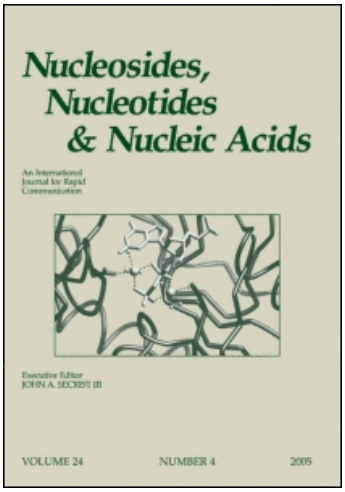


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Conformation and Antiherpes Activity of 3'- and 5'-Azido and Amino Analogs of 5-Methoxymethyl-2'-Deoxyuridine

Guy Tourigny[a]; Allan L. Stuart[b]; Irena Ekiel[c]; Philip J. Aduma[b]; Sagar V. Gupta[b]
[a] Departments of Chemistry, Veterinary Physiological Sciences, Saskatoon, Saskatchewan, Canada [b] University of Saskatchewan, Saskatoon, Saskatchewan, Canada [c] Division of Biological Sciences, National Research Council of Canada, Ottawa, Canada

To cite this Article Tourigny, Guy , Stuart, Allan L. , Ekiel, Irena , Aduma, Philip J. and Gupta, Sagar V.(1989) 'Conformation and Antiherpes Activity of 3'- and 5'-Azido and Amino Analogs of 5-Methoxymethyl-2'-Deoxyuridine', Nucleosides, Nucleotides and Nucleic Acids, 8: 7, 1189 — 1200
To link to this Article: DOI: 10.1080/07328318908054326
URL: http://dx.doi.org/10.1080/07328318908054326

NUCLEOSIDES & NUCLEOTIDES, 8(7), 1189-1200 (1989)

CONFORMATION AND ANTIHERPES ACTIVITY OF 3'- AND 5'-AZIDO AND AMINO ANALOGS OF 5-METHOXYMETHYL-2'-DEOXYURIDINE

Guy Tourigny,[†] Allan L Stuart,[††] Irena Ekiel,[†††]
Philip J. Aduma,[††] and Sagar V. Gupta[††]

Departments of Chemistry[†] and Veterinary Physiological Sciences,[††] University of Saskatchewan, Saskatoon, Saskatchewan, S7N 0W0, Canada, and Division of Biological Sciences,[†††] National Research Council of Canada, Ottawa, Canada, K1A 0R6.

Abstract

The molecular conformations of 3'- and 5'-azido and amino derivatives of 5-methoxymethyl-2'-deoxyuridine, 1, were investigated by nmr. The glycosidic conformation of 5-methoxymethyl-5'-amino-2',5'-dideoxyuridine, 5 had a considerable population of the syn form. The 5'-derivatives show a preference for the S conformation of the furanose ring as in 1. In contrast, the 3'-derivatives show preference for the N conformation. For 5-methoxymethyl-3'-amino-2',3'-dideoxyuridine, 3, the shift towards the N state is pH dependent. The preferred conformation for the exocyclic (C4',C5') side chain is g^+ for all compounds except 5 which has a strong preference for the t rotamer (79%). Compounds 1, 3 and 5 inhibited growth of HSV-1 by 50% at 2, 18 and 70 μg/ml respectively, whereas 2 and 4 were not active up to 256 μg/ml (highest concentration tested). The compounds were not cytotoxic up to 3,000 μM.

