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DESIGN AND SYNTHESIS OF 6-FLUOROPURINE ACYCLONUCLEOSIDES : POTENTIAL PRODRUGS OF ACYCLOVIR AND GANCICLOVIR

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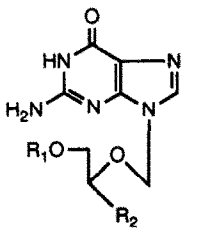
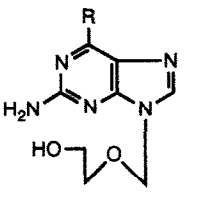
Abstract : 6-Fluoropurine acyclonucleosides **6** and **7** have been prepared as potential prodrugs of acyclovir and ganciclovir. It has been found that compounds **6** and **7** are 11.6 and 7.6 times more efficiently metabolized to acyclovir and ganciclovir by adenosine deaminase than the corresponding 6-aminopurine acyclonucleosides **4** and **12**, respectively.

Acyclovir (ACV, **1**)[2] and ganciclovir (DHPG, **2**)[3] are clinically useful antiherpetic agents that exhibit potent and selective activity against herpes viruses including herpes simplex virus type 1 (HSV-1) and 2 (HSV-2), human cytomegalovirus (HCMV), and varicella zoster virus (VZV). Both compounds appear to act by a similar mechanism. ACV and DHPG are selectively converted to their monophosphates by HSV (or VZV) encoded thymidine kinase.[2,4] HCMV does not encode a thymidine kinase[5] but induces a high level of host deoxyguanosine kinase.[6] These monophosphates are further phosphorylated by host cellular kinases to the corresponding triphosphate forms, which exert the antiviral effect by interfering with viral DNA synthesis through both a direct inhibitory effect on the viral DNA polymerase and a chain-terminating effect.[2,4] When ACV was administered orally in human, 15-20% of the dose was typically absorbed.[7] This degree of absorption is adequate to treat herpes simplex infections effectively, however, greater absorption is necessary in therapy against less sensitive viruses such as varicella zoster virus.[8]



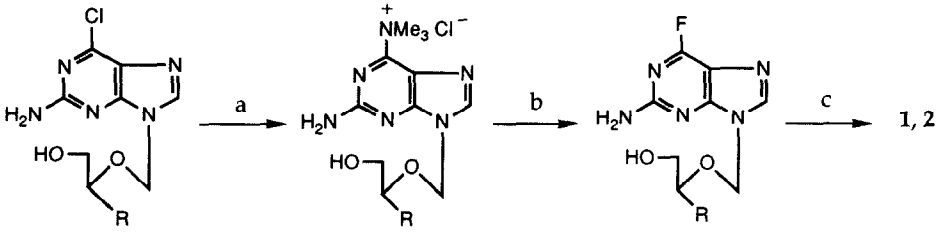


1 : R_1 = R_2 = H, Acyclovir
2 : R_1 = H, R_2 = CH_2OH, DHPG
5 : R_1 = L-valyl, R_2 = H

3 : R = H
4 : R = NH_2

It was reported that bioavailability of orally administered DHPG in human was only 4.6 and 3.0% for the 10- and 20-mg/kg multiple dosing regimens, respectively.[9] Therefore, much effort has been devoted in attempts to find prodrugs that are well absorbed after oral administration and then converted to ACV or DHPG. Recently, Schaeffer *et al.* have developed two promising prodrugs of acyclovir, 6-deoxyacyclovir **3**[8] and 2,6-diamino-9-[(2-hydroxyethoxy)methyl]purine **4**[10]. 6-Deoxyacyclovir **3** was well absorbed after oral administration and extensively oxidized to ACV by xanthine oxidase.[8] The 6-deoxy-6-amino congener of ACV, **4**, was readily deaminated to ACV by adenosine deaminase, an enzyme that is abundantly present in intestine and most other mammalian tissues.[11] Oral administration of **4** in dogs and rats resulted in peak plasma concentrations and total urinary recoveries of ACV greater than those observed after equivalent oral doses of ACV.[12] It has been also reported that the L-valyl ester of ACV, **5**, is 3-fold better absorbed than ACV upon oral administration and is now undergoing clinical evaluation.[13] Baer *et al.*[14] showed that adenosine deaminase dechlorinates 6-chloropurine ribonucleoside and 2-amino-6-chloropurine ribonucleoside to yield inosine and guanosine. On the basis of this finding, we envisioned that the more reactive fluoro atom at 6 position of purine nucleoside would be more readily defluorinated by adenosine deaminase than a chloro atom or an amino group. Furthermore, introduction of a fluoro atom at 6 position of ACV or DHPG was expected to increase water solubility, which would result in increased bioavailability. Therefore, the 6-deoxy-6-fluoro congeners of ACV and DHPG, **6** and **7**, have been synthesized as potential prodrugs of ACV and DHPG, respectively.

Scheme 1[a]



8 : R = H
9 : R = CH_2OH

10 : R = H
11 : R = CH_2OH

6 : R = H
7 : R = CH_2OH

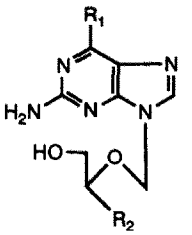
[a](a) NMe_3, DMF, rt, 3 h; (b) KF, DMF, 80 °C, 2 h; (c) adenosine deaminase, phosphate buffer solution (pH 7.5), rt, overnight

The 6-chloropurine acyclonucleosides **8**[15] and **9**[16] were treated with anhydrous trimethylamine in DMF to afford the corresponding quaternary trimethylammonium salts **10**[17] and **11**[18] in 81% and 70% yields, respectively. Reaction of trimethylammonium salts **10** and **11** with KF in DMF afforded 6-fluoropurine acyclonucleosides **6**[19] and **7**[20] in 60% and 56% yields, respectively. Enzymatic defluorination of **6** and **7** with an excess of calf intestinal mucosa adenosine deaminase in phosphate buffer solution at pH 7.5 resulted in complete conversion of these

prodrugs into ACV and DHPG.

