Bioorganic & Medicinal Chemistry 21 (2013) 359–364

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

C-3 halo and 3-methyl substituted 5′-nor-3-deazaaristeromycins: Synthesis and antiviral properties

Chong Liu, Qi Chen, Minmin Yang, Stewart W. Schneller *

Molette Laboratory for Drug Discovery, Department of Chemistry and Biochemistry, Auburn University, Auburn, AL 36849-5312, United States

ARTICLE INFO

Article history:
Received 28 July 2012
Revised 17 September 2012
Accepted 25 September 2012
Available online 22 October 2012

Keywords:
5′-Nor carbocyclic nucleosides
3-Deazaadenine
Antiviral analysis

ABSTRACT

To expand on the antiviral properties of 5′-noraristeromycin, synthetic entry into 3-substituted 3-deaza-5′-noraristeromyin derivatives (i.e., bromo, **4**; iodo, **5**; chloro, **6**; and, methyl, **7**) has been accomplished from a common intermediate. An extensive antiviral analysis showed **7** to be basically inactive (except for weak effects against VSV) and there were no general trends among the halo compounds (except versus reovirus-1 and influenza B). Individually, compound **4** was most favorable towards HCMV, VZV, HBV, and VV; product **5** against HBV, VSV, VV, influenza B, HCMV, and measles; and, target **6** towards Punta Toro, VSV, measles, parainflucenza-3, influenza A (H5N1), and influenza B. The methyl target **7** was inactive in all viral assays.

1. Introduction

Since the synthesis of carbocyclic thymidine in 1962[1] and carbocyclic adenosine in 1966[2] and its subsequent isolation from *Streptomyces citricolor* nov. sp. 2 years later[3] as aristeromycin (Ari, **1**), the search for medicinal agents from the carbocyclic nucleoside class has been enduring.[4] This has been in part due to the ability of **1** to function as an inhibitor of cellular *S*-adenosylhomocysteine hydrolase.[5] However, development of **1** as a therapeutic has been limited by its cytotoxicity as a consequence of metabolic conversion to Ari-5′-triphosphate and subsequent unfavorable utilization of this derivative by host cells.[5]

A number of years ago we sought a means to circumvent the nucleotide formation steps of **1** by focusing on 5′-noraristeromycin (**2**), which has shown promise both as an antiviral agent[6] and for inhibiting malarial infections.[7] Prompted by the antiviral properties of 3-deazaaristeromycin,[8] we investigated 3-deaza-5′-noraristeromycin[9] and found, surprisingly, it to be less active than **2**. We recently returned to this observation thinking the decreased activity of **3** may have been due to the change in electron density at C-3 on going from **2** to **3**. This suggested the preparation of the halo substituted compounds **4**, **5**, and **6**.[10] The precursor to the bromo target **12** in Scheme 1 also offered a synthetic entry into the 3-methyl derivative **7**.[11] Here we report the synthesis and antiviral results for the 3-bromo **4**, 3-iodo **5**, 3-chloro **6**, and 3-methyl **7** targets (Fig. 1).

2. Materials and methods

2.1. Chemistry

The synthesis of targets **4**–**6** (Scheme 1) began with the palladium (0) catalyzed reaction between 4-chloro-1*H*-imidazo[4,5-*c*]pyridine (6-chloro-3-deazapurine, **8**)[12] and (1*R*,4*S*)-4-hydroxycyclopent-2-en-1-yl acetate (**9**)[13] followed by silylation to give a mixture of **10** and **11**. This mixture was separated and **11** converted to **12** upon dihydroxylation. Isopropylidenation of **12** to **13** was followed by ammonolysis (via the hydrazine/Raney Ni process)[14] to **14**. Treatment of **14** with N-bromosuccinimide and N-iodosuccinimide led to **15** and **16**, respectively, which upon deprotection (HCl/MeOH) provided **4** and **5.**

For reasons that were unclear, reaction of **14** with N-chlorosuccinimide failed to give the requisite precursor to **6**. This difficulty was circumvented by protecting the amino of **14** as its diBoc derivative **17** that was converted to **6** via **18** upon reaction with N-chlorosuccinimide followed by acid deprotection (Scheme 1).

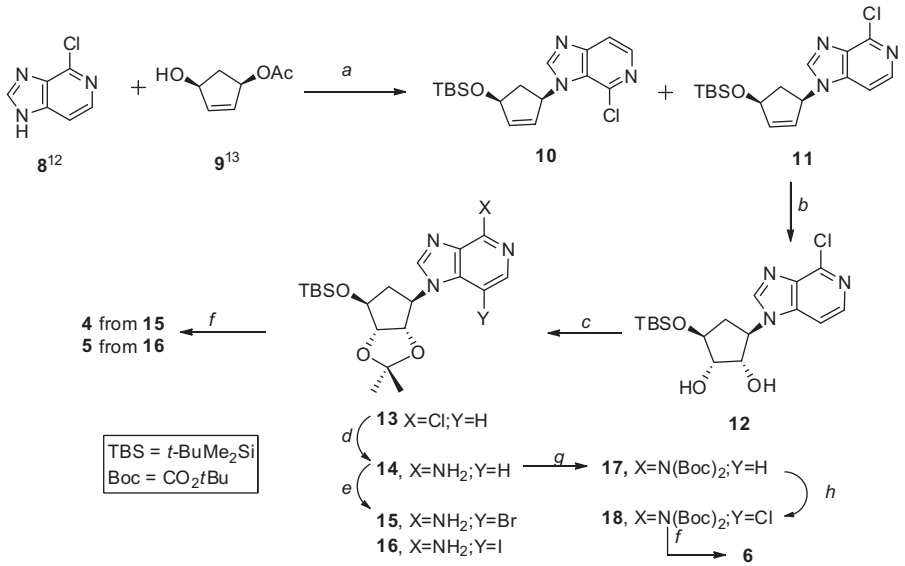
The successful preparation of the 3-methyl target **7** (Scheme 2) proceeded through the trisilyl derivative **19** (obtained from **12**). Following steps analogous to the **13**→**14**→**15/16** process, **19** was converted to **20** and this product then to **21**. Using a methylaluminum-halo exchange reaction, **21** became **22** that was transformed to **7** (Fig. 2) upon treatment with tetrabutylammonium fluoride.

