Bioorganic & Medicinal Chemistry xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

2- and 3-Fluoro-3-deazaneplanocins, 2-fluoro-3-deazaaristeromycins, and 3-methyl-3-deazaneplanocin: Synthesis and antiviral properties

Chong Liu, Qi Chen, John D. Gorden, 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 24 May 2015
Revised 11 July 2015
Accepted 19 July 2015
Available online xxxx

Keywords:
Carbocyclic nucleosides
Fluoro 3-deazaadenine nucleosides
Antiviral activity

ABSTRACT

The 3-deaza analogs of the naturally occurring adenine-based carbocyclic nucleosides aristeromycin and neplanocin possess biological properties that have not been optimized. In that direction, this paper reports the strategic placement of a fluorine atom at the C-2 and C-3 positions and a methyl at the C-3 site of the 3-deazaadenine ring of the aforementioned compounds. The synthesis and *S*-adenosylhomocysteine hydrolase inhibitory and antiviral properties of these targets are described. Some, but not all, compounds in this series showed significant activity toward herpes, arena, bunya, flavi, and orthomyxoviruses.

1. Introduction

The clinical success of entecavir (**1**)[1] and abacavir (**2**)[2] (Fig. 1) have given carbocyclic nucleosides a prominent place among antiviral drug therapeutics and, as a consequence, serve to invigorate the search for other carbocyclic antiviral leads.[1,3] While compounds **1** and **2** are guanine and diaminopurine based agents (as prodrugs of the active triphosphates),[4] finding carbocyclic nucleoside antivirals based on the adenine ring continues in our[5] and other[6] laboratories as a result of their inhibition of *S*-adenosylhomocysteine hydrolase.[7] Aristeromycin (**3**) and neplanocin A (**4** herein referred to as neplanocin) represent the parent structures in those studies.

Because of their structural similarity to adenosine, the naturally occurring **3** and **4** have been shown to possess biological characteristics,[8] including inhibition of *S*-adenosylhomocysteine hydrolase (SAHase)[7] and 5′-nucleotide formation[9] that have been designated as loci for their antiviral properties. The synthetic 3-deaza analogs of **3** and **4** (i.e., **5** and **6**) arose to expand on the structural features of **3** and **4** and have been found to possess similar antiviral profiles most often associated with their potent inhibition of SAHase (**6** > **5**),[10] which, in turn, affects AdoMet-dependent methylation reactions,[6] including those of viral origin.[6] Also, the class of 3-deazaadenine nucleosides has drawn attention since they are less susceptible to adenosine deaminase and adenosine kinase and, consequently, less toxic than their aza parents.[11]

Continuing our interest in the 3-deaza category,[12] we recently reported that 3-halo-3-deazaadenine carbocyclic nucleosides displayed promising activity[5d,e] that prompted us to further explore this structural characteristic with the synthesis and antiviral status of 2- and 3-fluoro-3-deazaneplanocins (**7** and **8**), 2-fluoro-3-deazaaristeromycins (**9**), and 3-methyl-3-deazaneplanocin (**10**) (Fig. 1).

Target **7a** was selected as the 3-deaza congener of the antiviral candidate 2-fluoroneplanocin[13] while **8a** offers the 3-fluorolog of the broad spectrum agent 3-bromo-3-deazaneplanocin.[5e] Compound **9a** places it (i) along side of 3-fluoro-3-deazaaristeromycin, which has favorable antiviral promise,[14] and (ii) as the 3-deaza analog of the anti-malarial prospect 2-fluoroaristeromycin.[15] The compound represented by **10** became part of this study to ascertain whether 3-alkyl-3-deazaneplanocins offer antiviral potential and to provide access to functionalized carbon units at the 3-deaza site for further agent discovery. The 5′-homo targets (**7b**, **8b**, and **9b**) have also been included as a consequence of the antiviral properties of 5′-homoneplanocin[16a] and 5′-homoaristeromycin.[16b] The 5′-nor derivative of **9a** (i.e., **9c**) follows from the significant antiviral properties of 5′-nor aristeromycin.[5d]

2. Results and discussion

2.1. Synthesis

The plan to the target compounds was designed to subject readily accessible cyclopentenols **11**[5e] or **12**[16a] (shown in Scheme 2)