INTRODUCTION

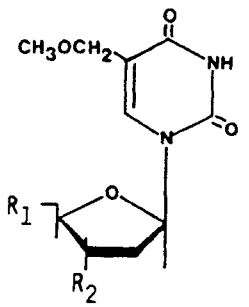
Several investigators have prepared 3'- and 5'-azido and amino derivatives of 5-substituted pyrimidine deoxyribonucleosides in an attempt to improve antiviral activity and/or decrease cytotoxicity.[1-4] In most cases, replacement of either hydroxyl group of the deoxyribofuranose moiety by an azido or amino group resulted in decreased antiviral activity. The loss of antiherpes activity of 5-bromovinyl-3'-amino-2',3'-dideoxyuridine was attributed to its slow rate of phosphorylation by virus-induced pyrimidine deoxyribonucleoside kinase.[4]

No explanation has been put forward for the loss of antiherpes activity of other 3' and 5'-azido and amino nucleoside analogs.[1-3]

We have previously reported that inversion of configuration of the 3'-hydroxyl group of 5-methoxymethyl-2'-deoxyuridine, 1 leads to complete loss of antiherpes activity, whereas 3'-O-derivatives were as active as the parent compound.[5-8] Relationship between antiherpes activity and conformation of 1 and its 3'- epimer, 5-methoxymethyl-1-(2'-deoxy-β-D-lyxofuranosyl)uracil revealed the importance of molecular geometry in determining the efficiency of phosphorylation by viral-kinase.[7] In this paper, the molecular conformations of 3' and 5'-azido and amino derivatives of 1 and their activity against herpes simplex virus will be discussed.

CHEMISTRY

5-Methoxymethyl-1-(5'-O-triphenylmethyl-2'-deoxy-β-D-lyxofuranosyl)uracil[6] was treated with methanesulfonyl chloride and lithium azide. Detritylation gave 5-methoxymethyl-3'-azido-2',3'-dideoxyuridine, 2. Reduction of 2 with hydrogen in the presence of Pd-PEI yielded 5-methoxymethyl-3'-amino-2',3'-dideoxyuridine, 3. 5-Methoxymethyl-5'-azido-2',5'-dideoxyuridine, 4 was prepared by the tosylation of 1 and azide substitution. Reduction with triphenylphosphine in pyridine gave 5-methoxymethyl-5'-amino-2',5'-dideoxyuridine, 5. 5-Methoxymethyl-2'-deoxyuridine-3'-p-aminophenylphosphate 6 was prepared as described by Stuart et al.[5] Structures are shown in FIG. 1.



1, $R_1 = R_2 = OH$

2, $R_1 = OH$, $R_2 = N_3$

3, $R_1 = OH$, $R_2 = NH_2$

4, $R_1 = N_3$, $R_2 = OH$

5, $R_1 = NH_2$, $R_2 = OH$

6, $R_1 = OH$, $R_2 = O\text{-}P(=O)(OH)\text{-}O\text{-}C_6H_4\text{-}NH_2$

FIG. 1.

TABLE 1. Proton chemical shifts in ppm relative to 3-methylsilyl-propanesulfonic acid, sodium salt in D_2O[a].

	Compound						
	1[b]	2	3	3	4	5	6
H-1'	6.27	6.20	6.28	6.20	6.28	6.17	6.27
H-2'	2.37	2.53	2.65	2.36	2.41	2.59	2.39
H-2"	2.42	2.55	2.64	2.27	2.51	2.41	2.55
H-3'	4.47	4.35	4.04	3.51	4.49	4.46	4.85
H-4'	4.03	4.04	4.25	3.81	4.11	4.11	4.20
H-5'	3.84	3.88	3.92	3.89	3.74	3.35	3.79
H-5"	3.76	3.80	3.83	3.77	3.60	3.21	3.72
H-6	7.98	7.96	7.96	7.89	7.86	7.73	7.94
CH_2	4.23 4.25	4.28	4.24	4.21	4.25	4.24	4.23
CH_3	3.36	3.35	3.34	3.34	3.36	3.37	3.35

[a]Spectra were recorded at the following pH: 2, 8.1; 3, 6.3 and 10.3; 4, 7.4; 5, 7.9; and 6, 5.5. [b]Data for 1 is included for comparison.[8]

