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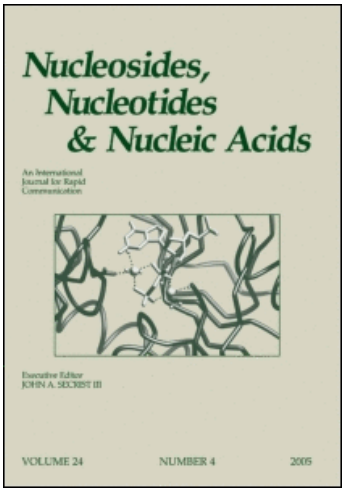

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LIN-BENZOARISTEROMYCIN

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LIN-BENZOARISTEROMYCIN

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ABSTRACT

A synthesis and an antiviral analysis of the *linear* extended derivative of aristeromycin (**2**) is described.

It has been 25 years since Leonard and co-workers introduced the concept of spatially separating the pyrimidino and imidazo units of the purine ring with 4 sp^2 carbon atoms (1). These derivatives were referred to as benzo-separated purines (as in adenine, **1**). Numerous variations, including nucleoside derivatives, based on the Leonard concept have arisen and have found biological applications (2). In view of extensive interest in carbocyclic nucleosides (3) and our particular focus on the antiviral properties of aristeromycin (**2**) (4), we sought *lin*-benzoaristeromycin (**3**) (5). The results of that study are reported herein.

The synthesis of **3** began by generating the anion of 8-methylthioimidazo[4,5-*g*]-quinazoline (**4**) (1) and reacting it with triflate **5** (6) to give a single regioisomer, **6** (7) (Scheme). The structure of **6** was proven by comparing its ^1H and ^{13}C NMR chemical shift values in the aromatic moiety with the *lin*-benzo-5′-noraristeromycin precursor (**7**), whose structure has been unambiguously assigned by us (8). Subjecting **6** to refluxing in methanol saturated with ammonia gave **8**. Hydrolysis of **8** using 2:1 trifluoroacetic acid-water mixture provided **3**. The overall yield of **3** from **4** and **5** was 12%.

Compound **3** was evaluated for its effectiveness towards the following viruses: parainfluenza-3, respiratory syncytial, vesicular stomatitis, sindbis, punta toro, coxsackie B4, reo, herpes simplex 1 (TK^+ and TK^-), herpes simplex 2, and vaccinia.

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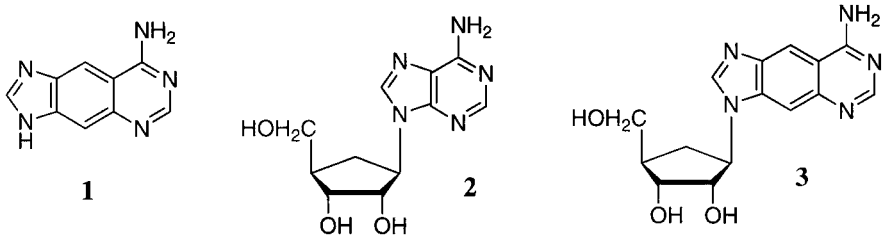
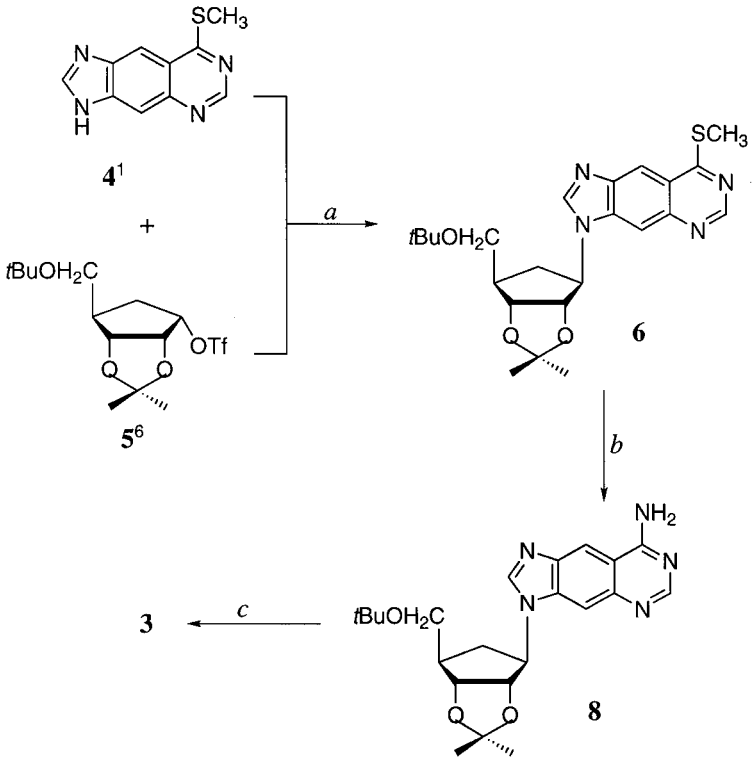
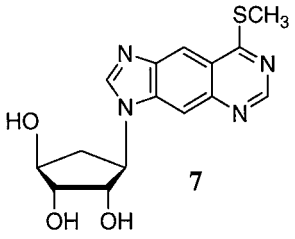


1 **2** **3**

Scheme[a]



[a]Reaction conditions: *a*, NaH, 18-C-6, DMF, room temp.; *b*, NH_3/MeOH, 120°C; *c*, CF_3CO_2H/H_2O, 50°C.