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

http://dx.doi.org/10.1016/j.bmc.2015.07.039
0968-0896/

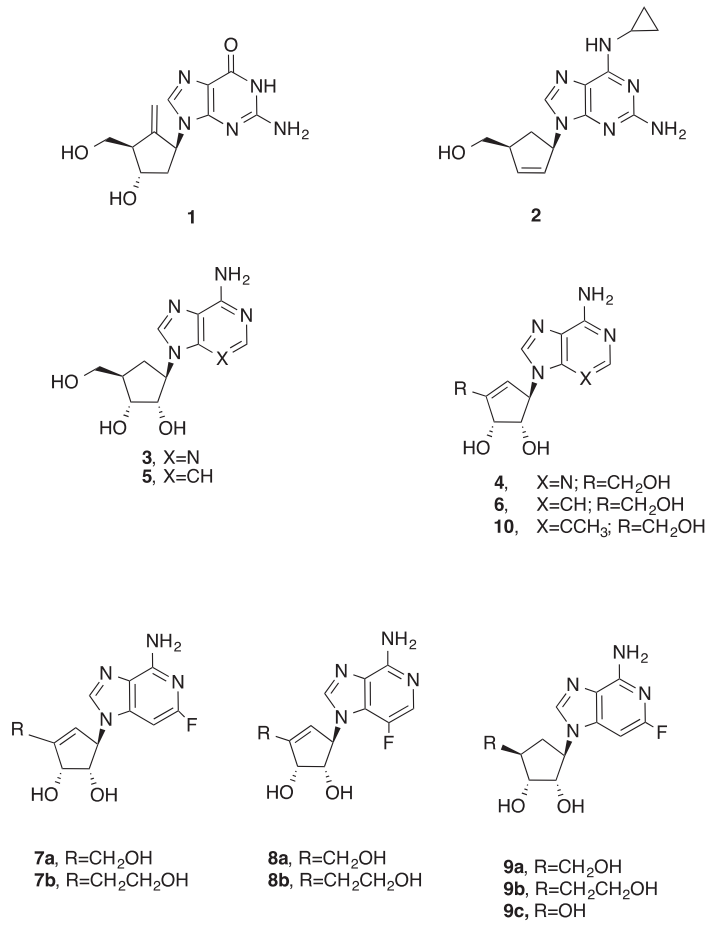


Figure 1. Relevant purine carbocyclic nucleosides.

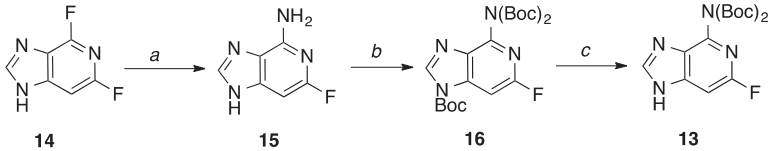
and cyclopentanols **25**,[5e] **26**,[14] and **27**[14] (shown in Scheme 3) to a Mitsunobu procedure[12a] with requisite 3-deazaadenines **13** (Scheme 1), **17**[14] and **18**[5e] (shown in Scheme 2). The preparation of **13** began with 4,6-difluoroimidazo[4,5-*c*]pridine (2,6-difluoro-3-deazaadenine, **14**)[17] with the awareness that the 6-fluoro (purine numbering) would be more susceptible to displacement by ammonia than a chloro at that position, which would require hydrazine and Raney nickel conditions as is common for 3-deazaadenine nucleosides.[12a] This conclusion was validated with the facile conversion of **14**–**15**. Realizing that the free amino on **15** would compete with the Mitsunobu coupling, it was transformed into the tri-Boc derivative **16** that was, in turn, converted to **13** with tetrabutylammonium fluoride.[5e] Besides NMR data, the structure of **13** was further confirmed by X-ray crystallography.

The five neplanocin analog targets (**7a**/**7b**, **8a**/**8b**, and **10**) were synthesized according to Scheme 2 employing **11**, **12** and **13**, **17**[14] and **18**,[5e] under Mitsunobu conditions[12a] to yield the coupling products **19**–**23**. That the coupling occurred on the purine N-9 position was confirmed by the X-ray crystal structures of **8a** and **8b**. Removal of the silyl protecting groups of **19**–**22** under acidic conditions gave targets **7a**, **7b**, **8a**, and **8b**. A palladium catalyzed cross-coupling reaction with trimethylaluminum converted **23** into **24**, which was followed by the same silyl deprotection as used previously to afford **10**.