2.2. Antiviral results

Table 1 reports those viruses, including both DNA and RNA, toward which **4**–**6** showed activity.[15,16] Noteworthy is the significant activity of **4** against HBV, varicella zoster, reovirus-1, and human

* Corresponding author. Tel.: +1 334 844 6947; fax: +1 334 844 0239.
E-mail address: schnest@auburn.edu (S.W. Schneller).

0968-0896/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmc.2012.09.051



Scheme 1. Synthesis of **3**, **4**, and **5**. Reagents and conditions: (a) (i) $Pd(Ph_3P)_4$, NaH, DMF/THF; (ii) TBSCl, imidazole, CH_2Cl_2, 34% for 11 for two steps; (b) OsO_4, NMO, CH_2Cl_2/H_2O, 81%; (c) $(CH_3)_2C(OMe)_2$, acetone, 99%; (d) (i) NH_2NH_2; (ii) Raney Ni, H_2O, 62%; (e) NBS for **15** and NIS for **16**, CH_2Cl_2, 87% and 61%, respectively; (f) HCl/MeOH, 84% for **4**, 70% for **5**, 80% for **6**; (g) $(Boc)_2O$, DMAP, THF, 84%; (h) NCS, CH_2Cl_2, 92%.

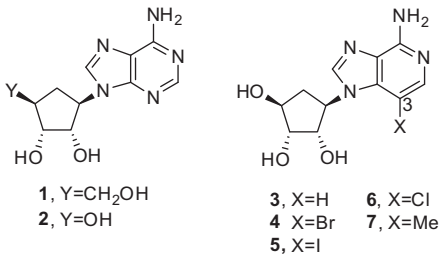
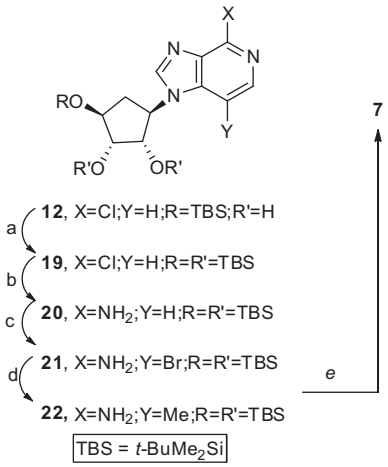


Figure 1.



Scheme 2. Synthesis of **7**. Reagents and conditions: (a), TBSCl, imidazole, CH_2Cl_2, 92%; (b) (i) N_2H_4, THF; (ii) Raney Ni, MeOH, 68% for two steps; (c) NBS, CH_2Cl_2, 85%; (d) $AlMe_3$, $Pd(PPh_3)_4$, THF, 92%; (e), TBAF, THF, 90%.

cytomegalovirus; **6** towards measles, influenza B, parainfluenza-3, H5N1, and reovirus-1; and **5** towards HBV. Compound **7** was inactive. While there are no clear general trends among the halo compounds, the data does offer candidates for further antiviral scrutiny.

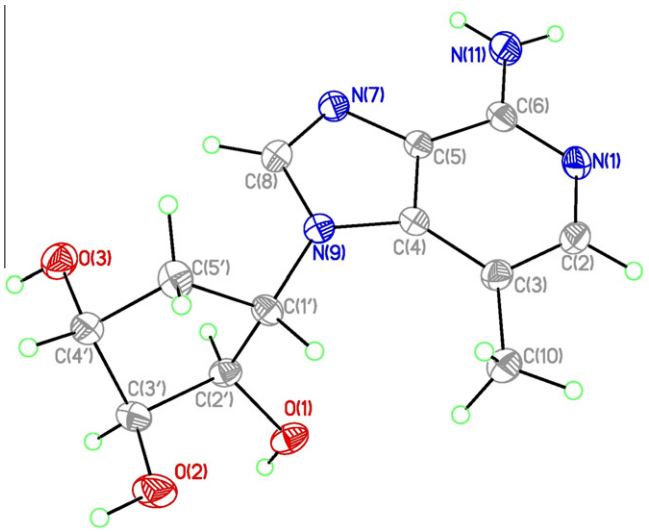


Figure 2. X-ray structure for **7**.

3. Conclusion

These results suggest that a more focused analog design based on the 3-halo series is to be pursued. At the same time, the results with **7** indicate that alkyl substituents at the C-3 center of 3-deaza-5′-noraristeromycin are unlikely to improve the antiviral diversity of this class of carbocyclic nucleosides.

