Pergamon

Tetrahedron 57 (2001) 9049–9053

TETRAHEDRON

An 8-aminoimidazo[4,5-*g*]quinazoline carbocyclic nucleoside: a ring-extended analog of 5′-noraristeromycin

Vasanthakumar P. Rajappan and Stewart W. Schneller*

Department of Chemistry, Auburn University, 179 Chemistry Building, Auburn, AL 36849-5312, USA

Received 9 July 2001; accepted 6 September 2001

Abstract—The antiviral properties of 5′-noraristeromycin (**3**) have been attributed to its inhibition of *S*-adenosylhomocysteine hydrolase. As part of an effort to establish the limiting structural parameters possible for the biological properties of **3**, a ring-extended analog possessing 8-aminoimidazo[4,5-*g*]quinazoline as the base (**7**) has been prepared and found to be less active than **3**.

1. Introduction

Over the years a number of nucleoside analogs have emerged as potent antiviral drugs.[1] Many of these compounds attribute their therapeutic property to structural changes in either the carbohydrate or base components of the natural nucleoside. Examples of variations in the carbohydrate region can be found with derivatives possessing only a portion of the ribofuranose moiety (for example, acyclovir (**1**))[2] and analogs where the ribofuranose oxygen is replaced by a methylene unit (carbocyclic nucleosides or carbanucleosides).[3] A representative of this latter variation is aristeromycin (**2**) from which 5′-noraristeromycin (**3**) has emerged as a compound with significant antiviral effects[4] that have been attributed to its selective inhibition of *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase[5] (Fig. 1).

In the case of base-varied analogs, coformycin (**4**) and pentostatin (**5**),[6] potent antileukemic drugs,[7] are ring-enlarged derivatives of inosine (or adenosine). The ring extended base series, represented by *lin*-benzoadenine nucleosides (**6**), is another example. In this latter modification, four sp^2 carbon atoms are inserted between the imidazole and pyrimidine rings of adenine (giving the

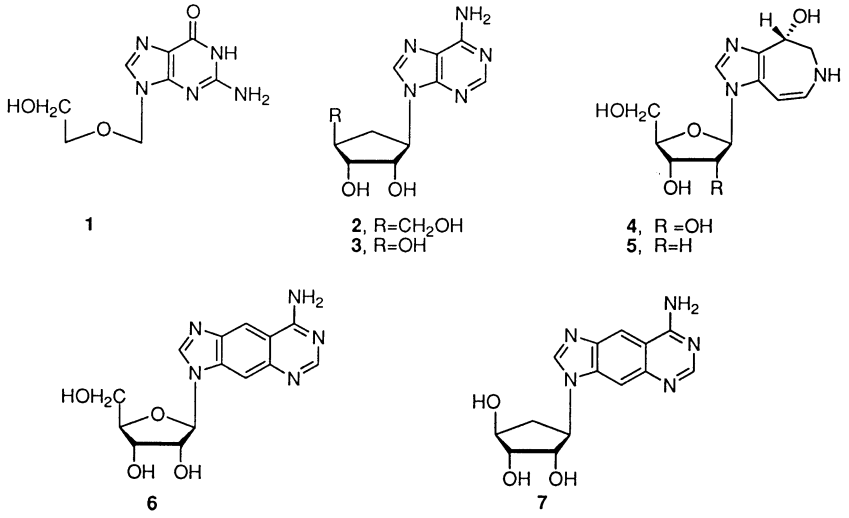
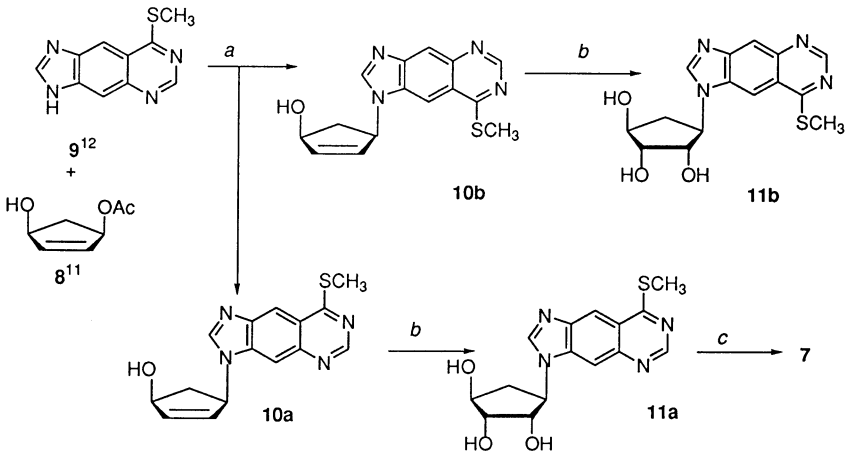