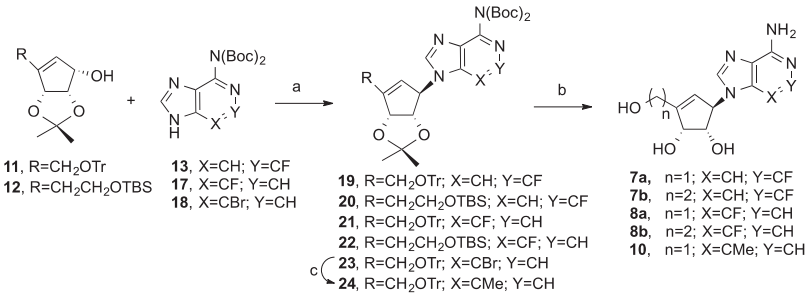
In a similar approach, the three aristeromycin targets **9a**–**c** were synthesized according to Scheme 3. Subjecting **13** to Mitsunobu coupling conditions with **25**,[5e] **26**,[14] and **27**[14] smoothly gave products **28**–**30**. Target compounds **9a**–**c** were subsequently obtained after acidic removal of the silyl protecting groups.

2.2. Antiviral and enzyme assay results

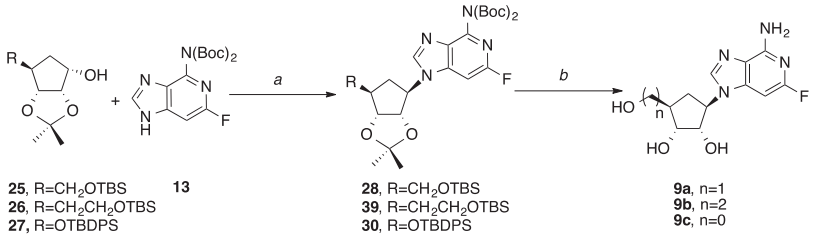
Tables 1 and 2 summarizes the viruses toward which the compounds synthesized showed activity.[14,18] The 3-deaza-3-fluoroneplanocin series (**8a**, **8b**) (Table 1) exhibit broad antiviral activities against herpes (dsDNA), arena ((−)ssRNA), bunya ((−)ssRNA), flavi ((+)ssRNA), and orthomyxoviruses ((−)ssRNA). Target **8a** showed potent activities against tacaribe virus, human cytomegalovirus (HCMV), influenza A (H5N1), influenza B and moderate activity against Rift Valley fever and dengue virus. The 5′ homo analog



Scheme 1. Synthesis of **13**. Reagents and conditions: (a) NH_3/MeOH, 93%; (b) $(Boc)_2O$, DMAP, THF; (c) TBAF, THF, 53% from **15**.



Scheme 2. Synthesis of 2-fluoro-(**7a**, **7b**), 3-fluoro-(**8a**, **8b**), and 3-methy-(**10**) 3-deazaneplanocins. Reagents and conditions: (a) DIAD, PPh_3, THF; (b) HCl/MeOH; (c) $AlMe_3$, $Pd(PPh_3)_4$, THF, yields in Section 3.



Scheme 3. Synthesis of 2-fluoro-3-deazaaristeromycin and its 5′-modified analogs (**9a–c**). Reagents and conditions: (a) DIAD, PPh_3, THF; (b) HCl/MeOH yields in Section 3.

Table 1
Antiviral data for the active compounds

	Cell-line	**8a**			**8b**			**10**		
		IC_{50} (μM)	CC_{50} (μM)	SI	IC_{50} (μM)	CC_{50} (μM)	SI	IC_{50} (μM)	CC_{50} (μM)	SI
Yellow fever	Vero	>224	224.0	–	1.5	>340	>240	3.6	>362	>100
Rift Valley fever	Vero 76	6.4	36.0	5.6	1.3	3.4	2.6	>36	36.0	–
Tacaribe	Vero 76	<0.36	114.2	>317	<0.34	190.4	>560	1.2	83.3	72.0
Dengue	Vero	7.1	35.7	5.0	15.0	108.8	7.3	>228	228.0	–
HCMV	HFF	0.3	>300	>1035	5.1	>300	759.0	6.4	247.0	38.6
Influenza A (H5N1)	MDCK	1.0	32.5	34.0	139.0	>340	>2.4	76.0	250.0	3.3
Influenza B	MDCK	<0.36	>357	>1000	1.0	>340	>340	1.1	>362	>320