4. Experimental section

4.1. General methods

Melting points were recorded on a Meltemp II melting point apparatus and the values are uncorrected. The combustion analyses were performed at Atlantic Microlab, Norcross, GA. ^1H and ^{13}C NMR spectra were recorded on either a Bruker AC 250 spectrometer (250 MHz for proton and 62.9 MHz for carbon) or a

Table 1
Antiviral activity of **4**, **5**, and **6** (in μM)[a,b,c]

Virus	Cell line	Compound **4**			Compound **5**			Compound **6**		
		EC_{50}	CC_{50}[a]/MCC[d]	SI	EC_{50}	CC_{50}[a]/MCC[d]	SI	EC_{50}	CC_{50}[a]/MCC[d]	SI
Punta Toro	Vero	>8	>8[d]	ND	>20	100[d]	ND	24	>200[d]	ND
HCMV	HFF	1.7	>300[a]	>175	1.2	219[a]	182	ND	ND	ND
Vaccinia	HEL	24	>200[d]	ND	4	>100[d]	ND	120	>200[d]	ND
Vesicular stomatitis	HEL	>200	>200[d]	ND	4	>100[d]	ND	8	>100[d]	ND
HBV	HepG 2.215	0.022	>10[a]	>454	0.808	>300[a]	>370	>10	>300[a]	ND
Measles	CV-1	>273	>273[a]	ND	2.9	67[a]	23	0.18	311[a]	>1727
Parainfluenza-3	Vero	8	>8[d]	ND	20	100[d]	ND	1.6	>200[d]	ND
Reovirus-1	Vero	1.6	>8[d]	ND	4	100[d]	ND	1.6	>200[d]	ND
VZV	HFF	0.11	>300[a]	>2631	>60	201[a]	<3.4	>300	>300[a]	ND
Flu A (H5N1)	MDCK	ND	ND	ND	44	>242[a]	>6	4.0	>311[a]	>77
Influenza B	MDCK	27	>273[a]	>100	2.2	>242[a]	>111	0.62	>311[a]	>500

ND: Not determined.
[a] CC_{50}: compound concentration that reduces cell viability by 50%.
[b] EC_{50}: compound concentration that reduces viral replication by 50%.
[c] SI: CC_{50}/EC_{50}.
[d] MCC: minimum compound concentration that causes a microscopically detectable alternation of normal cell morphology.

Bruker AV 400 spectrometer (400 MHz for proton and 100.6 MHz for carbon), referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Whitman Diamond silica gel 60-F254 precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. Column chromatography was performed on Whitman silica, 230–400 mesh and 60 Å using elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials.

4.2. 1-[(1*R*,4*S*)-4-(*t*-Butyldimethylsilyloxy)cyclopent-2-enyl]-4-chloro-1*H*-imidazo[4,5-*c*]pyridine (11)

Sodium hydride (1.75 g, 69.0 mmol) was added to a solution of 4-chloro-1*H*-imidazo[4,5-*c*]pyridine (**8**)[12] (10.0 g, 65.1 mmol) in dry DMF (90 mL). The reaction mixture was stirred at room temperature for 3 h, followed by the addition of *tetrakis*(triphenylphosphine)palladium (3.7 g, 3.2 mmol), triphenylphosphine (2.5 g, 9.5 mmol), and a solution of (+)-(1*R*,4*S*)-4-hydroxycyclopent-2-en-1-yl acetate (**9**)[13] (11.0 g, 77.5 mmol) in dry THF (90 mL). This mixture was stirred at 55 °C for 24 h. The solvent was removed under reduced pressure and the residue purified by column chromatography (EtOAc/MeOH, 10:1) to afford 17.08 g mixture of N-3 and N-1 coupling products as indicated by the NMR spectra. This mixture was used in the next step without further separation.

To a solution of the above mixture in CH_2Cl_2 (150 mL) containing imidazole (5.22 g, 76.8 mmol) was added *tert*-butyldimethysilyl chloride (7.99 g, 51.2 mmol). The reaction mixture was stirred at room temperature for 24 h. Water (80 mL) was added. The organic layer was separated, washed with brine and dried ($MgSO_4$). The solvent was removed and the residue purified by column chromatography (EtOAc/hexanes, 2:1) to afford **11** as a white solid (7.8 g, 34%), mp 91–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 5.6 Hz, 1H), 8.14 (s, 1H), 7.55 (d, J = 5.6 Hz, 1H), 6.23 (m, 1H), 5.95 (m, 1H), 5.34 (m, 1H), 4.93 (m, 1H), 2.99 (ddd, J = 14.6, 8.6, 7.3 Hz, 1H), 1.95 (dt, J = 14.6, 3.5 Hz, 1H), 0.92 (s, 9H), 0.15 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.0, 143.1, 141.3, 140.0, 139.3, 138.5, 130.3, 106.3, 75.4, 60.3, 41.4, 25.9, 18.2, −4.5, −4.6; Anal. Calcd for $C_{17}H_{24}ClN_3OSi$: C, 58.35; H, 6.91; N, 12.01. Found: C, 58.57; H, 6.95; N, 12.03.