Nuclear magnetic resonance analysis: The chemical shift data are summarized in TABLE 1. Chemical shifts were used for determining the conformation about the glycosidic bond in the 5'-substituted compounds. For the 5'-amino derivative, 5, H-2' is shifted downfield by 0.22 ppm and H-1' is shifted upfield by 0.1 ppm relative to 1. ^{13}C chemical shifts in the opposite direction are observed: C-2' upfield 1.3 ppm and C-1' downfield 2.2 ppm. The direction and magnitude of these chemical shifts indicate a considerable population of the syn form.[9] Further support for such a conclusion is provided by the value of the coupling constant ^3J(C-2, H-1') of 3.8 Hz, which is much higher

TABLE 2. Coupling constants (Hz).

	Compound						
	1[a]	2	3[b]	3[c]	4	5	6
J1'2'	6.2	5.8	6.1	4.3	6.5	6.9	7.1
J1'2"	6.5	6.4	6.7	7.4	6.8	6.9	6.3
J2'2"	-14.0	-14.5	-14.7	-14.0	-14.3	-14.1	-14.3
J2'3'	6.1	7.2	7.8	7.7	6.6	7.0	6.9
J2"3'	4.4	6.4	6.3	7.8	4.6	4.7	3.3
J3'4'	4.0	5.8	5.4	6.8	4.3	4.7	3.1
J4'5'	3.1	3.4	3.2	2.8	3.6	3.6	3.4
J4'5"	4.6	4.3	4.4	4.5	5.2	9.1	4.6
J5'5"	-12.2	-12.7	-12.6	-12.4	-13.6	-13.5	-12.4
J3'P	--	--	--	--	--	--	6.5

[a]Data for 1 is included for comparison.[8] [b]pH 6.3. [c]pH 10.3.

than for typical anti pyrimidine nucleosides.[10] On the basis of this data, we conclude that 5 at neutral pH exists as a syn $\rightleftharpoons$ anti equilibrium with similar populations of both forms. However, a different situation is present in the 5'-azido derivative, 4, for which the chemical shifts of H-1' and H-2' are nearly identical to that of the parent compound 1, which suggests that the anti form is preferred for 4. The chemical shift analysis of the 3'-derivatives to determine the conformation of the glycosidic bond was not conclusive.

The proton coupling constants and conformational populations are summarized in TABLES 2 and 3. Values for the equilibrium populations of the S and N-states were calculated using a pseudorotational model with the empirical parameters of the generalized Karplus relationship, as derived by Haasnoot et al.,[11] based on average values of the

TABLE 3. Conformation populations (%): S and N-conformers of the furanose ring and the three rotamers of the exocyclic C(5') side chain[a].

Conformer	Compounds						
	1[b]	2	3[c]	3[d]	4	5	6
S	60	48	48	40	59	55	70
N	40	52	52	60	41	45	30
g^+	58	59	59	62	60	15	56
g^{-}[e]	8	11	9	4	6	6	11
t	34	30	32	34	34	79	33

[a]The values reported are averages over all best fit conformational pairs with a deviation of < 5%. [b]Data for 1 is included for comparison. [c]pH 6.3. [d]pH 10.3. [e]Protons H-5' and H-5" were identified according to the method of Remin and Shugar.[22] For 5 this assignment was confirmed by NOE experiment.

pseudorotational parameter (P) and amplitude of puckering (τ_m) found in deoxyribonucleosides.[12] Calculations indicated that small modifications in the parameters of the two states present in the equilibrium do not significantly influence the relative populations. Although coupling constant values can be interpreted on the basis of the standard N-S equilibrium of the furanose ring, the values observed for J(2',3') are significantly higher than expected, especially in the 3'-amino and 3'-azido derivatives. This can be explained by the influence of the substituent electronegativity (only approximately taken into account in the calculations by the method of Haasnoot *et al.*[11]) or by the influence of the substituent on the geometry of the molecule. A significant improvement of the fit between experimental and calculated values of coupling constants was obtained by shifting the conformation equilibrium to 2'-*exo* $\rightleftharpoons$ 2'-*endo* (instead of the more common 3'-*endo* $\rightleftharpoons$ 2'-*endo*) and by flattening the ring (τ_m