Figure 1.

Keywords: purines; nucleosides; polycyclic heterocyclic compounds; antiviral.
* Corresponding author. Tel.: +1-334-844-5737; fax: +1-334-844-5748; e-mail: schnest@auburn.edu

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00909-7



Scheme 1. *Reaction conditions*: (a) NaH, $Pd(PPh_3)_4$, DMSO/THF; (b) OsO_4, NMO, THF/H_2O; (c) NH_3/MeOH, 110°C.

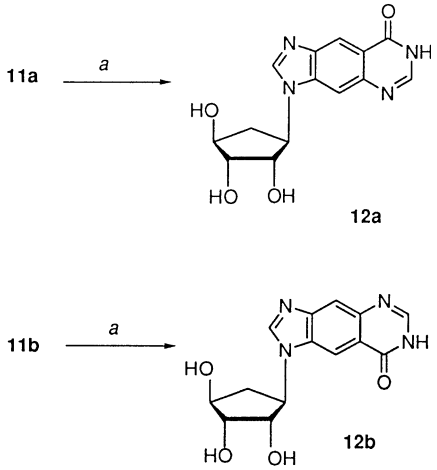
appearance of central benzene ring). The properties of these analogs have been studied by Leonard and co-workers[8] and others[9,10] who have shown that such derivatives provide revealing information about the binding domain of purine nucleoside (and nucleotide) metabolizing enzymes.

Throughout the structural variations of nucleosides that have been reported in the literature, there has been relatively limited attention[10] devoted to the simultaneous modification of both the base and carbohydrate units. To explore the limiting structural features necessary for the biological properties of **3**, this report describes the use of this double variation by combining the ring-extended feature of **6** with the carbocyclic feature of **3** to create **7** as a target compound.

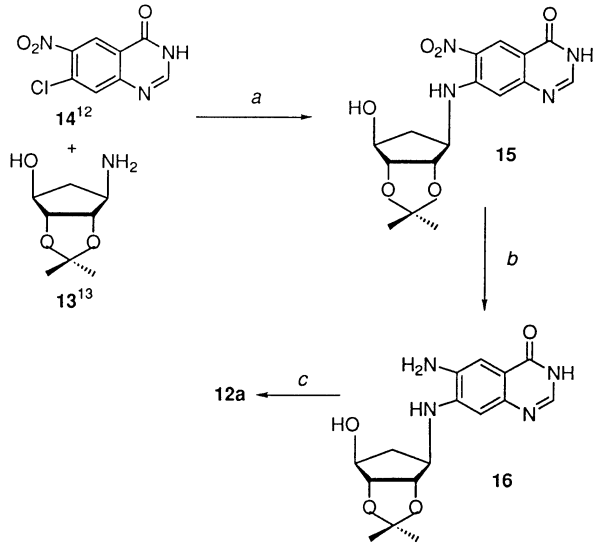
2. Chemistry

The synthesis of **7** began with the palladium (0) catalyzed coupling of the monoacetate **8**[11] with 8-methylthioimidazo[4,5-*g*]quinazoline (**9**)[12] to give two products, tentatively assigned for this presentation as the regioisomers **10a** and **10b**. After separation, dihydroxylation of **10a** and **10b** using osmium tetroxide and *N*-methylmorpholine *N*-oxide afforded corresponding triols **11a** and **11b** (Scheme 1).