4.3. (1*S*,2*S*,3*S*,5*R*)-3-(*t*-Butyldimethylsilyloxy)-5-(4-chloroimidazo[4,5-*c*]pyridin-1-yl)cyclopentane-1,2-diol (12)

Methylmorpholine-*N*-oxide (1.70 g, 46.6 mmol) was added to a solution of **11** (3.5 g, 10 mmol) in CH_2Cl_2 (50 mL) containing a small amount of H_2O (0.8 mL). After the solution was cooled to 0 °C, a catalytic amount of solid osmium tetraoxide (30 mg, 0.12 mmol) was added and the solution was stirred for 12 h at room temperature. The reaction mixture was quenched by addition of sodium bisulfate. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (EtOAc/hexanes, 3:1) to afford **12** as a white solid (3.11 g, 81%), mp 202–203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.92 (d, J = 5.6 Hz, 1H), 7.68 (d, J = 5.6 Hz, 1H), 5.76 (s, 1H), 5.10 (s, 1H), 4.75 (m, 1H), 4.31 (d, J = 6.4 Hz, 1H), 4.13 (d, J = 3.6 Hz), 1.99 (dd, J = 6.4, 17.2 Hz, 1H), 0.99 (s, 9H), 0.20 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.7, 141.9, 141.2, 138.6, 137.4, 106.8, 78.4, 76.6, 74.7, 62.7, 37.3, 26.0, 18.3, −4.6, −4.7; Anal. Calcd for $C_{17}H_{26}ClN_3O_3Si{\cdot}0.1H_2O$: C, 52.89; H, 6.79; N, 10.89. Found: C, 52.54; H, 6.83; N, 10.79. HRMS $[M+H]^+$ calcd for $C_{17}H_{26}ClN_3O_3Si$ 384.1510. Found: 384.1496.

4.4. 1-((3aS,4R,6S,6aS)-6-(tert-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)-4-chloro-1H-imidazo[4,5-c]pyridine (13)

To a solution of **12** (2.70 g, 7.0 mmol) and 2, 2-dimethoxypropane (10 mL) in the dry acetone (15 mL) was added a catalytic amount of *p*-toluenesulfonic acid (80 mg). After the reaction was stirred at room temperature for 12 h, solvent was removed and the residue was dissolved in CH_2Cl_2 (40 mL) and washed with saturated sodium bicarbonate, H_2O and brine. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to afford **13** as white foam (2.95 g, 99%). This material was used without further purification in the next step. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.22 (d, J = 5.6 Hz, 1H), 7.42 (d, J = 5.6 Hz, 1H), 4.77 (d, J = 1.6 Hz, 1H), 4.74 (d, J = 2.4 Hz, 1H), 4.58 (d, J = 5.6 Hz, 1H), 4.49 (d, J = 4.5 Hz, 1H), 2.82 (m, 1H), 2.24 (m, 1H), 1.54 (s, 3H), 1.32(s, 3H), 0.81 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 143.8, 143.1, 141.6, 140.3, 138.0, 112.0, 105.6, 87.4, 86.3, 77.7, 63.1, 37.2, 26.9, 26.0, 24.4, 18.4, −4.7, −4.8; Anal. Calcd for $C_{20}H_{30}ClN_3O_3Si$: C, 56.65; H, 7.13; N, 9.91. Found: C, 56.94; H, 7.26; N, 9.77.

4.5. 1-((3a*S*,4*R*,6*S*,6a*S*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine (14)

A solution of **13** (2.12 g, 5.00 mmol) in neat hydrazine (20 mL) and THF (10 mL) was brought to reflux for 2 h. After cooling to room temperature, the solution was concentrated under reduced

pressure. The residue was dissolved in MeOH (40 mL) and freshly prepared W2-Raney Ni (prepared from 40 g of alloy) was added to it. The reaction mixture was heated to reflux for 1 h. The hot reaction mixture was filtered and washed with hot MeOH (3 × 15 mL). The combined filtrates were evaporated to dryness. The residue was purified via column chromatography (EtOAc/MeOH = 10:1) to afford **14** as a white solid (1.25 g, 62%), mp 140–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.89 (d, J = 5.6 Hz, 1H), 6.86 (d, J = 5.6 Hz, 1H), 5.18 (br, 2H), 4.80 (d, J = 5.6 Hz, 1H), 4.70 (m, 1H), 4.57 (d, J = 5.6 Hz, 1H), 4.50 (d, J = 4.4 Hz, 1H), 2.78 (m, 1H), 2.22 (d, J = 14.8 Hz, 1H), 1.54 (s, 3H), 1.32 (s, 3H), 0.91(s, 9H), 0.14 (s, 3H), 0.11(s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 151.9, 141.1, 140.5, 139.2, 127.5, 111.8, 98.0, 87.6, 86.3, 77.8, 62.5, 37.4, 26.9, 26.1, 24.5, 18.4, −4.7; Anal. Calcd for $C_{20}H_{32}N_4O_3Si$: C, 59.37; H, 7.97; N, 13.85. Found: C, 59.16; H, 8.06; N, 13.69.

4.6. (1*S*,2*R*,3*S*,4*R*)-4-(4-Amino-7-bromo-1*H*-imidazo[4,5-*c*]pyridin-1-yl)cyclopentane-1,2,3-triol (4)

A solution of **14** (1.62 g, 4.00 mmol) in dry CH_2Cl_2 (80 mL) was cooled to −15 °C. N-Bromosuccinimide (1.06 g, 6.00 mmol) was added to the solution portionwise and the resulting mixture was stirred for 30 min. The mixture was then concentrated in vacuo and the residue was purified by flash column chromatography (EtOAc/hexanes, 2:1) to afford 7-bromo-1-[(3a*S*,4*R*,6*S*,6a*S*)-6-(*tert*-butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]-1*H*-imidazo[4,5-*c*]pyridin-4-amine **(15)** (1.68 g, 87%) as a yellow solid, which was used immediately in the next step.