31-32°), especially in the N-type state. For the 5'-derivatives, 4 and 5, the population of the S-state is comparable to that of the parent compound, 1. These values are within the range reported for deoxyribonucleosides.[12] The 3'-derivatives, 2 and 3, exhibit a small increase in the population of the N-state. A similar, but larger shift in conformational equilibrium towards the N-state has been observed for the 3'-amino derivatives of adenosine.[13] For the 3'-amino derivative, the shift towards the N-state is pH dependent: 60% at pH 10.3 and 52% at pH 6.3.

The populations of the three rotamers about the C(4')-C(5') bond were calculated using the parameters of the generalized Karplus-type relationship developed by Haasnoot et al.[14] The preferred conformation for the 3'derivatives, 2 and 3, is g^+ (59 and 62% respectively) which is similar to that of 1 (58%) even though there is a significant difference in the conformation equilibrium of the furanose ring. In contrast, 5'-substitution results in an appreciable decrease of the g^+ rotamer population. The 5'-amino derivative, 5, has a strong preference for the t rotamer (79%). A similar destabilization of the g^+ rotamer in 5-Iodo-5'-amino-2',5'-dideoxyuridine[15] and 5'-amino-5'-deoxythymidine[16] has been reported. Furthermore, our studies indicate that the conformation of the exocyclic group is pH and solvent dependent, and that at physiological pH values, the group is nearly rigid with the t rotamer in 79% of the molecules. Since the exocyclic group is nearly rigid, a Nuclear Overhauser Enhancement Method was used to confirm this assignment. However, it is interesting to note that N_3 or NH_2 substitution at 5'-postion has little effect on the conformational equilibrium of the furanose ring.

For comparison, the conformation of 5-methoxymethyl-2'-deoxyuridine-3'-p-aminophenylphosphate 6, which has a bulky substituent at the 3'-position was determined. Results indicate that the conformational populations of the furanose ring and the C(5') exocyclic side chain are similar to that of 1 (TABLE 3). These results indicate that the presence of the bulky p-aminophosphate group at the 3'-exo position has little effect on the conformer populations of the nucleoside. Similarly, acetylation of the 3'OH of 1 had little effect on conformation.[17] Substitution of the 3'-OH group by an amino group leads to a small change in conformer populations of furanose ring which becomes more significant at high pH.

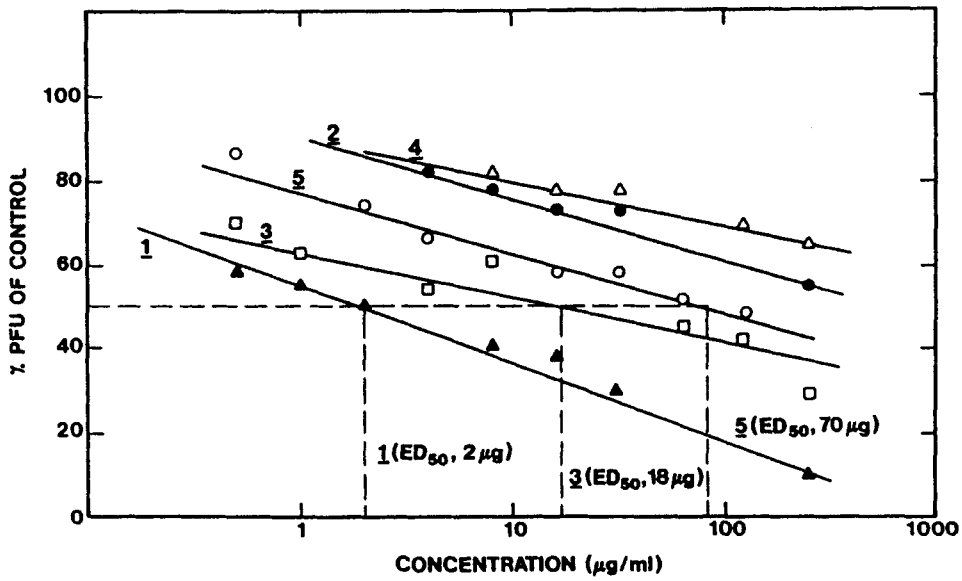


FIG. 2. Dose response curves for compounds 1 to 5 against HSV-1 strain KOS in Vero cells. Virus input was 50 PFU.

