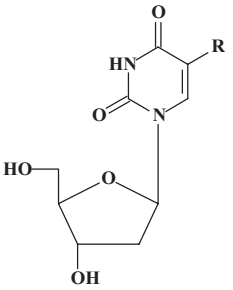



**FIGURE 2** From the furo[2,3-*d*]pyrimidin-2(3*H*)-one 2′-deoxynucleoside (compound **9**)[10] to Cf 1743.

## 5. NUCLEOSIDE ANTIBIOTICS TUBERCIDIN, TOYOCAMYCIN AND SANGIVAMYCIN

Of a wide variety of purine nucleoside analogues which were known to inhibit the replication of a broad spectrum of RNA viruses, tubercidin,

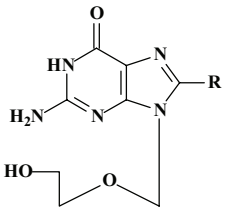



| | | $EC_{50}$ (μg/ml) for HSV-1 |
|---|---|---|
| R = C≡CH | : 5-ethynyl-dUrd | 0.5 |
| R = C≡C-$CH_3$ | : 5-propynyl-dUrd | 0.3 |
| R = C≡C-$CH_2$-$CH_3$ | : 5-butynyl-dUrd | 4 |
| R = C≡C-$CH_2$-$CH_2$-$CH_3$ | : 5-pentynyl-dUrd | 4 |
| R = C≡C-$CH_2$-$CH_2$-$CH_2$-$CH_3$ | : 5-hexynyl-dUrd | 108 |
| R = C≡C-$CH_2$-$CH_2$-$CH_2$-$CH_2$-$CH_3$ | : 5-heptynyl-dUrd | > 400 |

**FIGURE 3** Antiviral activity of 5-alkynyl-2′-deoxyuridines (data taken from De Clercq et al.[2])

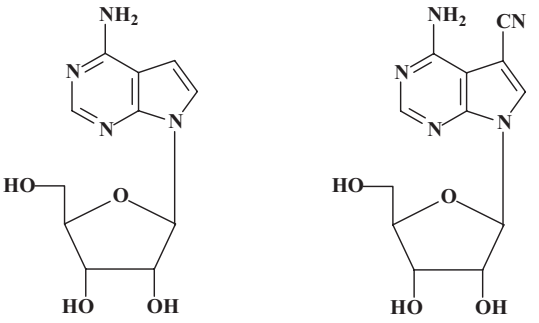


toyocamycin, and sangivamycin (Figure 5), emerged as potent inhibitors of the replication of several rhinovirus types, with a minimum inhibitory concentration well below 1 $\mu$g/ml.[21] Starting from these nucleoside




| | | $EC_{50}$ (μg/ml) for HSV-1 |
|---|---|---|
| R = H | : Acyclovir | 0.05 |
| R = $CH_3$ | : 8-Methylacyclovir | 0.5 |
| R = $NH_2$ | : 8-Aminoacyclovir | 0.7 |
| R = Br | : 8-Bromoacyclovir | 0.5 |
| R = I | : 8-Iodoacyclovir | 0.4 |

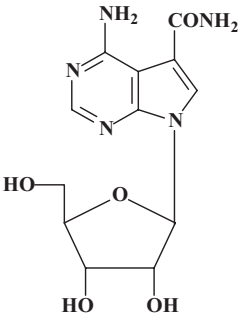
**FIGURE 4** Antiviral activity of 8-substituted acyclovir derivatives (data taken from Robins et al.[18])