Compound **15** (798 mg, 1.65 mmol) was dissolved in a mixture of 2 N HCl (20 mL) and MeOH (20 mL). This reaction mixture was stirred at room temperature for 3 h and neutralized with basic ion-change resin (Amberlite IRA-67). After filtration, the solvent was evaporated in vacuo. The residue was subjected to column chromatography (EtOAc/MeOH/NH_4OH = 8/2/1) to yield **4** as a yellow solid (507 mg, 84%), mp 206–208 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 7.88 (s, 1H), 7.75 (br, 2H), 5.41 (m, 1H), 5.26 (d, J = 2.8 Hz, 1H), 5.18 (s, 1H), 5.05(s, 1H), 4.60 (t, J = 4.0 Hz, 1H), 3.92 (s, 1H), 3.79 (d, J = 4.4 Hz, 1H), 2.76 (m, 1H), 1.59 (m, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 149.7, 142.6, 136.1, 134.7, 127.6, 89.3, 76.5, 76.0, 73.1, 59.3, 39.9; Anal. Calcd for $C_{11}H_{13}BrN_4O_3$·HCl·0.1 H_2O: C, 39.92; H, 4.02; N, 16.93. Found: C, 39.84; H, 3.94; N, 16.58. HRMS (EI) calcd for $C_{11}H_{13}BrN_4O_3$ 328.0170. Found: 328.0171.

4.7. (1*S*,2*R*,3*S*,4*R*)-4-(4-Amino-7-iodo-1*H*-imidazo[4,5-*c*]pyridin-1-yl)cyclopentane-1,2,3-triol (5)

In a similar manner as that above, the reaction of **14** (881 mg, 2.18 mmol) with N-iodosuccinimide in DMF afforded 1-[(3a*S*,4*R*,6*S*,6a*S*)-6-(*tert*-butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]7-iodo-1*H*-imidazo[4,5-*c*]pyridin-4-amine **(16)** (705 mg, 61%) as a yellow solid that was used immediately in the next step.

In the same manner as described above for **4,** reaction of compound **16** (479 mg, 0.90 mmol) with HCl gave **5** as a yellow solid (260 mg, 70%), mp 233–234 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 7.87 (s, 1H), 6.48 (br, 2H), 5.44 (m, 1H), 5.21 (d, J = 3.9 Hz, 1H), 5.09 (d, J = 6.7 Hz, 1H), 4.98 (d, J = 3.9 Hz, 1H), 4.66 (m, 1H), 3.89 (s, 1H), 3.78 (s, 1H), 2.75 (m, 1H), 1.44 (m, 1H); ^{13}C NMR(100.6 MHz, DMSO-d_6) δ 149.4, 143.9, 138.8, 138.1, 127.6, 76.9, 76.2, 73.6, 59.2, 58.8, 40.0; Anal. Calcd for $C_{11}H_{13}IN_4O_3$•HCl: C, 32.02; H, 3.42; N, 13.58. Found: C, 31.99; H, 3.32; N, 13.28.

4.8. 1-[(3a*S*,4*R*,6*S*,6a*S*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]-1*H*-imidazo[4,5-*c*]pyridin-*bis*-Boc-4-amine (17)

To a solution 100 mL flask containing **14** (405 mg, 1 mmol) and DMAP (25 mg, 0.2 mmol) was added 25 mL of THF. Then Boc_2O (0.7 mL, 3 mmol) was added under an N_2 atmosphere. The reaction mixture was stirred for 8 h at room temperature. TLC (EtOAc/hexanes, 2:3) analysis indicated the disappearance of the starting material and the presence of a single product. The excess THF was removed by rotary evaporation to give a yellow oil. The crude product was purified by flash chromatography (EtOAc/hexanes, 1:2) on silica gel to give **17** as white foam (505 mg, 84%), mp 73–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 5.8 Hz, 1H), 8.26 (s, 1H), 7.44 (d, J = 5.8 Hz, 1H), 4.77 (m, 2H), 4.56 (d, J = 6.2 Hz, 1H), 4.47 (d, J = 3.8 Hz, 1H), 2.80 (m, 1H), 2.2 (d, J = 15 Hz, 1H), 1.63 (s, 3H), 1.41 (s, 18H), 1.33 (s, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 151.5, 144.7, 143.5, 141.1, 137.0, 116.4, 106.1, 87.5, 86.3, 82.9,77.4, 62.8, 37.2, 28.1, 26.9, 26.1, 24.5, 18.4, −4.7; Anal. Calcd for $C_{30}H_{48}N_4O_7Si$: C, 59.58; H, 8.00; N, 9.26. Found: C, 59.63; H, 8.02; N, 9.18.