BIOLOGICAL

The antiviral activity of compounds 1 to 5 against Herpes simplex virus type 1 (HSV-1) strain KOS are shown in FIG. 2. The concentration required to inhibit the growth of virus by 50% (ED_{50}) for compounds 1, 3 and 5 were 2, 18 and 70 μg/ml respectively. A similar decrease in antiherpes activity was also reported for the 5'-amino derivatives of 5-halo-2'-deoxyribonucleosides[2,18] and for the 3'-amino derivative of 5-bromovinyl-2'-deoxyuridine.[4] In contrast, the azido derivatives, compounds 2 and 4 were devoid of activity against HSV-1 up to a concentration of 256 μg/ml (hignest concentration tested). It is noteworthy that 6, which has a bulky substituent at the 3'-position, is almost as active as the parent compound.[5] Compounds 2-5 did not show any visible signs of toxicity up to 3,000 μM (monolayers). Compounds 2-5 were also devoid of adverse effect on normal cell metabolism as determined by incorporation of methyl-^{3}H-thymidine and 6-^{3}H-deoxyuridine into host cell DNA up to 1,200 μM (the highest concentration tested). Earlier studies have shown that 1 has very low mamma-

lian toxicity.[19-21] It is interesting to note that the amino analogues, 3 and 5 are even less cytotoxic than the parent compound, 1.

EXPERIMENTAL SECTION

Tritiated thymidine [methyl-^{3}H], specific activity 20 Ci/mmole, and tritiated deoxyuridine [6-^{3}H], specific activity 17.5 Ci/mmole, NSC solubilizer and chemicals for radioactivity counting were obtained from Amersham/Searle, Canada. All other chemicals used were of reagent grade. Thin layer chromatography (TLC) was performed using silica gel sheets (Machinery-Nagel) at 22°. Compounds were detected as quenching spots when viewed under UV light. R_f values are ± 0.05. Evaporations under reduced pressure were performed on a Buchi rotary evaporator at 30-35°. A Beckman recording spectrophotometer, Model DU-8 was used to measure the spectra of compounds. Radioactivity was determined using a liquid scintillation counter (Beckman Model LS 8,000). The composition of scintillation fluid was: PPO, 5 g; POPOP, 75 mg; toluene, 1 litre. Melting points were determined with a Gallenkamp apparatus and are uncorrected. Microanalyses (C, H, N) were performed by the Department of Chemistry, University of Saskatchewan, Saskatoon.

NMR Spectroscopy: The NMR experiments were carried out using Bruker 200 and 500 MHz AM Spectrometers. Spectra were recorded in the Fourier transform mode. Solutions were made in D_2O at the following concentrations: 2 (12 mM, pH 8.1), 3 (26 mM, pH 6.3 and 10.3), 4 (10 mM, pH 7.4), 5 (24 mM, pH 7.9) and 6 (19 mM, pH 5.5). The pH of NMR samples in D_2O refer to uncorrected pH meter readings. Chemical shifts were measured relative to internal trimethylsilylpropane sulfonic acid, sodium salt (TSP). The spectra were simulated with the aid of standard Bruker software and final coupling constants have a precision of 0.2 Hz.