Control drugs: Yellow fever, infergen IC_{50} = 0.00001 μg/mL, CC_{50} > 0.01; Rift Valley fever, ribavirin, IC_{50} = 37.3 μM, CC_{50} > 1000 μM; Tacaribe, ribavirin, IC_{50} = 26.7 μM, CC_{50} > 1000 μM; Dengue, infergen IC_{50} = 0.0002 μg/mL, CC_{50} > 0.1 μg/mL; HCMV, ganciclovir, IC_{50} = 3.6 μM, CC_{50} > 100 μM; Infuenza B, ribavirin IC_{50} = 9.0 μM, CC_{50} > 100 μM.

Table 2
Antiviral data for additional active compounds

	Cell-Line	**7a**			**7b**			**9a**			**9b**			**9c**		
		IC_{50} (μM)	CC_{50} (μM)	SI	IC_{50} (μM)	CC_{50} (μM)	SI	IC_{50} (μM)	CC_{50} (μM)	SI	IC_{50} (μM)	CC_{50} (μM)	SI	IC_{50} (μM)	CC_{50} (μM)	SI
Yellow fever	Vero	6.8	>100	>50	29	>100	>3.4	2.1	>355	>170	–	–	–	15	>100	>6.7
HCMV	HFF	8.7	217.5	25	<0.1	>300	>300	–	–	–	–	–	–	–	–	–
HBV	HepG 22.2.15	0.67	11	17	0.99	7.5	8	–	–	–	–	–	–	–	–	–
Measles	CV-1	8.5	>100	>12	89.8	>100	>1	9.6	>355	>37	162	>338	>2.1	30.2	>100	>3

Control drugs: HBV, lamivudine, IC_{50} = 0.039 μM, CC_{50} = 2176 μM; measles, 3-deazaguanine, IC_{50} = 4.1 μM, CC_{50} = 250 μM. For yellow fever and HCMV, see Table 1.

8b maintained the potent activity against tacaribe virus and improved (relative to **8a**) activity against yellow fever and Rift Valley fever while displaying, in varying degrees, reduced activity toward dengue, HCMV, influenza A (H5N1) and influenza B. The 3-methyl analog **10** has similar antiviral trend as **8b** except for the loss of activity against Rift Valley fever virus and dengue virus.

3-Deaza-2-fluoroneplanocin **7a** produced broad-spectrum antiviral activities against yellow fever, HCMV, HBV (particularly noteworthy) and measles viruses (Table 2). With a C-5′ modified side chain, compound **7b** gave potent results toward HCMV and maintained the activity (relative to **7a**) against HBV. 3-Deaza-2-fluoroaristeromycin **9a** (Table 2) produced high activity against yellow fever virus and moderate activity against measles virus. The two C-5′-side chain modified analogs (**9b**, **9c**) lost both antiviral activities (Table 2).

Because of the potent inhibitory properties of 3-deazaneplanocin and 3-deazaaristeromycin toward *S*-adenosylhomocysteine (AdoHcy) hydrolase,[14] and as their generally accepted mode of antiviral properties, the target compounds in this study were evaluated against this enzyme (Table 3). Of the compound collection, **8a** is the most potent AdoHcy hydrolase inhibitor and showed the best antiviral profile. This suggests inhibition of AdoHcy hydrolase activity could serve, in the future, as an indicator of possible antiviral activity for **8a** analogs. On the other hand, **7a** and **7b**

Table 3
AdoHcy hydrolase inhibition activities (nM)

	7a	7b	8a	8b	9a	9b	9c	10
IC_{50}	1400	>10,000	6.8	145	3320	3750	1000	41

Control inhibitor: 3-deazaneplanocin (**6**) IC_{50} = 9.3.[14]

lacked hydrolase inhibition, but displayed some high antiviral activities. This may indicate that they are acting by a mechanism not exclusively involving the hydrolase.

