5′-Homoaristeromycin. Synthesis and antiviral activity against orthopox viruses

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Abstract—An efficient synthesis of 5′-homoaristeromycin has been developed. This permitted an extensive antiviral analysis, which found potent activity toward vaccinia, cowpox, and monkeypox viruses. For comparative purposes, 5′-homoadenosine was made available by a newly designed route and found to be inactive.

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Inhibitors of S-adenosyl-L-homocysteine (AdoHcy) hydrolase have shown promise as antiviral agents1,2 by disrupting essential viral macromolecular methylation processes.3 Carbocyclic nucleosides4 represent a prominent class of compounds whose antiviral potential has been traced to such an effect.5 Within that group, carbocyclic adenosine (aristeromycin, 1) is at the center of these investigations4 but its promise is limited by a toxicity arising from 5′-phosphate formation.6

Structural modifications of 1 with the aim of reducing phosphate-based toxicity have yielded meaningful drug candidates.6 An approach not explored, however, is extension of the C-5′ hydroxymethyl side chain by a methylene group to provide the C-5′ homolog of aristeromycin (2). This analog can be expected7 to have displaced the phosphate-susceptible hydroxyl from the phosphate-transfer zone in the kinases responsible for metabolism to 1 to its nucleotides. In support of this, 2 has been reported8,9 to be inactive against HSV-1 and HSV-2, possibly, due to its failure to be phosphorylated (Fig. 1).

To investigate 2 more thoroughly as a possible antiviral agent a more practical synthesis of it was necessary. For comparative antiviral purposes, 5′-homoadenosine (3) was also sought by a much more efficient way than exists

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Figure 1.

1. X = CH₂, n = 1
2. X = CH₂, n = 2
3. X=O, n=2

in the literature.9 The results of this effort are communicated here.

Existing methods8,10,11 for preparing 5′-homoaristeromycin (2) suffer from too many steps, limited scale-up, low yields and, in one case, resulting in a racemic product. Therefore, an efficient and stereoselective synthesis of 2 was needed. Starting from enone 412 (Scheme 1), 1,4-addition of ethyl trimethylsilylacetaetate followed by in situ cleavage of the trimethylsilyl group furnished, stereoselectively, the ketone ester 5 as the only product. The stereochemistry at C-4 of 5 was derived from the fact (i) that a 1,4-addition to the concave structure of 5 can be expected13 to give a β (up) product and (ii) that 5 was converted into the known 2. Reduction of 5 with sodium borohydride provided the coupling precursor 6, which has been reported via a more tedious way.14 Mitsunobo coupling reaction of 6 with 6-chloropurine furnished 7. Selective reduction of 7 with diisobutylaluminum hydride (DIBAL) yielded the desired alcohol 8.
Ammonolysis of 8 (to 9) followed by hydrolytic deprotection smoothly afforded 2 in good overall yield.\textsuperscript{15}

The known syntheses of 6′-homoadenosine\textsuperscript{9} (3) either involved many steps\textsuperscript{9a,c} or suffer a low yield of the final product.\textsuperscript{9b,c} Our plan (Scheme 2) envisioned beginning with homologation of 10.\textsuperscript{16} Side chain oxidation of 10 followed by Wittig olefination afforded 11. Submitting 11 to regioselective hydroboration with 9-BBN followed by oxidative hydrolysis, smoothly provided 12 in high yield. Hydrolysis of 12 with acetic acid produced a tetroloid, which was fully protected with acetic anhydride to provide the anomeric acetate 13. The coupling reaction of 13 with N-pivaloyl protected adenine under Vorbrüggen glycosylation conditions yielded the desired N-9 product 14 as the only isolated product. Deprotection of 14 with ammonia furnished 3 in good overall yield\textsuperscript{17} from d-ribose.

Compounds 2 and 3 were evaluated against a wide variety of both DNA viruses and RNA viruses.\textsuperscript{18} From this, very significant effects were seen for 2 toward vaccinia (IC\textsubscript{50} 1.2\,\mu g/mL), cowpox (IC\textsubscript{50} 0.12\,\mu g/mL), and monkeypox (IC\textsubscript{50} 0.12\,\mu g/mL) viruses, all in Vero 76 cells with CC\textsubscript{50} > 100\,\mu g/mL. This observation is particularly noteworthy since it is well known that vaccinia is susceptible to AdoHcy hydrolase inhibitors but cowpox was thought not to be.\textsuperscript{18e} In any case, details of this investigation and the, possibly, less notable activity of 2 toward other viruses\textsuperscript{18} will be forthcoming, including its potency toward variola.\textsuperscript{19} Analog 3 was inactive in all of the assays employed.\textsuperscript{18}

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References and notes
15. Selected data for 2: mp 178–179°C; 1H NMR (400 MHz, DMSO-d6) δ 8.20 (s, 1H), 8.11 (s, 1H), 7.17 (s, 2H), 4.90 (d, J = 6.27 Hz, 1H), 4.68 (d, J = 4.63 Hz, 1H), 4.57 (m, 1H), 4.43 (t, J = 5.12 Hz, 1H), 4.35 (m, 1H), 3.71 (m, 1H), 3.46 (m, 2H), 2.24 (m, 1H), 1.97 (m, 1H), 1.74 (m, 2H), 1.58 (m, 1H); 13C NMR (100 MHz, CDCl3) δ 156.0, 152.1, 149.6, 140.2, 119.3, 74.9, 74.3, 59.9, 59.4, 40.0, 37.4, 32.5. Anal. Calcd for C17H17N2O6S: C, 51.60; H, 6.18; N, 25.08. Found: C, 51.39; H, 6.18; N, 24.81.
17. Selected data for 3: mp 223–224°C (lit.5c 231.5–232.5°C); 1H NMR (250 MHz, DMSO-d6) δ 8.27 (s, 1H), 8.10 (s, 1H), 7.24 (s, 2H), 5.79 (d, J = 5.3Hz, 1H), 5.36 (d, J = 5.7Hz, 1H), 5.11 (d, J = 5.1Hz, 1H), 4.61 (m, 1H), 4.44 (t, J = 5.1Hz, 1H), 4.03 (m, 1H), 3.93 (m, 1H), 3.42 (m, 2H), 1.76 (m, 2H); 13C NMR (62.9 MHz, DMSO-d6) δ 156.1, 152.6, 149.4, 139.9, 119.2, 87.4, 81.0, 73.4, 72.9, 57.5, 36.6. Anal. Calcd for C11H15N2O4S: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.85; H, 5.48; N, 24.63.
18. For leading references on the procedures used for the assays see (a) Ref. 5; (b) Siddiqi, S. M.; Chen, X.; Schneller, S. W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. J. Med. Chem. 1994, 37, 551; (c) Seley, K. L.; Schneller, S. W.; Korba, B. Nucleosides Nucleotides 1997, 16, 2095; (d) http://www.usu.edu/iar/Brochure/brochure.html (September 6, 2004); and; (e) Baker, R. O.; Bray, M.; Huggins, J. W. Antiviral Res. 2003, 57, 13.