Structural confirmation of the two regioisomers **11a** and **11b** was considered at this stage. Since preliminary indications suggested that a definitive NMR spectral distinction between **11a** and **11b** would be difficult, a chemical study was undertaken. In that direction, compounds **11a** and **11b** were hydrolyzed in presence of 1N HCl to give **12a** and **12b**, respectively, (structures still tentatively assigned at this point) (Scheme 2). To provide an authentic reference compound corresponding to the tentative structure **12a**, an unequivocal preparation began by reacting amine **13**[13] with the quinazoline **14**[12] (Scheme 3) to yield **15**. Catalytic hydrogenation of the nitro group of **15** afforded the amino compound **16**. An acid promoted cyclization of **16** with triethyl orthoformate followed by hydrolysis gave a compound whose ^1H- and ^{13}C NMR spectra were exactly that of the product assigned previously as **12a**. A mixed melting point determination was also consistent with **12a** being the same via Scheme 2 (from **11a**) and Scheme 3.



Scheme 2. *Reaction conditions*: (a) 1N HCl, reflux.



Scheme 3. *Reaction conditions*: (a) 1-BuOH, Et_3N, reflux; (b) Pd/C, H_2, 45 psi; (c) (i) EtO_3CH, HCl, rt, (ii) H_2O, 80°C.

With the regioisomers now assigned, the final product **7** was obtained in quantitative yield by heating **11a** in methanol saturated with anhydrous ammonia in a sealed tube (Scheme 1).

3. Results

Compound **7** was evaluated for its effectiveness towards the following viruses: hepatitis B, influenza A, influenza B, parainfluenza-3, respiratory syncytial, varicella zoster (TK^+ and TK^-), cytomegalo, vesicular stomatitis, sindbis, punta toro, coxsackie B4, reo, herpes simplex 1 (TK^+ and TK^-), herpes simplex 2, human immunodeficiency, and vaccinia. No activity was found. Compound **7**, like **3**, was also found to have no toxicity effects on the viral host cells.

4. Discussion and conclusion

The work of Leonard and coworkers[8a,b] found that defined structural changes for substrates and inhibitors, such as those in **7**, assisted in setting the steric and size limitations for active and cofactor sites for various enzymes. Thus, the lack of activity for **7** suggests that the enzyme proposed to be involved in the antiviral activity of **3** (namely, AdoHcy hydrolase) is not sufficiently flexible to accommodate the extension imposed on **3** by **7**. This, in turn, adds to what is already known about binding capabilities of *S*-adenosylhomocysteine hydrolase.[14]

5. Experimental

5.1. General

Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. Combustion analyses were performed by Atlantic Microlabs Inc., Norcross, Georgia. ^1H and ^{13}C NMR spectra were recorded at 250 and 60 MHz, respectively, and are referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), dd (doublet of doublet) dt (doublet of triplet), m (multiplet), and br (broad). The HRMS was recorded at an ionization potential of 70 eV. The optical rotation was determined using the sodium-D line 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 was with the indicated solvent system. Yields refer to chromatographically and spectroscopically homogeneous materials.