5-Methoxymethyl-3'-azido-2',3'-dideoxyuridine, 2: Methanesulfonyl chloride (0.74 mL, 9.6 mmol) was added to a solution of 5-methoxymethyl-1-(5'-O-triphenylmethyl-2'-deoxy-β-D-lyxofuranosyl)uracil[6] (1.6 g, 3.1 mmol) in 15 mL of dry pyridine and the solution was stirred at 4°C for 16 h. After addition of H_2O (0.4 mL) and stirring for 1 h, the reaction mixture was added dropwise to 300 mL of ice-water. The precipitate was recovered by filtration, dissolved in $CHCl_3$ and the

solution was washed successively with 0.1 M HCl, H_2O, 5% $NaHCO_3$, H_2O and dried over Na_2SO_4. The solvent was evaporated to yield 5-methoxymethyl-1-(5'-O-triphenylmethyl-3'-O-mesyl-2'-deoxy-β-D-lyxofuranosyl) uracil (1.8 g) as an amorphous powder. The mesyl derivative was dissolved in 10 mL of dry DMF, a threefold excess of LiN_3 was added and the mixture was stirred at 100°C for 3 h under anhydrous conditions. The solution was cooled and added to vigorously stirred ice-water. The precipitate was isolated by filtration, washed thoroughly with H_2O and dried to yield 5-methoxymethyl-5'-O-triphenylmethyl-3'-azido-2',3'-dideoxyuridine (1.4 g, 85%). For detritylation, 14.0 mL of 80% HOAC was added and the mixture was kept at 50°C for 3 h. After cooling, triphenylmethanol was removed by filtration and the solvent was evaporated. The oily residue was dissolved in a minimum amount of $CHCl_3$ and the solution was applied to a silica gel column (2.5 x 90 cm) previously equilibrated with $CHCl_3$. The column was eluted with 450 mL of $CHCl_3$ followed by a 95:5 mixture of $CHCl_3$-MeOH. The fractions containing 2 (as monitored by TLC, R_f 0.30, EtOAc) were combined and evaporated to give an oily residue which on storage at 4°C gave a white amorphous powder (0.47 g, 61%), mp 76-78°C; UV λ_{max} (MeOH) 264 nm, ε 10,800 and λ_{min} 231 nm, ε 2,450; Anal. Calc. for $C_{11}H_{15}N_5O_5 \cdot 1/2\ H_2O$: C 43.14, H 5.26, N 22.87; found: C 43.24, H 5.53, N 22.43.

5-Methoxymethyl-3'-amino-2',3'-dideoxyuridine, 3: A solution of 2 (0.15 g, 0.49 mmol) in 75 mL of methanol was hydrogenated under 35 psi of hydrogen pressure at room temperature in the presence of 0.60 g of Pd-PEI for 8 h. The catalyst was removed by filtration, the filtrate acidified with HCl and the solvent was evaporated. Recrystallization from EtOH gave 3 as the hydrochloride salt (0.068 g, 45%); mp 163-164°C, uv λ_{max} (MeOH) 265 nm, ε 11,100 and λ_{min} 232 nm, ε 2,100; Anal. Calc. for $C_{11}H_{18}N_3O_5Cl$: C 39.47, H 6.32, N 12.55; found: C 39.69, H 6.17, N 12.09.

5-Methoxymethyl-5'-O-p-toluenesulfonyl-2'-deoxyuridine: p-Toluenesulfonyl chloride (2.5 g, 13 mmol) was added to a solution of 1 (3.0 g, 11 mmol) in 15 mL of dry pyridine and the reaction mixture was stirred at 4°C for 24 h. After evaporation of the solvent, the oily residue was repeatedly shaken with ether (5 x 50 mL) and water (5 x 100 mL) and the washings were discarded. The residue was dissolved in

