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5′-Amino-5′-deoxyaristeromycin and Its Antiviral Properties

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Abstract—An efficient, three-step synthesis of 5′-amino-5′-deoxyaristeromycin (**5**), from a protected form of aristeromycin (**6**), is described. Compound **5** was evaluated against a large number of viruses. It showed weak activity towards vaccinia, herpes simplex virus 2, and cytomegalovirus. No other activity was observed. Compound **5** displayed some cytotoxicity towards the host cell lines human foreskin fibroblast, Daudi, and human T-lymphocyte (CEM).
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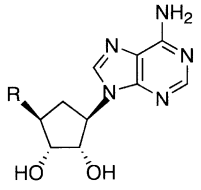
Introduction

Analogues of the naturally occurring nucleosides have been the focus of considerable attention in the search for medicinal agents to treat infectious diseases.[1] The carbocyclic nucleoside aristeromycin **1**,[2] which was synthesized[3] prior to being isolated from *Streptomyces citricolor*,[4] can be considered among that group and, initially, was thought to have promise. However, the therapeutic potential of **1** is limited by its significant toxicity likely due to its structural resemblance to adenosine and, thus, conversion to its 5′-nucleotide(s),[5] which are responsible for the undesirable side-effects (Fig. 1).[6]

In an attempt to retain the favorable biological properties of **1**, variation of the 5′-center has been investigated (for example, the 5′-deoxy **2**).[7] The most encouraging results from that approach have come from 5′-noraristeromycin **3**[8] and the aristeromycin derivative lacking the C-4′ hydroxymethylene **4**.[9] No attention has considered replacing the 5′-hydroxyl of **1** with bioisosteric/isoelectronic groups such as amino. In that direction, this report describes a simple synthesis of **5** and its evaluation against a number of viruses, as representatives of infectious diseases.

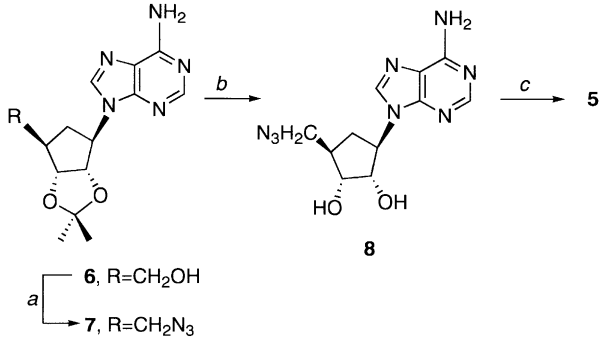


1, R=CH_2OH
2, R=CH_3
3, R=OH
4, R=H
5, R=CH_2NH_2

Figure 1.

Chemistry

Subjecting the 2′,3′-isopropylidene derivative of aristeromycin (**6**)[10] (Scheme 1) to treatment with diphenyl/phosphoryl azide under Mitsunobu conditions provided **7**. Acidic deprotection of the isopropylidene group of **7** led to 5′-azido-5′-deoxyaristeromycin **8**, which was reduced with H_2/Pd/C to afford the desired compound **5** in overall 39% yield.



Scheme 1. Reagents: (a), $(PhO)_2P(O)N_3$, PPh_3, DIAD, THF, 0 °C (91%); (b) on **7**, CF_3CO_2H, rt (76%); (c) 30 psi H_2/10% Pd/C, 36 h (56%).

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Antiviral Results

The aristeromycin derivative **5** displayed activity towards vaccinia virus (EC_{50} 76.5 μg/mL, CPE inhibition in HFF cells; cidofovir, EC_{50} 2 μg/mL); HSV-2 (EC_{50} 27.3 μg/mL, CPE inhibition in HFF cells; acyclovir, EC_{50} 1.6 μg/mL); and, human cytomegalovirus (EC_{50} 17.5 μg/mL, CPE inhibition in HFF cells; ganciclovir, EC_{50} 0.3 μg/mL). No activity was found towards the following viruses: HSV-1 (TK^+ and TK^-), varicella zoster, Epstein–Barr, cowpox, adeno, measles, parainfluenza type 3, respiratory syncytial A, rhino type 2, influenza A (H1N1 and H3N2), influenza B, Venezuelan equine encephalitis, West Nile, yellow fever, HIV-1 and HIV-2, vesicular stomatitis, reo, sindbis, coxsackie B4, and Punto Toro.

There was some cytotoxicity associated with **5** towards three of the viral host cells (IC_{50} in μg/mL for **5**, acyclovir, and ganciclovir): non-stationary HFF (3.1, >100, 40): Daudi (23.6, >50, 40); CEM (117±26.2).

