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# (±)-7-DEAZAARISTEROMYCIN LACKING THE HYDROXYMETHYL SUBSTITUENT

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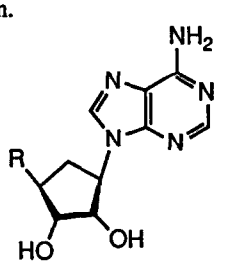
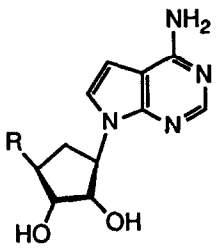
**Abstract:** As part of a plan to uncover new nucleoside based inhibitors of *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase that are incapable of undergoing competing nucleotide formation, a derivative of 7-deazaaristeromycin (carbocyclic tubercidin) (**5**) has been prepared that lacks the C-5' hydroxymethyl side-chain. This compound did not exhibit appreciable cytotoxicity or activity against a number of DNA and RNA viruses and was not inhibitory towards AdoHcy hydrolase.

A common feature of many agents currently under consideration as anti-human cytomegalovirus agents is their ability to inhibit the virally induced DNA polymerase[1] after conversion to their 5'- or "5'-like" monophosphate and, in turn, triphosphate derivatives. A prominent example that follows this sequence of events with a clinically useful anti-HCMV outcome is 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG or ganciclovir).[2-5] Unfortunately, undesirable side-effects[6] are associated with DHPG that are the likely consequence of the phosphorylation sequence. A potentially more favorable approach to designing other nucleoside derived anti-HCMV agents would be to study compounds less likely to undergo the initial phosphorylation. Among a number of possibilities in this direction, we considered shortening[7] or eliminating[8] the C-5' hydroxymethyl moiety of aristeromycin (**1**). This led to C-5'-nor aristeromycin (**2**) as a potent, non-toxic anti-HCMV agent that was also effective against a number of other viruses.[7] These properties for **2** were attributed[7] to inhibition of *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase and revealed a new enzymic target for anti-HCMV agent design.




(-)-**1**, R=$CH_2OH$
(-)-**2**, R=OH

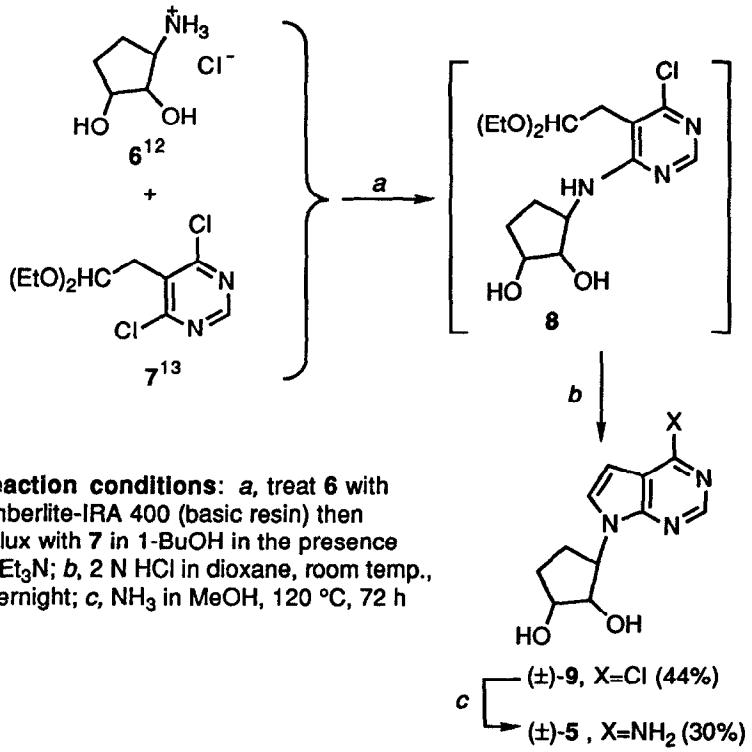



(±)-**3**, R=$CH_2OH$
(-)-**4**, R=OH
(±)-**5**, R=H

As part of our effort to develop antiviral agents based on 7-deaza carbocyclic nucleosides,[9] we turned our attention to similar modifications of carbocyclic 7-deazaadenosine (**3**, 7-deazaaristeromycin), which has AdoHcy

hydrolase inhibitory properties[10] but shows cytotoxicity that, by analogy to tubercidin, is likely the result of phosphorylation at its C-5' center. Following the same side-chain alteration rationale described above that led to **2**, compounds **4** and **5** arose as desirable targets. Compound **4** has been reported by us elsewhere.[11] Compound **5** is reported here.