The rates for deamination of **4**, 2,6-diamino-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]-purine **12** and adenosine, for dechlorination of **8** and **9**, and for defluorination of **6** and **7** in the presence of calf intestinal mucosa adenosine deaminase in buffered solutions of varying substrate concentrations were determined according to a published procedure[16]. The data were plotted according to the method of Lineweaver and Burk, and the results are shown in Table I.

Table I. Some Kinetic Constants with Calf Intestinal Mucosa Adenosine Deaminase[a]



substrate	R_1	R_2	*Km* (μM)[b]	*Vmax* (μmoles/min/unit)[b]
4	NH_2	H	268.5 ± 14.2	$8.16 \times 10^{-4} \pm 0.41 \times 10^{-4}$
8	Cl	H	102.8 ± 4.9	$3.41 \times 10^{-4} \pm 0.16 \times 10^{-4}$
6	F	H	340.9 ± 20.7	$1.20 \times 10^{-2} \pm 0.08 \times 10^{-2}$
12	NH_2	CH_2OH	553.6 ± 36.2	$1.04 \times 10^{-3} \pm 0.06 \times 10^{-3}$
9	Cl	CH_2OH	290.3 ± 12.1	$3.26 \times 10^{-4} \pm 0.15 \times 10^{-4}$
7	F	CH_2OH	542.5 ± 25.8	$7.73 \times 10^{-3} \pm 0.34 \times 10^{-3}$
adenosine			50.45 ± 3.9	$7.60 \times 10^{-1} \pm 0.47 \times 10^{-1}$

[a] Purchased from Sigma Chem. Co. [b] Mean ± S.D. value of 3 determinations.

From these enzyme kinetic studies, it has been found that the 6-fluoropurine acyclonucleosides **6** and **7** were 11.6 and 7.6 times more efficient substrates for adenosine deaminase in terms of *Vmax*/*Km* than the 6-aminopurine acyclonucleosides **4** and **12**. In addition, the compounds **6** and **7** showed fair increases of water solubility compared to ACV and DHPG, respectively (3.8 *vs.* 1.5 and 8.0 *vs.* 4.3 mg/mL at 25 °C). These results suggest that 6-fluoropurine acyclonucleosides **6** and **7** might have clinical usefulness as prodrugs of ACV and DHPG suitable for oral administration.

References and Notes

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17. **10** : mp 156.5-157 °C (dec); ^{1}H NMR (DMSO-d_6) δ 8.58 (s, 1 H, C_8H), 7.39 (s, 2 H, NH_2), 5.55 (s, 2 H, NCH_2O), 4.82 (t, J = 5.3 Hz, 1 H, OH), 3.73 (s, 9 H, NMe_3), 3.56-3.46 (m, 4 H, CH_2CH_2); MS (EI) *m/e* 266 (M^+-HCl), 252 (M^+-CH_3Cl); HRMS calcd for $C_{11}H_{18}N_6O_2$ (M^+-HCl) *m/e* 266.1491, found 266.1482.
18. **11** : mp 157-159 °C (dec); ^{1}H NMR (DMSO-d_6) δ 8.58 (s, 1 H, C_8H), 7.37 (s, 2 H, NH_2), 5.64 (s, 2 H, NCH_2O), 4.78 (t, J = 5.6 Hz, 2 H, 2 OH), 3.73 (s, 9 H, NMe_3), 3.62 (m, 1 H, CH) 3.45 (m, 2 H, CH_2), 3.32(m, 2 H, CH_2); MS (EI) *m/e* 296 (M^+-HCl), 282 (M^+-CH_3Cl); HRMS calcd for $C_{12}H_{20}N_6O_3$ (M^+-HCl), *m/e* 296.1597, found 296.1557.
19. **6** : mp 169-170 °C (dec); ^{1}H NMR (DMSO-d_6) δ 8.24 (s, 1 H, C_8H), 7.01 (s, 2 H, NH_2), 5.48 (s, 2 H, NCH_2O), 4.69 (t, J = 5.3 Hz, 1 H, OH), 3.47 (m, 4 H, CH_2CH_2); MS (EI) *m/e* 227 (M^+), 209 (M^+-H_2O), 197 (M^+-HCHO); HRMS calcd for $C_8H_{10}FN_5O_2$ *m/e* 227.0818, found 227.0816.
20. **7** : mp 184-186 °C (dec); ^{1}H NMR (DMSO-d_6) δ 8.22 (s, 1 H, C_8H), 6.98 (s, 2 H, NH_2), 5.57 (s, 2 H, NCH_2O), 4.62 (t, J = 5.5 Hz, 2 H, 2 OH), 3.57 (m, 1 H, CH), 3.43 (m, 2 H, CH_2), 3.30 (m, 2 H, CH_2); MS (EI) *m/e* 257 (M^+), 227 (M^+-HCHO), 209 (M^+-HCHO-H_2O); HRMS calcd for $C_9H_{12}FN_5O_3$ *m/e* 257.0924, found 257.0910.

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