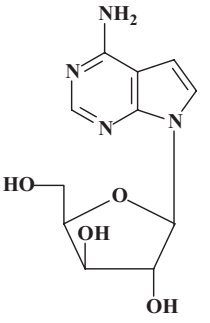

**Tubercidin**




**Toyocamycin**




**Sangivamycin**




***Xylo*-tubercidin**

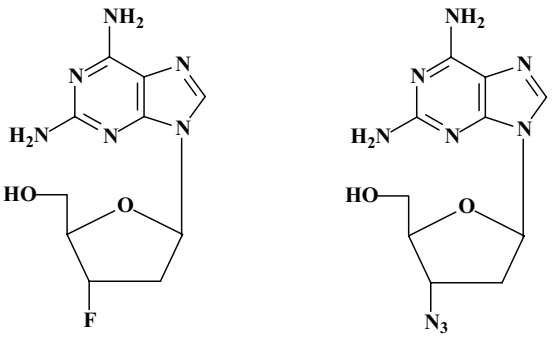


**FIGURE 5** Formulae of purine nucleoside analogues tubercidin, toyocamycin, sangivamycin and *xylo*-tubercidin.

antibiotics, sugar-modified analogues were prepared,[22] the *xylo*-tubercidin analogue exhibiting the most potent anti-HSV-1 and anti-HSV-2 activity with the lowest cytotoxicity.[22] This compound was further evaluated *in vivo*, and found, when administered intraperitoneally (ip) over a dosage range of 10 to 50 mg/kg per day, to achieve a significant reduction in the mortality rate of mice infected (ip) with HSV-2.[23] Under the same conditions, acyclovir did not offer any protection even when administered at doses up to 250 mg/kg per day. Despite these promising results, *xylo*-tubercidin has not been followed up further as a potential (topical or systemic) treatment of HSV-2 infections.

## 6. 2,6-DIAMINOPURINE 2′,3′-DIDEOXYRIBOSIDE DERIVATIVES AS POTENT ANTI-HIV AGENTS

Following up on the original observations in 1985 and 1986 of Mitsuya et al.[24] and Mitsuya and Broder[25] concerning the anti-HIV activity



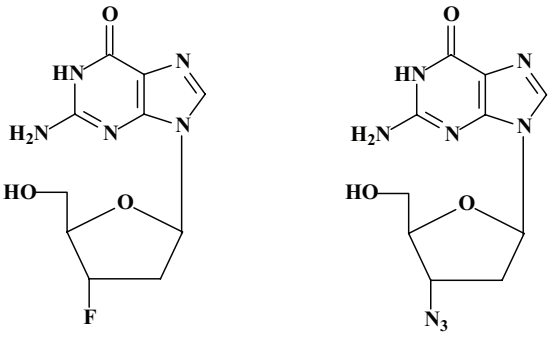




**FIGURE 6** Formulae of 3′-azido- and 3′-fluoro- analogues of 2,6-diaminopurine 2′,3′-dideoxyribosides and 2′,3′-dideoxyguanosines.



of 3′-azido-2′,3′-dideoxythymidine (AZT), 2′,3′-dideoxycytidine (ddC), 2′,3′-dideoxyinosine (ddI) and 2′,3′-dideoxyadenosine (ddA), we reported in 1987 and 1988 that 2,6-diaminopurine 2′,3′-dideoxyriboside (ddDAPR), 3′-azido-2,6-diaminopurine 2′,3′-dideoxyriboside (AzddDAPR), 3′-fluoro-2,6-diaminopurine 2′,3′-dideoxyriboside (FddDAPR), and 3′-fluoro-2′,3′-dideoxyguanosine (FddGuo) (Figure 6) had potent and selective activity against HIV;[26–28] ddDAPR and its 2′,3′-didehydro derivative being potent inhibitors of the deamination of 2′,3′-dideoxyadenosine (ddA).[29] ddDAPR and ddI were also found to strongly potentiate the antiretroviral activity of ribavirin, both in vitro and in vivo.[30]

AzddDAPR proved to be more potent by about one order of magnitude in inhibiting HIV replication than either ddDAPR, AzddAdo, or AzddGuo.[31] Although the pronounced anti-HIV activity of AzddDAPR

justified its evaluation as a putative therapeutic agent for HIV infections,[31] the compound was not further developed for this purpose.

## 7. MECHANISM-BASED INHIBITORS OF S-ADENOSYLHOMOCYSTEINE (SAH) HYDROLASE

The acyclic nucleoside analogue (*S*)-9-(2,3-dihydroxypropyl)adenine [(*S*)-DHPA] was the first antiviral agent[32] to be (later) recognized to exert its antiviral action through the inhibition of S-adenosylhomocysteine (SAH) hydrolase, and the therewith associated S-adenosylmethionine (SAM)-dependent methylation reactions (including those involved in the maturation of viral mRNAs). Following (*S*)-DHPA, various acyclic and carbocyclic adenosine analogues were identified as broad-spectrum antiviral agents,[33] the most potent of the series being 3-deazaneplanocin A.[34,35] The main indication of 3-deazaneplanocin A and related SAH hydrolase inhibitors would be the treatment of such severe hemorrhagic fever virus infections as Ebola.[34,35]

Mechanism-based inactivation of SAH hydrolase has been pursued by Morris Robins and his coworkers as a new strategy towards antiviral agents: that is, 2′-deoxy-2′-methylene tubercidin;[36] 6′-(*E*)- and (*Z*)-halohomovinyl adenosine derivatives,[37] 5-carboxaldehyde and 5-oximes of adenosine,[38] 4′-haloacetylene adenosine derivatives,[39] and dihalohomovinyl adenosine analogues[40,41] (Figure 7).