4.9. 7-Chloro-1-((3a*S*,4*R*,6*S*,6a*S*)-6-(*tert*-butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-1*H*-imidazo[4,5-*c*]pyridin-*bis*-Boc-4-amine (18)

A solution of **17** (480 mg, 0.79 mmol) in dry CH_2Cl_2 (50 mL) was cooled to −30 °C. N-Chlorosuccinimide (211 mg, 1.58 mmol) was added to the solution portionwise and the resulting mixture was stirred for 8 h. The mixture was then concentrated in vacuo and the residue was purified by column chromatography (EtOAc/hexanes, 1:1) to afford **18** (466 mg, 92%) as a white solid, mp 74–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.24 (s, 1H), 5.62 (d, J = 7.8 Hz, 1H), 5.00 (d, J = 5.8 Hz, 1H), 4.62 (d, J = 5.8 Hz, 1H), 4.43 (d, J = 4.5 Hz, 1H), 2.79 (m, 1H), 2.11 (d, J = 15.3 Hz, 1H), 1.52 (s, 3H), 1.41 (s, 18H), 1.34 (s, 3H), 0.86 (s, 9H), 0.11 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 151.3, 145.1, 143.6, 140.8, 138.1, 136.4, 114.3, 111.5, 87.9, 86.7, 83.2, 78.1, 77.4, 63.3, 39.1, 28.1, 26.8, 26.1, 24.4, 18.3, −4.7, −4.8; Anal. Calcd for $C_{30}H_{47}ClN_4O_7Si$: C, 56.37; H, 7.41; N, 8.76. Found: C, 56.49; H, 7.43; N, 8.70.

4.10. (1*S*,2*R*,3*S*,4*R*)-4-(4-Amino-7-chloro-1*H*-imidazo[4,5-*c*]pyridin-1-yl)cyclopentane-1,2,3-triol (6)

In the same manner as described above for **4,** reaction of compound **18** (403 mg, 0.63 mmol) with 2 N HCl gave **6** as a yellow solid (162 mg, 80%), mp 209–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 7.61 (s, 1H), 6.41 (br, 2H), 5.25 (m, 1H), 5.19 (d, J = 3.75 Hz, 1H), 5.10 (d, J = 6.75 Hz, 1H), 4.98 (d, J = 3.75 Hz, 1H), 4.52 (m, 1H), 3.90 (s, 1H), 3.76 (s, 1H), 2.73 (m, 1H), 1.56 (m, 1H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 152.18, 140.81, 140.02, 134.62, 128.39, 102.50, 77.14, 76.49, 73.71, 59.72, 39.82; Anal. Calcd for $C_{11}H_{13}ClN_4O_3$•HCl•0.8H_2O: C, 39.37; H, 4.69; N, 16.70. Found: C, 39.32; H, 4.48; N, 16.50. HRMS $[M+H]^+$ calcd for $C_{11}H_{13}ClN_4O_3$ 285.0754. Found: 285.0763.

4.11. 4-Chloro-1-[(1*R*,2*S*,3*R*,4*S*)-2,3,4-*tris*(*t*-butyldimethylsilyloxy)cyclopentyl]-1*H*-imidazo[4,5-*c*]pyridine (19)

To a solution of **12** (1.64 g, 4.27 mmol) in the dry CH_2Cl_2 (50 mL) was added *t*-butyldimethylsilyl chloride (TBSCl) (1.50 g, 9.60 mmol) followed by imidazole (2.07 g, 13.8 mmol). After the reaction mixture was stirred at room temperature overnight, H_2O (20 mL) was added. Then the organic layer was separated, washed with brine and dried ($MgSO_4$). The solvent was removed in vacuo

and the residue purified by column chromatography (EtOAc/hexanes, 1:1) to afford **19** as a white solid (2.4 g, 92%), mp 102–104 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.15 (d, J = 5.5 Hz, 1H), 8.09 (s, 1H), 7.76 (d, J = 5.5 Hz, 1H), 4.67–4.76 (m, 2H), 4.07 (dd, J = 5.5, 1.3 Hz, 1H), 3.84 (d, J = 1.0 Hz, 1H), 2.88 (m, 1H), 1.97 (m, 1H), 0.99 (s, 9H), 0.95 (s, 9H), 0.71 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H), 0.15 (s, 3H), 0.13 (s, 3H), −0.26 (s, 3H), −0.68 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 144.8, 143.3, 140.9, 139.3, 138.4, 106.5, 78.7, 77.9, 75.0, 60.8, 36.8, 25.8, 25.7, 18.0, 17.8, −4.5, −4.5, −4.7, −4.8, −5.0, −5.9; Anal. Calcd for $C_{29}H_{54}ClN_3O_3Si_3$: C, 56.87; H, 8.89; N, 6.86. Found: C, 56.80; H, 8.89; N, 6.75.

4.12. 1-[(1*R*,2*S*,3*R*,4*S*)-2,3,4-tris(*t*-Butyldimethylsilyloxy) cyclopentyl]-1*H*-imidazo[4,5-c]pyridin-4-amine (20)