$CHCl_3$, dried and the solvent was removed to yield a white amorphous solid (3.4 g, 72%). Recrystallization from EtOAc gave white needles: mp 151-152°C; UV λ_{max} (MeOH) 263 nm, ε 9,400 and λ_{min} 241 nm, ε 3,800; ^{1}HNMR (dmso-d_6) δ 7.80, 7.48 (d,d,4,J_{AB} = 8.05 Hz, ArH), 7.58 (s,1 H-6), 6.14 (t,1,H-1'), 4.3-4.1 (m,3,H-3', H-5', H-5"), 4.05 (s,2,CH_2), 3.8-3.4 (m,1,H-4'), 3.24 (s,3,OCH_3), 2.42 (s,3,p-CH_3), 2.3-2.0 (m,2,H-2', H-2"); Anal. Calc. for $C_{18}H_{22}N_2O_8S$: C 50.70, H 5.20, N 6.56; found: C 51.09, H 5.41, N 6.45.

5-Methoxymethyl-5'-azido-2',5'-dideoxyuridine, 4: Lithium azide (0.40 g, 8.2 mmol) was added to a solution of 5-methoxymethyl-5'-O-p-toluenesulfonyl-2'-deoxyuridine (1.07 g, 2.5 mmol) in 8 mL of dry DMF and the mixture was stirred under anhydrous conditions at 80°C for 2 h. The solvent was removed and the residue was recrystallized from MeOH to yield 4 (0.41 g, 55%); mp 159-160°C, UV λ_{max} (MeOH 264 nm, ε 9,900 and λ_{min} 231 nm, ε 2,200; Anal. Calc. for $C_{11}H_{15}N_5O_5 \cdot 1/2\ H_2O$: C 43.14, H 5.26, N 22.87; found: C 42.95, H 5.31, N 22.94.

5-Methoxymethyl-5'-amino-2',5'-dideoxyuridine, 5: A mixture of 4 (0.15 g, 0.49 mmol) and triphenylphosphine (0.23 g, 0.88 mmol) in 1.5 mL anhydrous pyridine was stirred at 30°C for 1 h. NH_4OH (0.2 mL) was added and the solution was stirred for 2 h. After removal of the solvent, the residue was triturated with H_2O, filtered and the aqueous phase was extracted successively with benzene (2 x 10 mL) and ether (2 x 10 mL). The pH was adjusted to 4 with HCl and the solvent was evaporated to yield an amorphous powder. Recrystallization from EtOH gave 5 as the hydrochloride salt (0.11 g, 70%); mp 222-225°C (dec); UV λ_{max} (MeOH) 264 nm, ε 10,400 and λ_{min} 231 nm, ε 2,300; Anal. Calc. for $C_{11}H_{18}N_3O_5Cl$: C 42.93, H 5.90, N 13.65; found: C 43.36, H 6.21, N 13.12.

Biological Activity

(i) Cell Culture and Virus: HSV-1 strain KOS was used. Vero cells were grown in Eagle minimal essential medium (MEM) and virus stock was prepared as previously described.[21]

(ii) Drug Inhibition Assay: Antiviral activity was determined according to procedures described previously.[21] The confluent cell monolayers were infected with 50 plaque gorming units of virus/well. After 1 h, the unadsorbed virus was removed by washing with plain MEM solution. Each compound dissolved in assay media (MEM containing 4%

FCS) at the appropriate concentration was added. For plaque assays, 1 unit of neutralizing antibody was included in the culture fluid. After 72 h incubation at 37°C and 5% CO_2, plaques were stained and enumerated. In each experiment, toxicity controls (containing test compound and medium only), cell controls (containing medium only) and virus controls (containing virus and medium only) were run simultaneously. From dose response curves, the concentration of each compound required to cause 50% reduction in plaque numbers was determined. The cytotoxicity of each compound was determined microscopically.

(iii) Deoxyribonucleoside Uptake Studies: Effects of compounds on the incorporation of methyl-^{3}H-thymidine and 6-^{3}H-deoxyuridine into DNA were investigated using rabbit kidney (RK-13) cells according to procedures described previously.[5] Control cells (without exposure to drug or label) were processed in an identical manner for each experiment. The data were expressed as percentage inhibition as compared with control versus drug concentration.