**Scheme**




**Reaction conditions**: *a*, treat **6** with Amberlite-IRA 400 (basic resin) then reflux with **7** in 1-BuOH in the presence of $Et_3N$; *b*, 2 N HCl in dioxane, room temp., overnight; *c*, $NH_3$ in MeOH, 120 °C, 72 h

Thus, (1α,2α,3β)-3-amino-1,2-cyclopentanediol hydrochloride (**6**)[12] was neutralized and allowed to react with 4,6-dichloro-5-(2,2-diethoxyethyl)pyrimidine (**7**)[13] in the presence of triethylamine to give an intermediate (assumed to be **8**). This latter product was not fully characterized but was cyclized to (±)-(1α,2α,3β)-3-(4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-1,2-cyclopentanediol (**9**)[14] upon treatment with acid. Ammonolysis of **9** yielded the desired (±)-(1α,2α,3β)-3-(4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-1,2-cyclopentanediol (**5**).[15]

Using AD-169 and Davis strains in HEL cells,[7,17] **5** did not show any anti-HCMV activity ($MIC_{50} \geq 100$ μg/mL) and displayed no appreciable effect on the growth viability ($MIC_{50}$ 130 μg/mL) in the host cells. As expected, in view of these results, **5** was not inhibitory towards AdoHcy hydrolase ($IC_{50} > 100$ μM) under conditions where neplanocin A, carbocyclic 3-deazaadenosine (C-c$^3$Ado), 3-deazaneplanocin A and (*S*)-DHPA proved inhibitory to the enzyme ($IC_{50}$ 0.0072, 0.018, 0.031, and 0.28 μM, respectively).

The effect of compound **5** on a number of other viruses was evaluated and no activity was found against ($MIC_{50}$ in μg/mL, host cell line): HSV-1 (KOS), TK$^-$ HSV-1 (B2006), HSV-2 (G), vaccinia, and vesicular

stomatitis (> 200, $E_6SM$); vesicular stomatitis, polio-1, and coxsackie B4 (> 200, HeLa); respiratory syncytial (Long) (> 100, HeLa); coxsackie B4, reo-1, Semliki forest, and Sindbis (> 200, Vero); parainfluenza 3 (VR-93) (150, Vero); influenza A (Ishikawa) and influenza B (Singapore) (> 100, MDCK); and, HIV-1 ($III_B$/LAI) and HIV-2 (ROD) (> 130, MT-4). Interestingly, **5** did show some activity towards Junin and Tacaribe ($MIC_{50}$ in μg/mL, 84 and 64, respectively, in Vero cells).

In analyzing the toxicity properties of **5** towards cell lines other than HEL, the following $MIC_{50}$ values were obtained: morphology $E_6SM$(> 200), morphology HeLa (>200), morphology Vero (≥ 200), morphology MDCK (≥ 100), and growth/viability MT-4 (> 130).

The virus strains, cell systems, and assays used to determine antiviral activity and cytotoxicity have been described previously.[7,17-20] In all of these assays the reference compounds (BVDU, ribavirin, neplanocin A, and carbocyclic 3-deazaadenosine) showed the expected antiviral activity.[7]

From these results, it is clear that removal of the hydroxmethyl side-chain from 7-deazaaristeromycin has a significant impact on its antiviral properties when considered in parallel with the same modification on the parent aristeromycin.[8]

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## References and Notes

1. Mar, E.-C.; Chiou, J.-F.; Cheng, Y.-C.; Huang, E.-S. *J. Virol.* **1985**, *53*, 776-780.
2. (a) Smith, K.O.; Galloway, K.S.; Kennell, W.L.; Ogilvie, K.K.; Radatus, B.K. *Antimicrob. Agents Chemother.* **1982**, *22*, 55-61. (b) Ashton, W.T.; Karkas, J.D.; Field, A.K.; Tolman, R.L. *Biochem. Biophys. Res. Commun.* **1982**, *108*, 1716-1721. (c) Martin, J.C.; Dvorak, C.A.; Smee, D.F.; Matthews, T.R.; Verheyden, J.P.H. *J. Med. Chem.* **1983**, *26*, 759-761. (d) Field, A.K.; Davies, M.E.; DeWitt, C.; Perry, H.C.; Liou, R.; Germershausen, J.; Karkas, J.D.; Ashton, W.T.; Johnston, D.B.R.; Tolman, R.L. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 4139-4143.
3. Cheng, Y.-C.; Huang, E.-S.; Lin, J.-C.; Mar, E.-C.; Pagano, J.S.; Dutschman, G.E.; Grill, S.P. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 2767-2770.
4. Smee, D.F.; Martin, J.C.; Verheyden, J.P.H.; Matthews, T.R. *Antimicrob. Agents Chemother.* **1983**, *23*, 676-682.
5. (a) Mar, E.-C.; Cheng, Y.-C.; Huang, E.-S. *Antimicrob. Agents Chemother.* **1983**, *24*, 518-521. (b) Tocci, M.J.; Livelli, T.J.; Perry, H.C.; Crumpacker, C.S.; Field, A.K. *Antimicrob. Agents Chemother.* **1984**, *25*, 247-252.
6. (a) Shepp, D.H.; Dandliker, P.S.; de Miranda, P.; Burnette, T.C.; Cederberg, D.M.; Kirk, L.E.; Meyers, J.D. *Ann. Intern. Med.* **1985**, *103*, 368-373. (b) Reed, E.C.; Dandliker, P.S.; Meyers, J.D. *Ann. Intern. Med.* **1985**, *105*, 214-215. (c) Collaborative DHPG Treatment Study Group, *New Engl. J. Med.* **1986**, *314*, 801-805. (d) Laskin, O.L.; Stahl-Bayliss, C.M.; Kalman, C.M.; Rosecan, L.R. *J. Infect.*