5.1.1. 3-[(1*R*,4*S*)-4-Hydroxy-2-cyclopentenyl]-8-methylthioimidazo[4,5-*g*]quinazoline (10a) and 1-[(1*R*,4*S*)-4-hydroxy-2-cyclopentenyl]-8-methylthioimidazo-[4,5-*g*]-quinazoline (10b). To a suspension of NaH (25 mg, 1 mmol, 95% in oil) in anhydrous DMSO (5 mL) in a 50 mL round-bottomed flask kept under N_2 was added 8-methylthioimidazo[4,5-*g*]quinazoline (**9**)[12] (216 mg, 1 mmol). The mixture was stirred at room temperature for 15 min until the solution became clear. To this solution was added, successively, tetrakistriphenylphosphine palladium (115 mg, 0.1 mmol), triphenylphosphine (52.4 mg, 0.2 mmol) and monoacetate **8**[11] (355 mg, 2.5 mmol) in anhydrous THF (10 mL). The flask was immediately transferred to an oil bath, preheated at 50°C. The mixture was stirred under N_2 at 50°C for 12 h. After rotary evaporation of solvents at reduced pressure, the residue was suspended in CH_2Cl_2 (40 mL) and filtered. The filtrate was extracted with brine (2×30 mL) and the organic layer, after drying (Na_2SO_4), was filtered and rotary evaporated to a thick brown residue, which was loaded onto a silica gel column. The impurities were eluted using CH_2Cl_2/MeOH (100:1 and 50:1, respectively). The next components (desired products) were eluted using CH_2Cl_2/MeOH (30:1 followed by 15:1). The fractions from the 30:1 elution were pooled and the solvent evaporated. Trituration (hexane) of the residue gave **10a** as a tan powder (100 mg, 33.33%). An analytical sample was recrystallized from EtOAc: mp 211–212°C. ^1H NMR (DMSO-d_6) δ 8.93 (s, 1H, Ar–H), 8.65 (s, 1H, Ar–H), 8.37 (s, 1H, Ar–H), 8.29 (s, 1H, Ar–H), 6.26 (dd, J=5.0 and 2.5 Hz, 1H), 6.11 (dd, J=5.0 and 2.5 Hz, 1H), 5.69 (dt, J=7.5 and 5.0 Hz, 1H), 5.46 (d, J=5.0 Hz, 1H), 4.81 (m, 1H), 3.02 (m, 1H), 2.72 (s, 3H, SCH_3), 1.83 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 151.72, 149.63, 144.70, 143.23, 140.19, 138.84, 130.94, 119.36, 113.04, 108.65, 74.15, 59.86, 12.61. Anal. Calcd for $C_{15}H_{14}N_4SO{\cdot}0.2EtOAc$: C, 60.06; H, 4.98; N, 17.73; S, 10.15. Found: C, 60.00; H, 4.86; N, 17.51; S, 9.86.

Following combining the 15:1 fractions and evaporation, trituration (hexane) afforded 80 mg (28%) of **10b** as a shiny yellow powder: mp 219–220°C. ^1H NMR (DMSO-d_6) δ 8.92 (s, 1H, Ar–H), 8.68 (s, 1H, Ar–H), 8.47 (s, 1H, Ar–H), 8.22 (s, 1H, Ar–H), 6.27 (dd, J=7.5 and 2.5 Hz, 1H), 6.11 (dd, J=7.5 and 2.5 Hz, 1H), 5.76 (d, J=5.0 Hz, 1H), 5.42 (d, J=5.0 Hz, 1H), 4.83 (m, 1H), 3.05 (m, 1H), 2.72 (s, 3H, SCH_3), 1.83 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 151.74, 149.65, 144.72, 143.34, 138.88, 140.19, 130.95, 119.19, 113.05, 108.67, 74.16, 59.87, 12.61. Anal. Calcd for $C_{15}H_{14}N_4SO$: C, 60.38; H, 4.82; N, 18.78; S, 10.75. Found: C, 60.52; H, 4.82; N, 18.64; S, 10.65.

5.1.2. 3-[(1*R*,2*S*,3*R*,4*S*)-2,3,4-Trihydroxycyclopent-1-yl]-8-methylthioimidazo-[4,5-*g*]quinazoline (11a). To a solution of **10a** (1.49 g, 5 mmol) in THF (200 mL) was added 50% *N*-methylmorpholine *N*-oxide in H_2O (1.82 mL, 10 mmol) followed by H_2O (10 mL) and OsO_4 (100 mg). This mixture was stirred at room temperature for 5 h at which time a TLC analysis showed the reaction to be complete. The mixture was filtered through a pad of silica gel and washed with CH_2Cl_2/MeOH (5:1). The filtrate was evaporated. The residue was adsorbed on silica gel and this mixture loaded onto a silica gel column. The impurities were eluted using CH_2Cl_2/MeOH (first, 20:1 and then a 5:1). The latter solvent ratio yielded fractions containing product. After combining the fractions, evaporation of the solvent gave a residue that was triturated (hexane) to provide **11a** as a light yellow powder (850 mg, 51%). A sample for microanalysis was recrystallized from ether: mp 260–262°C. ^1H NMR (DMSO-d_6) δ 8.93 (s, 1H, Ar–H), 8.71 (s, 1H, Ar–H), 8.44 (s, 1H, Ar–H), 8.37 (s, 1H, Ar–H), 5.45 (s, 1H), 5.10 (m, 2H), 4.88 (dd, J=7.5 Hz, 1H),