ACKNOWLEDGEMENTS

This investigation was supported by a Research Grant, MA-5833, from the Medical Research Council of Canada. The authors greatfully acknowledge the technical assistance of Miss Rachelle Brandell. We also thank Drs. D. Bundle and J.R. Brisson for allowing the use of their NMR spectrometers at the National Research Council, Ottawa, Canada.

REFERENCES

1. Lin, T.S.; Neenan, J.P.; Cheng, Y.C.; Prusoff, H. J. Med. Chem. 1976, 19, 195.
2. Lin, T.S.; Prusoff, W.H. J. Med. Chem. 1978, 21, 106.
3. Lin, T.S.; Fischer, P.H.; Prusoff, W.H. Biochem. Pharmac. 1982, 31, 125.
4. DeClercq, E.; Descamps, J.; Balzarini, J.; Fukui, T.; Allaudeen, H.S. Biochem. J. 1983, 211, 439.
5. Stuart, A.L.; Ayisi, N.K.; Tourigny, G.; Gupta, V.S. J. Pnarm. Sci. 1985, 74, 246.
6. Quail, J.W.; Ekiel, I.; El-Kabbani, O.A.L.; Tourigny, G.; Delbaere, L.T.J.; Stuart, A.L.; Gupta, V.S. Can. J. Chem. 1986, 64, 1355.

7. Gupta, V.S.; Tourigny, G.; Stuart, A.L.; DeClercq, E.; Quail, J.W.; Ekiel, I.; El-Kabbani, O.A.L.; Delbaere, L.T.J. Antiviral Res. 1987, 7,69.
8. El-Kabbani, O.A.L.; Ekiel, I.; Delbaere, L.T.J.; Tourigny, G.; Stuart, A.L.; Gupta, V.S. Nucleosides and Nucleotides 1986, 5, 95.
9. Cadet, J.; Taieb, C.; Remin, M.; Niemczura, W.P.; Hruske, F.E. Biochim. Biophys. Acta. 1980, 608, 435.
10. Davies, D.B. Stud. Biopnys. 1976, 55, 29.
11. Haasnoot, C.A.G.; de Leeuw, F.A.A.M.; de Leeuw, H.P.M.; Altona, C. Org. Magn. Res. 1981, 15, 43.
12. Davies, D.B. Prog. Nucl. Magn. Reson. Spectr. 1978, 12, 136.
13. Plach, H.; Westnox, E.; Ludemann, H.D.; Mengel, R. Eur. J. Biochem. 1977, 80, 295.
14. Haasnoot, C.A.G.; de Leeuw, F.A.A.M.; de Leeuw, H.P.M.; Altona, C. Rec. Trav. Cnem. Phys. Bas. 1979, 98, 576.
15. Birnbaum, G.I.; Lin, T.S.; Snian, G.T.; Prusoff, W.H. J. Am. Chem. Soc. 1979, 101, 3353.
16. Nottoli, E.; Lambert, J.B.; Letsinger, R.L. J. Amer. Chem. Res. 1977, 99, 3486.
17. Quail, J.W.; Tourigny, G.; Delbaere, L.T.J.; El-Kabbani, O.A.L.; Stuart, A.L.; Gupta, V.S. Acta Cryst. (in press).
18. Lin, T.S.; Chai, C.; Prusoff, W.H. J. Med. Chem. 1976, 19, 915.
19. Gupta, V.S. Drugs of the Future. 1981, 6, 32.
20. Meldrum, J.B.; Gupta, V.S.; Doige, C.E. Toxicol. Appl. Pharmacol. 1980, 53, 530.
21. Ayisi, N.K.; Gupta, V.S.; Meldrum, J.B.; Taneja, A.K.; Babiuk, L.A. Antimicrob. Agents Chemother. 1980, 17, 558.
22. Remin, M.; Shugar, D. Biochem. Biophys. Res. Commun. 1972, 48, 6361.

Received July 27, 1988.