Conclusions

Compound **5** was screened against various viruses and was found to be active (albeit weak) against vaccinia, herpes simplex virus-2, and human cytomegalovirus. However, its significant toxicity, which may be due to its inhibition of adenosine kinase,[11] is reminiscent of aristeromycin precluding any further study of **5** as an antiviral agent. However, the synthetic availability of **5** provides a starting point for developing various carbocyclic adenosine derivatives for non-therapeutic biochemical studies.[12,13]

Experimental

Chemistry

Melting points were recorded on a Meltemp II melting point apparatus and the values were uncorrected. The combustion analysis was performed at Atlantic Microlab, Norcross, GA, USA. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer (operated at 250 and 62.5 MHz, respectively) all referenced to internal tetramethylsilane (TMS) at 0.0 ppm. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Whatman Diamond silica gel 60-F_{254} precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. Column chromatography was performed on Whatman silica, 230–400 mesh, 60 Å and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials.

(1′*R*,2′*S*,3′*R*,4′*R*)-9-[4′-(Aminomethyl)-2′,3′-dihydroxycyclopent-1′-yl]-adenine (5). The protected aristeromycin **6**[10] (305.3 mg, 1 mmol) and triphenylphosphine (786.9 mg, 3 mmol) in freshly distilled THF (20 mL) was brought to 0 °C and to this solution was added a solution of diphenylphosphoryl azide (825.6 mg, 3 mmol) and di*iso*propyl azodicarboxylate (606.6 mg, 3 mmol) in anhydrous THF. This mixture was stirred at 0 °C for 2.5 h, following at which time tlc analysis (CH_2Cl_2–MeOH, 9:1) showed the reaction to be complete. After evaporation of the solvent, the residue was loaded onto a silica gel column. The faster moving impurities were eluted (first using CH_2Cl_2–EtOAc, 10:1, then 5:1) followed by product fractions (CH_2Cl_2–EtOAc, 1:1). Evaporation of the solvent gave 7 (300 mg, 91%) as a white powder: mp 166–168 °C; ^1H NMR ($CDCl_3$) δ 8.34 (s, 1H), 7.84 (s, 1H), 5.78 (s, 2H), 5.10 (dd, $J=5$ Hz, 6, 1H), 4.75 (m 1H), 4.66 (m, 1H), 3.59 (d, $J=2$ Hz, 2H), 2.44 (s, 1H), 1.57 (s, 3H), 1.52 (m, 1H), 1.39 (m, 1H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.71, 153.01, 140.10, 130.03, 120.68, 114.44, 83.63, 81.93, 61.85, 53.33, 44.05, 34.80, 27.64, 25.28.

The product **7** (300 mg, 0.91 mmol) from the above reaction was stirred with trifluoroacetic acid (10 mL) for 1 h. After evaporation of solvent under reduced pressure, the residue was co-evaporated with 2-propanol (2×50 mL) and it was dissolved in a small amount of CH_2Cl_2–MeOH (4:1) and loaded onto a silica gel column. The faster moving impurities were eluded first (CH_2Cl_2–MeOH, 25:1) followed by product (CH_2Cl_2–MeOH, 10:1). Evaporation of the solvent afforded **8** (200 mg, 76%) as a white powder: mp 196–198 °C; ^1H NMR (DMSO-d_6) δ 8.31 (s, 1H), 8.21 (s, 1H), 7.71 (s, 2H), 4.74 (dd, $J=10$, 7.5 Hz, 1H), 4.36 (dd, $J=7.5$ Hz, 5, 1H), 3.82 (dt, $J=5$, 2.5 Hz, 1H), 3.51 (d, $J=7.5$ Hz, 2H), 3.16 (s, 1H), 2.29 (m, 1H), 2.16 (m, 1H), 1.78 (dd, $J=10$, 10 Hz, 1H), 1.19 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 154.58, 150.28, 149.39, 140.94, 119.16, 74.34, 72.08, 59.43, 53.45, 42.75, 30.08.

Compound **8** (120 mg, 0.45 mmol) was dissolved in MeOH (30 mL) to which 10% Pd/C (100 mg) was added. This mixture was hydrogenated in a Parr apparatus at 30 psi for 36 h. The mixture was filtered through a pad of Celite and the pad washed with copious amounts of MeOH. The combined MeOH washings were evaporated under reduced pressure to obtain the amino derivative **5** (60 mg, 56%) as an off-white solid. An analytical sample was recrystallized from EtOH: mp 170–172 °C; ^1H NMR (DMSO-d_6) δ 8.22 (s, 1H), 8.12 (s, 1H), 7.20 (s, 2H), 4.66 (dd, $J=10$, 7.5 Hz, 1H), 4.35 (dd, $J=7.5$ Hz, 5, 1H), 3.81 (m, 5H), 3.17 (m, 1H), 2.65 (m, 1H), 2.30 (m, 1H), 1.96 (m, 1H), 1.73 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 155.99, 152.08, 149.68, 140.19, 119.32, 74.58, 72.50, 59.53, 45.53, 44.88, 30.37. Anal. calcd for $C_{11}H_{16}N_6O_2 \cdot 0.40H_2O$: C, 48.66; H, 6.24; N, 30.95. Found: C, 48.98; H, 6.44; N, 30.72.

Antiviral assays. The antiviral and toxicity analyses were performed following standard procedures reported previously by us.[14,15]

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