These mechanism-based inhibitors of SAH hydrolase have yielded interesting new insights in the molecular mechanisms inhibiting SAH hydrolase. However, their antiviral potency and/or selectivity was considered too weak for them to be further explored from an antiviral therapeutic viewpoint.

## 8. BACK TO THE FURO[2,3-*d*]PYRIMIDIN-2(3*H*)-ONE NUCLEOSIDE DERIVATIVES

Following the furo[2,3-*d*]pyrimidin-2-(3*H*)-one lead various acyclic 3-[(2-hydroxyethoxy)methyl] analogues of furo- and pyrrolo[2,3-*d*]pyrimidine nucleosides were synthesized, but, unfortunately, none of the compounds showed significant antiviral activity against VZV, CMV, or any other DNA or RNA viruses[42] (Figure 8). Starting from this lead, 6-(alkyn-1-yl)furo[2,3-*d*]pyrimidin-2(3*H*)-one nucleoside derivatives were synthesized (Figure 8) and they showed some activity against VZV or CMV.[43] However, virtually no antiviral activity was noted with the 5-(alkyn-1-yl)-1-(*p*-toluenesulfonyl)uracil derivatives.[44]

Further work along these lines led to the identification of 6-(alkyl-heteroaryl)furo[2,3-*d*]pyrimidin-2(3*H*)-one nucleosides[1] that were 20-fold more potent inhibitors of VZV replication than acyclovir, but

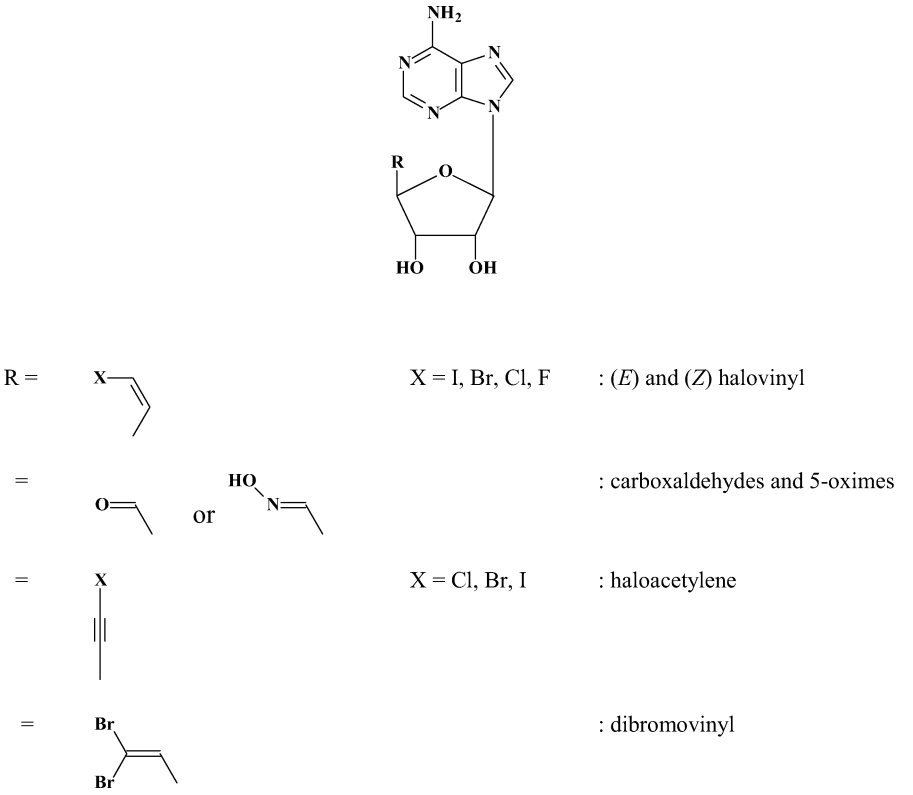



**FIGURE 7** Mechanism-based inhibitors of S-adenosylhomocysteine hydrolase (SAH).



still 6-fold less potent than BVDU, and 60-fold weaker than the 6-(4-pentylphenyl)prototype Cf 1743.[1] It was in this article that Morris Robins et al. mentioned that "the strongly hydrophobic *p*-alkylphenyl prodrugs led to unmatched anti-VZV potencies in vitro".[1]