A solution of **19** (2.2 g, 3.6 mmol) in neat hydrazine (20 mL) and THF (10 mL) was brought to reflux for 2 h. After cooling to room temperature, the solution was concentrated under reduced pressure. The residue was dissolved in MeOH (40 mL) and W2-Raney Ni (20 g) added to it. The reaction mixture was heated to reflux for 1 h. The hot reaction mixture was filtered and the insoluble material washed with hot MeOH (3 × 15 mL). The combined filtrates were evaporated to dryness. The residue was purified via column chromatography (EtOAc/MeOH, 10:1) to afford **20** as a white solid (1.44 g, 68%), mp 140–142 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.79 (d, J = 5.8 Hz, 1H), 7.17 (d, J = 5.8 Hz, 1H), 5.17 (br, 2H), 4.61–4.73 (m, 2H), 4.04 (dd, J = 5.5, 1.3 Hz, 1H), 3.82 (d, J = 1.3 Hz, 1H), 2.81 (m, 1H), 1.98 (m, 1H), 0.98 (s, 9H), 0.94 (s, 9H), 0.72 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), −0.26 (s, 3H), −0.63 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 151.9, 141.5, 140.3, 138.1, 128.1, 99.0, 78.9, 74.9, 60.3, 36.6, 25.8, 18.0, 17.8, −4.5, −4.7, −4.8, −5.0, −5.9; Anal. Calcd for $C_{29}H_{56}N_4O_3Si_3{\cdot}0.2H_2O$: C, 58.38; H, 9.53; N, 9.39. Found: C, 58.17; H, 9.47; N, 9.18. HRMS (EI) calcd for $C_{29}H_{56}N_4O_3Si_3$ 592.3660. Found: 592.3662.

4.13. 7-Bromo-1-[(1*R*,2*S*,3*R*,4*S*)-2,3,4-*tris*(*t*-butyldimethylsilyloxy) cyclopentyl)]-1*H*-imidazo[4,5-*c*]pyridin-4-amine (21)

Reaction of compound **20** (886 mg, 1.49 mmol) with N-bromosuccinimide (399 mg, 2.24 mmol) in dry CH_2Cl_2 (100 mL) was completed in 2 h at 0 °C. The mixture was then concentrated in vacuo and the residue purified by column chromatography (EtOAc/hexanes, 1:1) to afford bromide **21** (850 mg, 85%) as a white solid, mp 116–117 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.86 (s, 1H), 5.91 (m, 1H), 5.39 (br, 2H), 4.60 (dd, J = 8.0, 3.0 Hz, 1H), 3.98 (d, J = 5.0 Hz, 1H), 3.80 (s, 1H), 2.96 (m, 1H), 1.67 (dd, J = 14.5, 4.5 Hz, 1H), 0.94 (s, 9H), 0.92 (s, 9H), 0.70 (s, 9H), 0.12 (s, 6H), 0.11 (s, 6H), −0.24 (s, 3H), −0.51 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 151.5, 143.4, 140.8, 136.3, 128.6, 90.8, 81.6, 79.0, 74.9, 57.8, 40.6, 25.9, 25.8, 18.1, 18.0, −4.3, −4.5, −4.6, −4.7, −4.9, −5.5; Anal. Calcd for $C_{29}H_{55}BrN_4O_3Si_3$: C, 51.84; H, 8.25; N, 8.34. Found: C, 52.10; H, 8.28; N, 8.24.

4.14. (1*S*,2*R*,3*S*,4*R*)-4-(4-Amino-7-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)cyclopentane-1,2,3-triol (7)

To a solution of **21** (660 mg, 0.98 mmol) in dry THF (50 mL) was added $Pd(Ph_3P)_4$ (100 mg, 0.087 mmol). Then, $AlMe_3$ (1.96 mL, 3.92 mmol, 2 M in THF) was added to this mixture dropwise at room temperature. After stirring at room temperature for 1 h, the reaction mixture was heated to reflux for 2 h. The reaction mixture was allowed to cool to the room temperature. The solvent was evaporated in vacuo and the residue subjected to flash chromatography (EtOAc/MeOH, 12:1) to yield 7-methyl-1-[(1*R*,2*S*,3*R*,4*S*)-2,3,4-*tris*(*t*-butyldimethyl-silyloxy)cyclopentyl]-1*H*-imidazo-[4,5-*c*] pyridin-4-amine (**22**) as a white solid (550 mg, 92%), which was used in the next step without further purification; ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (s, 1H), 7.42 (s, 1H), 5.31 (m, 1H), 4.53 (dd, J = 8.4, 3.2 Hz, 1H), 4.11 (d, J = 5.6 Hz, 1H), 3.90 (d, J = 1.6 Hz, 1H), 3.02 (m, 1H), 2.52 (s, 3H), 1.92 (dd, J = 14.8, 5.2 Hz, 1H), 1.00 (s, 9H), 0.96 (s, 9H), 0.68 (s, 9H), 0.20 (s, 6H), 0.16 (s, 6H), −0.21 (s, 3H), −0.51(s, 3H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 152.3, 141.5, 141.0, 140.3, 127.5, 109.3, 83.5, 80.2, 75.9, 59.9, 40.3, 26.3, 26.2, 18.9, 18.8, 16.1, −4.0, −4.4, −4.6, −4.7, −4.8, −5.6.

Tetrabutylammonium fluoride (3.2 mL, 3.2 mmol, 1 M in THF) was added to a solution of **22** (480 mg, 0.81 mmol) in dry THF (80 mL). The reaction mixture was stirred at room temperature for 6 h. The solvent was removed in vacuo and the residue purified by column chromatography (EtOAc/MeOH, 10:1) to afford **7** (191 mg, 90%) as a white solid, mp 297–299 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.37 (s, 1H), 5.89 (br, 2H), 5.22 (d, J = 3.6 Hz, 1H), 5.08 (d, J = 6.8 Hz, 1H), 4.88–4.95 (br m, 2H), 4.32 (m, 1H), 3.93 (m, 1H), 3.76 (s, 1H), 2.73 (m, 1H), 2.43 (s, 3H), 1.68 (m, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 151.2, 140.4, 139.5, 137.9, 126.6, 106.5, 77.9, 76.8, 73.4, 59.2, 38.9, 15.2; Anal. Calcd for $C_{12}H_{16}N_4O_3$: C, 54.54; H, 6.10; N, 21.20. Found: C, 54.22; H, 6.21; N, 20.95.