*Dis.* **1987**, *155*, 323-327. (e) Stanat, S.C.; Reardon, J.E.; Erice, A.; Jordan, M.C.; Drew, W.L.; Biron, K.K. *Antimicrob. Agents Chemother.* **1991**, *35*, 2191-2197.

7. Patil, S. D.; Schneller, S. W.; Hosoya, M.; Snoeck, R.; Andrei G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1992**, *35*, 3372-3377.
8. Borchardt and his colleagues[8a,b] have reported the synthesis and antiviral properties of aristeromycin lacking the entire C-5' hydroxylmethyl group but no anti-HCMV data was provided. (a) Wolfe, M. S.; Borchardt, R. T. *J. Med. Chem.* **1991**, *34*, 1521-1530. (b) Wolfe, M. S.; Lee, Y.; Barlett, W. J.; Borcherding, D. R.; Borchardt, R. T. *J. Med. Chem.* **1992**, *35*, 1782-1791.
9. (a) Chen, X.; Siddiqi, S.M.; Schneller, S.W. *Tetrahedron Lett.* **1992**, *33*, 2249-2252. (b) Siddiqi, S.M.; Chen, X.; Schneller, S.W. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1279-1282.
10. Secrist, J.A., III; Clayton, S.J.; Montgomery, J.A. *J. Med. Chem.* **1984**, *27*, 534-536.
11. Siddiqi, S.M.; Chen, X.; Schneller, S.W. *Nucleosides Nucleotides*, in press.
12. Whitten, J.P.; McCarthy, J.R.; Whalon, M.R. *J. Org. Chem.* **1985**, *50*, 4399-4402.
13. Montgomery, J.A.; Hewson, K. *J. Med. Chem.* **1967**, *10*, 665-667.
14. Compound **9**: off-white solid; mp 159-161 °C, $^1$H NMR (DMSO-$d_6$) δ 1.1–2.6 (m, 4 H, H-4' and H-5'), 3.3 (s, 1 H, OH), 4.0 (s, 1 H, OH), 4.3 (m, 1 H, H-3'), 4.5-5.2 (m, 2 H, H-1' and H-2'), 6.7 (d, $J$ = 3.8 Hz, 1 H, H-5), 7.9 (d, $J$ = 3.8 Hz, 1 H, H-6), 8.6 (s, 1 H, H-2); $^{13}$C NMR (DMSO-$d_6$) δ 27.2, 29.9, 60.9, 72.5, 77.9, 98.6, 99.6, 130.7, 149.5, 150.5, 150.9.
15. Compound **5**[16]: off-white solid; mp 205-207 °C, $^1$H NMR (DMSO-$d_6$) δ 1.1–2.6 (m, 4 H, H-4' and H-5'), 4.2 (m, 1 H, H-3'), 4.4-5.7 (m, 4 H, H-1', H-2', and 2 x OH), 6.8 (d, $J$ = 2.9 Hz, 1 H, H-5), 7.5 (d, $J$ = 2.9 Hz, 1 H, H-6), 7.9 (s, 1 H, H-2), 8.2 (s, 2 H, $NH_2$); $^{13}$C NMR (DMSO-$d_6$) δ 28.5, 30.1, 60.3, 72.4, 78.5, 101.5, 104.0, 124.1, 148.0, 150.0, 154.2.
16. Satisfactory elemental microanalytical data was obtained for **5**.
17. Schols, D.; De Clercq, E.; Balzarini, J.; Baba, M.; Witvrouw, M.; Hosoya, M.; Andrei, G.; Snoeck, R.; Neyts, J.; Pauwels, R.; Nagy, M.; Györgyi-Edelényi, J.; Machovich, R.; Horváth, I.; Löw, M.; Görög, S. *Antiviral Chem. Chemother.* **1990**, *1*, 233-240.
18. De Clercq, E.; Descamps, J.; Verhelst, G.; Walker, R.T.; Jones, A.S.; Torrence, P.F.; Shugar, D. *J. Infect. Dis.* **1980**, *141*, 563-574.
19. De Clercq, E. *Antimicrob. Agents Chemother.* **1985**, *28*, 84-89.
20. Hosoya, M.; Balzarini, J.; Shigeta, S.; De Clercq, E. *Antimicrob. Agents Chemother.* **1991**, *35*, 2515-2520.