## 9. AND WHAT HAPPENED WITH THE FURO[2,3-*d*]PYRIMIDIN-2(3*H*)-ONE DERIVATIVE Cf 1743 ?

As reviewed earlier,[17] the antiviral activity of Cf 1743 (Cf standing for Cardiff) (and the other furo[2,3-*d*]pyrimidine based BCNAs) is confined to VZV, and this antiviral activity depends on a specific phosphorylation by the VZV-encoded thymidine kinase; but, how the compound eventually acts in inhibiting VZV replication (i.e., by suppressing viral DNA synthesis) has so far not been resolved. Unlike BVDU, the furo[2,3-*d*]pyrimidine nucleoside analogues are not susceptible to degradation by human or bacterial thymidine phosphorylase, which may otherwise release the free aglycone. Also, the latter is not inhibitory to dihydropyrimidine dehydrogenase, an enzyme involved in the degradation of thymine, uracil and the anticancer

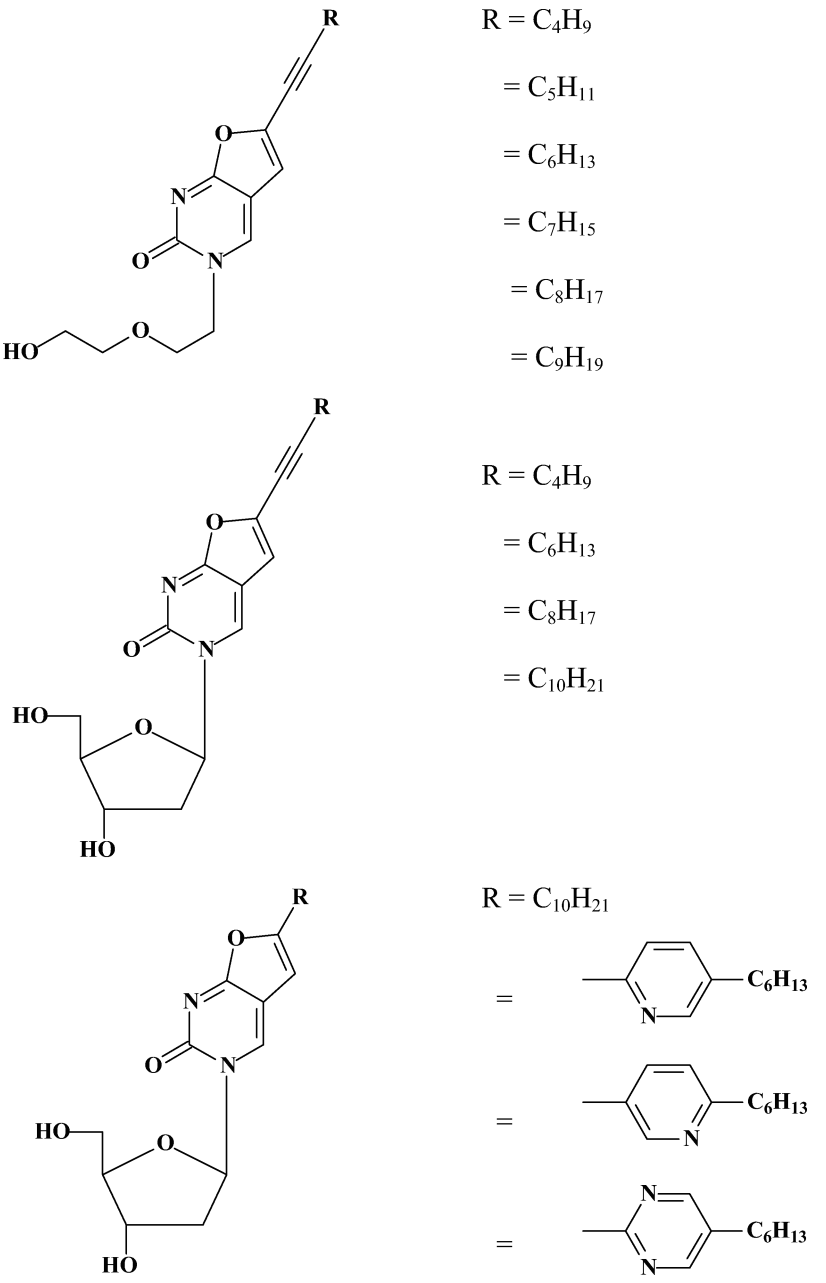
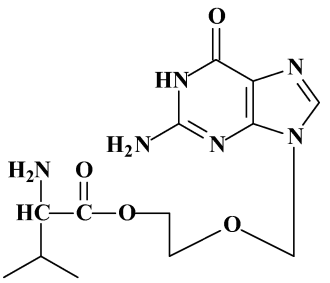
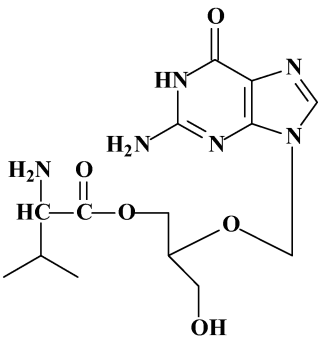