4.15. X-ray crystallography data

4.15.1. X-ray data for compound 7

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 702061. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e mail: deposit@ccdc.cam.ac.uk

Acknowledgements

This research has been partially supported by funds from the Department of Health and Human Services (Al 56540), which is appreciated. Also, support from the Molette Fund and Auburn University is appreciated. We are grateful for the assistance of Dr. John Gorden at Auburn University. We are also indebted to the following individuals for providing the antiviral data following their standard protocols: Dr. Donald Smee, Utah State University; Dr. Brent Korba, Georgetown University; Dr. Mark Prichard, University of Alabama at Birmingham; and, other laboratories who are part of the non-clinical evaluation program funded by the National Institute of Allergy and Infectious Diseases. We also acknowledge the assistance of Dr. Erik De Clercq, Katholieke Universiteit, for antiviral data.

References and notes

1. Murdock, K. C.; Angier, R. B. *J. Am. Chem. Soc.* **1962**, *84*, 3758.
2. Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 3885.
3. Kusaka, T.; Yamamoto, H.; Shibata, M.; Muroi, M.; Kishi, T.; Mizuono, K. *J. Antibiot.* **1968**, *21*, 255.
4. (a) Wang, J.; Rawal, R. K.; Chu, C. K. *Med. Chem. Nucleic Acids* **2011**, 1; (b) Rodriguez, J. B.; Comin, M. J. *Mini Rev. Med. Chem.* **2003**, *3*, 95; (c) Schneller, S. W. *Curr. Top. Med. Chem.* **2002**, *2*, 1087.
5. Wolfe, M. S.; Borchardt, R. T. *J. Med. Chem.* **1991**, *34*, 1521.
6. Patil, S. D.; Schneller, S. W.; Hosoya, M.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1992**, *35*, 3372.
7. Kitade, Y.; Kozaki, A.; Miwa, T.; Nakanishi, M. *Tetrahedron* **2002**, *58*, 1271.
8. Hasobe, M.; Liang, R.; Ault-Riche, D. B.; Borcherding, D. R.; Wolfe, M. S.; Borchardt, R. T. *Antiviral. Chem. Chemother.* **1993**, *4*, 245.
9. Siddiqi, S. M.; Chen, X.; Rao, J.; Schneller, S. W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1995**, *38*, 1035.
10. (a) There are literature reports for using 3-halo substituted 3-deazaadenosines in structural and biological investigations: Minakawa, N.; Kojima, N.; Matsuda, A. *J. Org. Chem.* **1999**, *64*, 7158.; (b) Liu, M.-C.; Luo, M.-Z.; Mozdziesz, D. W.; Lin,

T.-S.; Dutschman, G. E.; Gullen, E. A.; Cheng, Y.-C.; Sartorelli, A. C. *Nucleosides Nucleotides Nucleic Acids* **1975**, *2001*, 20.
11. Alkyl substitutions (including methyl) have found a place in structural studies for 3-deazaadenosine: (a) Aoyagi, M.; Minakawa, N.; Matsuda, A. *Tetrahedron Lett.* **1993**, *34*, 103; (b) Acevedo, O. L.; Andrews, R. S.; Cook, P. D. *Nucleosides Nucleotides* **1993**, *12*, 403; (c) Yamagata, Y.; Kato, M.; Fujii, S.; Aoyagi, M.; Minakawa, N.; Matusda, A. *Nucleosides Nucleotides* **1994**, *13*, 1327; (d) Irani, R. J., ; SantaLucia, J., Jr. *Nucleosides Nucleotides Nucleic Acids* **2002**, *21*, 737.
12. Tseng, C. K. H.; Marquez, V. E.; Fuller, R. W.; Goldstein, B. M.; Haines, D. R.; McPherson, H.; Parsons, J. L.; Shannon, W. M.; Arnett, G.; Hollingshead, M.; Driscoll, J. S. *J. Med. Chem.* **1989**, *32*, 1442.
13. Siddiqi, S. M.; Chen, X.; Schneller, S. W. *Nucleosides Nucleotides* **1993**, *12*, 267.
14. Yang, M. M.; Zhou, J.; Schneller, S. W. *Tetrahedron* **2006**, *62*, 1295.
15. For leading references on the procedures used for the assays see: (a) Roy, A.; Serbessa, T.; Schneller, S. W. *Bioorg. Med. Chem.* **2006**, *14*, 4980; (b) http://www.usu.edu/iar/people.html (July 8, **2012**).; (c) http://www.southernresearch.org/life-sciences/infectious-diseases/virology (July 8, **2012**).
16. There was no activity for any of the target compounds Rift Valley Fever (Vero 76), Tacaribe (Vero 76), Dengue (Vero), West Nile (Vero), yellow fever (Vero), cowpox (HFF), rhinovirus (HeLa Ohio-1), adenovirus (A549), respiratory syncytial virus (MA-104), Epstein-Barr virus (HFF), coxsackie virus B4 (Vero), sindbis (Vero), HSV-1 (HEL), HSV-2 (HEL), feline coronavirus (CRFK), influenza A (H1N1 and H3N2) (MDCK), parainfluenza (MA104), HIV-1 (CEM), and HIV-2 (CEM).