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No activity was found. This observation suggests that extending the ring system of aristeromycin in the linear way represented by **3** prevented its association with the enzymes (kinases and *S*-adenosyl-L-homocysteine hydrolase) (9) responsible for its antiviral characteristics.

EXPERIMENTAL

Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. The combustion analysis was performed at Atlantic Microlab, Norcross, GA. ^{1}H and ^{13}C 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. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), m (multiplet) and br (broad). The optical rotation was measured on a JASCO DIP-360 polarimeter. 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 (^{1}H and ^{13}C NMR) homogeneous materials.

8-Amino-3-[(1′*R*,2′*S*,3′*R*,4′*R*)-2′,3′-dihydroxy-4′-hydroxymethyl]cyclopent-1′-yl]imidazo[4,5-g]quinazoline (3). To a suspension of **4** (1) (1.5 g, 7 mmol), NaH (175 mg, 7 mmol) and 18-crown-6 (1.85 g, 7 mmol) in anhydrous DMF (50 mL) heated at 70°C for 1 hour and then cooled to 0°C was added a solution of **5** (6) (1.79 g, 5.25 mmol) in anhydrous DMF (15 mL). The mixture was stirred at 0°C for 9 hours and then at room temperature for 24 hours. The mixture was filtered, the filtrate evaporated and the residue adsorbed onto silica gel and this was loaded onto a silica gel column. Impurities were eluted with CH_2Cl_2-MeOH (60:1) followed by elution of the product fractions with CH_2Cl_2-MeOH (40:1 mL). After evaporation of the solvent, the residue was triturated with ether and filtered. The filtrate on evaporation gave 950 mg (40%) of 3-[(1′*R*,2′*S*,3′*R*,4′*R*)-4′-*tert*-butoxymethyl-2′,3′-isopropylidenedioxycyclopent-1′-yl]-8-methylthioimidazo-[4,5-*g*]quinazoline (**6**) as a light yellow gummy residue; ^{1}H NMR ($CDCl_3$) δ 8.97 (s, 1H), 8.48 (s, 1H), 8.40 (s, 1H), 8.33 (s, 1H), 5.30 (m, 1H), 4.65 (m, 3H), 3.57 (m, 2H), 2.65 (s, 3H), 2.56 (m, 1H), 1.75 (s, 3H), 1.43 (s, 3H), 1.38 (m, 1H), 1.23 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 158.94, 138.67, 137.45, 133.97, 131.76, 123.12, 107.84, 105.34, 101.01, 92.03, 72.80, 68.80, 60.36, 57.74, 49.95, 48.83, 31.19, 19.56, 15.58, 14.82, 12.52.

To a saturated solution of ammonia in anhydrous methanol (70 mL) was added a solution of **6** (500 mg, 1.13 mmol) in methanol (50 mL). The mixture was heated in a pressure reactor at 120°C (oil bath) for 36 hours. After cooling the mixture was filtered, the filtrate evaporated and the residue placed on a silica gel column. The product was eluted using CH_2Cl_2-MeOH (15:1). After evaporation of the

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solvent, the residue was triturated with ether to give 280 mg (60%) of 8-amino-3-[(1′*R*,2′*S*,3′*R*,4′*R*)-4′-*tert*-butoxymethyl-2′,3′-isopropylidenedioxycycl-opent-1′-yl]-imidazo[4,5-*g*]quinazoline (**8**) as a light yellow powder, which was used in the next reaction without further purification, mp 154–156°C; ^{1}H NMR (DMSO-d_6) δ 8.54 (s, 1H), 8.53 (s, 1H), 8.38 (s, 1H), 7.94 (s, 1H), 7.87 (br s, 2H), 5.15 (dd, $J = 5$, 7.5 Hz, 1H), 4.85 (m, 1H), 4.60 (m, 1H), 3.48 (d, $J = 7.5$ Hz, 2H), 3.39 (m, 1H), 2.46 (m, 1H), 2.05 (m, 1H), 1.54 (s, 3H), 1.28 (s, 3H), 1.14 (s, 9H).

A solution of **8** (140 mg, 0.34 mmol) in CF_3CO_2H-H_2O (15 mL, 2:1) was heated at 50°C for 3 hours. After evaporation of the solvent, the residue was adsorbed onto silica gel (1 g) and this was loaded onto a silica gel column. The product was eluted using CH_2Cl_2-MeOH (4:1). Evaporation of the solvent and trituration of the residue with ether gave **3** as an off white powder (80 mg, 75%), mp >280°C (charred) $[\alpha]_D^{24}$ −17.90 (c 0.41 in Me_2SO); ^{1}H NMR (DMSO-d_6): δ 8.70 (s, 1H), 8.56 (s, 1H), 8.37 (s, 1H), 7.93 (s, 1H), 7.89 (br s, 2H), 5.11 (m, 2H), 4.83 (dd, $J = 7.5$, 10 Hz, 1H), 4.42 (ddd, $J = 5$, 5, 5 Hz, 1H), 3.89 (d, $J = 2.5$ Hz, 1H), 3.52 (m, 3H), 2.48 (m, 1H), 2.13 (m, 1H), 1.59 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 162.21, 152.87, 147.84, 147.53, 143.76, 133.92, 114.57, 108.23, 104.13, 74.77, 71.70, 62.98, 59.90, 45.38, 29.32. *Anal*. Calcd. for $C_{15}H_{17}N_5O_3 \cdot 0.60\,H_2O$: C 55.24; H 5.62; N 21.47. Found: C 55.39; H 5.45; N 21.16.

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