**FIGURE 8** Structures of 6-(alkyn-1-yl)- and 6-(alkyl-heteroaryl)furo[2,3-*d*]pyrimidin-2(3*H*)-one nucleoside derivatives.

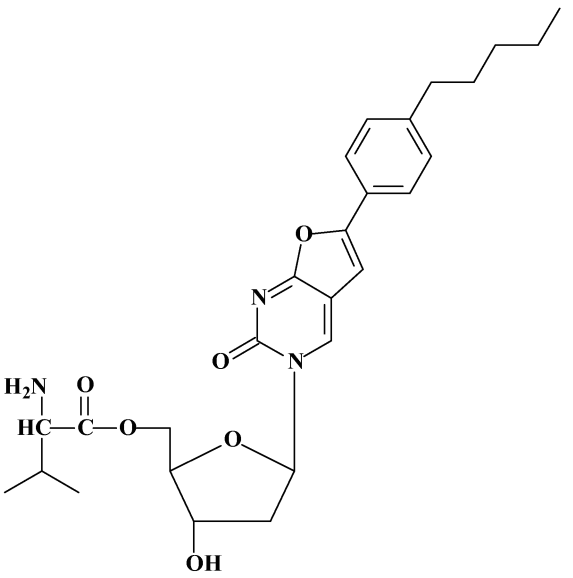
agent 5-fluorouracil [the aglycone of BVDU, (*E*)-5-(2-bromovinyl)uracil has, in fact, been shown to enhance the toxicity of 5-fluorouracil by interference with its degradation].[17]



Valaciclovir



Valganciclovir



FV-100

**FIGURE 9** Structures of the valine esters of acyclovir, ganciclovir and Cf 1743.

Given the exquisite potency of Cf 1743 against VZV, which exceeds that of acyclovir by a factor of 10,000-fold and has been demonstrated for all laboratory VZV strains and clinical VZV isolates that were looked at,[45] the compound was selected for further development as a potential antiviral drug for the treatment of VZV infections (such as herpes zoster). Following the prodrug concept that had proven so successful for the valine esters of acyclovir and ganciclovir, valaciclovir and valganciclovir (Figure 9), the valine ester of Cf 1743 (termed FV-100; FV standing for FermaVir)) was

constructed, so as to achieve sufficient oral bioavailability (Figure 9).[46] FV-100 has entered phase I clinical trials[47] and will proceed (in 2009) to phase II clinical trials for the treatment of herpes zoster (shingles).

## CONCLUSION

The furo[2,3-*d*]pyrimidin-2(3*H*)-one is the hallmark for new nucleoside analogues active against VZV. The compound Cf 1743 has remained the most potent and selective VZV inhibitor of this class. Although several new 6-(alkyl-heteroaryl)furo[2,3-*d*]pyrimidin-2(3*H*)-one derivatives have been synthesized, some of which proved more potent against VZV than acyclovir, the 6-(4-pentylphenyl) derivative Cf 1743 has so far not been superseded or even equalled in terms of anti-VZV potency. Its valine ester, FV-100, has proceeded smoothly through phase I clinical trials, and is expected to enter phase II clinical trials for treatment of herpes zoster in 2009.



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