4.61 (s, 1H), 4.05 (s, 1H), 3.83 (s, 1H), 2.72 (s, 4H, H and SCH_3), 1.97 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 151.72, 150.49, 143.75, 143.17, 139.02, 119.30, 113.03, 108.96, 77.13, 75.53, 73.93, 60.84, 35.54, 12.64. Anal. Calcd for $C_{15}H_{16}N_4O_3S{\cdot}0.5H_2O$: C, 52.77; H, 5.02; N, 16.41; S, 9.39. Found: C, 52.79; H, 4.87; N, 16.13; S, 9.57.

5.1.3. 1-[(1*R*,2*S*,3*R*,4*S*)-2,3,4-Trihydroxycyclopent-1-yl]-8-methylthioimidazo-[4,5-*g*]quinazoline (11b). Following a procedure similar to that for the preparation of **11a**, **10b** (200 mg, 0.67 mmol) yielded, after silica gel column purification with CH_2Cl_2/MeOH (15:1 to remove impurities and 4:1 to elute product), **11b** as a light yellow powder (105 mg, 47%): mp 231–233°C. ^1H NMR (DMSO-d_6) δ 8.92 (s, 1H, Ar–H), 8.73 (s, 2H, Ar–H), 8.22 (s, 1H, Ar–H), 5.52 (s, 1H), 5.12 (m, 2H), 4.85 (dd, J=7.5 Hz, 1H), 4.61 (dd, J=7.5 Hz, 1H), 4.04 (s, 1H), 3.83(s, 1H), 2.72 (s, 4H, H and SCH_3), 1.98 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 151.43, 150.15, 142.95, 134.34, 119.93, 117.29, 105.49, 77.35, 75.95, 74.08, 61.16, 35.85, 12.94. Anal. Calcd for $C_{15}H_{16}N_4O_3S{\cdot}1H_2O$: C, 51.42; H, 5.18; N, 15.99; S, 9.15. Found: C, 51.51; H, 5.19; N, 15.97; S, 9.08.

5.1.4. 7-[(1*R*,2*S*,3*R*,4*S*)-2,3-*O*-Isopropylidene-2,3,4-trihydroxycyclopent-1-yl]amino-6-nitro-4-quinazolone (15). To a suspension of **14**[12] (451 mg, 2 mmol) in 1-butanol (20 mL) was added **13**[13] (400 mg, 2.3 mmol) followed by Et_3N (2.5 mmol). The mixture was refluxed for 48 h. The solution was then allowed to cool to room temperature and the yellow precipitate that formed was obtained by filtration and dried to provide **15** (422 mg, 58%) as a yellow powder, which was of sufficient purity to be used directly in the next step. For microanalytical purposes, a sample was prepared by further purification via either eluting from a column using CH_2Cl_2/MeOH (8:1) or by recrystallizing from EtOAc: mp 186–188°C. ^1H NMR (DMSO-d_6) δ 12.17 (s, 1H), 8.78 (s, 1H), 8.61 (d, J=7.5 Hz, 1H), 8.11 (s, 1H), 6.93 (s, 1H), 5.68 (d, J=2.5 Hz, 1H), 4.49 (s, 2H), 4.17 (s, 1H), 4.06 (dd, J=7.5 Hz, 1H), 2.33 (m, 1H), 1.83 (m, 1H), 1.41 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 160.20, 153.68, 149.39, 146.54, 132.18, 127.21, 111.74, 110.31, 108.49, 86.25, 84.36, 75.91, 59.08, 35.82, 26.63, 24.26. Anal. Calcd for $C_{16}H_{18}N_4O_6{\cdot}0.75MeOH$: C, 52.07; H, 5.48; N, 14.50. Found: C, 51.80; H, 5.21; N, 14.89.

5.1.5. 6-Amino-7-[(1*R*,2*S*,3*R*,4*S*)-2,3-*O*-isopropylidene-2,3,4-trihydroxycyclopent-1-yl]amino-4-quinazolone (16). Compound **15** (220 mg, 0.60 mmol) was dissolved in MeOH (50 mL) and 10% Pd–C (100 mg) was added to the solution. This mixture was treated with H_2 in a Parr hydrogenator at 45 psi for 1 h. The reaction mixture was filtered through a pad of Celite™ and the filtrate concentrated under reduced pressure. The residue was triturated (hexane) to afford a dull white powder, which was obtained by filtration and then dried to yield **16** (160 mg, 79%). An analytical sample was obtained by recrystallization from ether: mp 275–280°C dec.: ^1H NMR (DMSO-d_6) δ 11.55 (s, 1H), 7.74 (s, 1H), 7.21 (s, 1H), 6.59 (s, 1H), 5.36 (m, 2H), 4.94 (brs, 2H), 4.42 (s, 2H), 4.12 (s, 1H), 3.78 (dd, J=7.5 Hz, 1H), 2.32 (m, 1H), 1.84 (m, 1H), 1.41 (s, 3H), 1.22 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 160.07, 143.54, 141.87, 141.50, 135.56, 112.60, 109.92, 107.45, 104.29, 85.87, 83.96, 75.34, 58.76, 36.00, 26.51, 24.14. Anal. Calcd for $C_{16}H_{20}N_4O_4{\cdot}0.75H_2O$: C, 55.56; H, 6.27; N, 16.20. Found: C, 55.28; H, 6.03; N, 15.83.

5.1.6. 3-[(1*R*,2*S*,3*R*,4*S*)-2,3,4-Trihydroxycyclopent-1-yl]-imidazo[4,5-*g*]quinazolin-8-one (12a). *From* **16**. To a suspension of **16** (100 mg, 0.3 mmol) in triethyl orthoformate (7 mL) kept at 0°C under N_2 was added of conc. HCl (1 mL). This mixture was stirred at room temperature for 48 h and then the solvent was evaporated. Distilled H_2O (10 mL) was added to the residue. The resultant solution was heated at 80°C for 2 h. After cooling, the solution was carefully neutralized with 3N NaOH solution and the solvent was then evaporated under reduced pressure. The residue was co-evaporated with EtOH (3×10 mL). The residue from this treatment was adsorbed on silica gel and loaded on a silica gel column. Elution with CH_2Cl_2/MeOH (3:1) and evaporation of the combined fractions gave **12a** (40 mg, 44%) as a light yellow powder. The microanalytical sample was recrystallized from H_2O: mp 280–283°C dec.: ^1H NMR (DMSO-d_6) δ 12.10 (br, s, 1H), 8.53 (d, J=7.5 Hz, 1H), 8.38 (s, 1H), 8.12 (s, 1H), 8.00 (s, 1H), 5.43 (d, J=2.5 Hz, 1H), 5.12 (d, J=5.0 Hz, 1H), 4.84 (dd, J=10.0 and 7.5 Hz, 1H), 4.52 (s, 1H), 4.24 (m, 1H), 4.00 (m, 1H), 3.80 (s, 1H), 2.70 (m, 1H), 1.87 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 161.45, 147.66, 143.78, 143.18, 137.96, 117.66, 116.19, 108.35, 76.61, 75.11, 73.34, 60.18, 35.19. Anal. Calcd for $C_{14}H_{14}N_4O_4{\cdot}1HCl$: C, 49.64; H, 4.46; N, 16.54. Found: C, 49.32; H, 4.76; N, 16.28.

From **11a**. *Compound* **11a** (50 mg, 0.15 mmol) was suspended in 1N HCl (5 mL) and the mixture was refluxed for 4 h. After cooling the mixture to room temp, the pH of the solution was adjusted to 7 using 3N NaOH. The solvent was evaporated under reduced pressure and the residue was co-evaporated with EtOH (2×10 mL). Purification of the residue was accomplished via silica gel column chromatography eluting with CH_2Cl_2/MeOH (3:1). Evaporation of the combined fractions containing product afforded pure **12a** (22 mg, 48%) as a light yellow powder. Recrystallization of this material from H_2O gave an analytical sample identical (NMR and mixed melting point) to **12a** obtained from **16**. Anal. Calcd for $C_{14}H_{14}N_4O_4{\cdot}0.6HCl$: C, 51.87; H, 4.54; N, 17.28. Found: C, 51.76; H, 4.82; N, 17.06.

5.1.7. 1-[(1*R*,2*S*,3*R*,4*S*)-2,3,4-Trihydroxycyclopent-1-yl]-imidazo[4,5-*g*]-quinazolin-8-one (12b). Hydrolysis of **11b** (80 mg, 0.24 mmol) was carried out in the same manner as the hydrolysis of **11a** to produce **12a** (49 mg, 67%). Compound **12b** thus obtained was recrystallized from EtOH/isopropyl alcohol to provide an analytically pure sample: mp >290°C dec.: ^1H NMR (DMSO-d_6) δ 12.15 (s, 1H), 8.63 (s, 1H), 8.61 (s, 1H), 8.00 (s, 1H), 7.91 (s, 1H), 5.46 (d, J=2.5 Hz, 1H), 5.22 (d, J=7.5 Hz, 1H), 5.13 (d, J=2.5 Hz, 1H), 4.88 (dd, J=10 Hz, 1H), 4.53 (dd, J=5 Hz, 1H), 4.01 (s, 1H), 3.81 (s, 1H), 2.71 (m, 1H), 1.91 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 161.54, 148.48, 143.46, 142.84, 133.12, 118.27, 116.29, 108.36, 76.83, 75.63, 73.49, 60,25, 35.69, HRMS Calcd for $C_{14}H_{14}N_4O_4$ 302.1015, found 302.1009.

5.1.8. 8-Amino-3-[(1*R*,2*S*,3*R*,4*S*)-2,3,4-trihydroxycyclopentyl]imidazo[4,5-*g*]-quinazoline (7). A solution of **11a** in anhydrous MeOH saturated with NH_3 was heated in an oil

bath at 110°C for 40 h in a sealed tube. After cooling, the MeOH was evaporated and the gray residue obtained was triturated (ether) to result in **7** (140 mg, 93%). This material was recrystallized from H_2O: mp >290°C; $[\alpha]^{24}_D = -34.82°$ (*c* 0.37, DMSO). ^{1}H NMR (DMSO-d_6) δ 8.63 (s, 1H), 8.45 (s, 1H), 8.32 (s, 1H), 8.08 (s, 1H), 7.70 (br, s, 2H) 5.35 (d, *J*=2.5 Hz, 1H), 5.06 (m, 2H), 4.82 (dd, *J*=10 Hz, 1H), 4.59 (dd, *J*=5 Hz, 1H), 4.01 (s, 1H), 3.80 (s, 1H), 2.70 (m, 1H), 1.98 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 162.53, 153.85, 148.17, 145.12, 143.22, 137.77, 113.39, 110.55, 107.06, 76.80, 75.01, 73.51, 60.17, 35.24. Anal. Calcd for $C_{14}H_{15}N_5O_3 \cdot 1.5H_2O$: C, 51.22; H, 5.53; N, 21.33. Found: C, 51.43; H, 5.53; N, 21.35.

Acknowledgements

This research was supported by funds from the Department of Health and Human Services (AI31718 and AI48495) and this is appreciated. We are indebted to Robert Sidwell of Utah State University for providing the influenza A, influenza B, and respiratory syncytial assays; to Brent Korba of Georgetown University for the hepatitis B virus assay; and, to Erik De Clercq of Rega Institute, Leuven, Belgium for the following viral assays: varicella zoster, cytomegalo, vesicular stomatitis, sindbis, punta toro, coxsackie B4, reovirus, herpses simplex, human immunodeficiency, and vaccinia. We are also grateful to Dr Katherine Seley of the Georgia Institute of Technology for assistance in obtaining the optical rotation and HRMS data.

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