2.3. Conclusion

Placement of a fluorine atom on biological molecules has opened new leads for drug discovery.[19] Similar consequences have arisen herein with 3-deazaneplanocin and 3-deazaaristeromycin from the newly synthesized 2-fluoro- (**7**) and 3-fluoro-3-deazaneplanocins (**8**) and, to a less extent, 2-fluoro-3-dezaaristeromycins (**9**). Antiviral activity has been found for DNA viruses (HCMV, herpes; HBV, hepadna) and for RNA viruses (yellow fever and dengue, flavi; Rift Valley fever, bunya; Tacaribe, arena; influenza A and B, orthomyxo; and measles, paramyxo). Antiviral results for **8a** correlates with its inhibition of AdoHcy hydrolase while this correlation was not found for **7a** and, certainly, **7b**. The **9** series was both poor AdoHcy hydrolase inhibitors and antiviral candidates and, with the comparatively moderate hydrolase activity and their small range of antiviral effects, **8b** and **10** appear act by more than hydrolase inhibition. It should be noted that the 3-fluoro-3-deazaneplanocin (**8a**) reported here offers greater activity diversity than the corresponding 3-fluoro-3-deazaaristeromycin congener.[14]

3. Experimental section

3.1. Chemistry

The combustion analyses were performed at Atlantic Microlab, Norcross, GA. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker AV 600 spectrometer (600 MHz for proton and 150 MHz for carbon) or a Bruker AV 400 spectrometer (400 MHz for proton and 100 MHz for carbon), referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The mass spectral data was determined using a Waters Micromass Q-TOF Premier Mass Spectrometer. The 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, and 60 Å using elution with the indicated solvent system.

3.1.1. 4-(*N*,*N*-Di-*tert*-butyloxycarbonylamino)-6-fluoroimidazo[4,5-*c*]pyridine (13)

A solution of **14**[17] (1.1 g, 7.1 mmol) in MeOH (30 mL) was saturated with NH_3 at 0 °C and then heated at 90 °C for 24 h in a Parr stainless steel, sealed reaction vessel. The solvent was removed under reduced pressure, and the residue purified by column chromatography (EtOAc/MeOH, 7:1) to afford **15** as a white solid (1.0 g, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.51 (br, 1H), 8.02 (s, 1H), 6.50 (br, 2H), 6.20 (s, 1H) HRMS Calcd for $C_6H_5FN_4$ $[M+H]^+$: 153.0576 Found 153.0591.

To a suspension of **15** (0.95 g, 6.25 mmol) and 4-(dimethylamino)pyridine (DMAP, 77 mg, 0.63 mmol) in dry THF (50 mL) was added 5.5 g (25 mmol) of $(Boc)_2O$. After stirring for 24 h at room temperature, the reaction mixture was quenched by adding H_2O (50 mL) followed by extraction with EtOAc and the extracts dried (anhydrous Na_2SO_4). The solvent was removed by evaporation under reduced pressure to give an oil residue (**16**, 2.4 g), which was used directly for the next step.

Tetrabutylammonium fluoride (11 mL, 1M in THF, 11 mmol) was added to a solution of **16** in THF (40 mL). This reaction mixture was stirred at room temperature for 6 h. The solvent was removed by evaporation under reduced pressure and the residue purified by column chromatography (EtOAc/MeOH, 10:1) to afford **13** (1.1 g, 53% from **15**) as a white solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.66 (br, 1H), 8.16 (s, 1H), 7.06 (s, 1H), 1.40 (s, 18H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 180.6, 159.4, 155.8, 151.1, 144.6, 84.0, 77.2, 53.6, 27.8; HRMS calcd for $C_{16}H_{22}N_4O_4F$ $[M+H]^+$ 353.1625, Found 353.1639.

3.1.2. General procedure for the Mitsunobu reaction of 3-deazaadenines with cyclopentanols and cyclopentenols and the hydrolysis of coupling products

To a solution of cyclopentanols **11**, **12**, **25**–**27** (1 mmol) and triphenylphosphine (1.5 mmol) in THF (10 mL) was added 3-deazaadenines **13**, **17**, or **18** (1 mmol). This suspension was cooled to 0 °C and DIAD (1.5 mmol) added dropwise. After completion of the addition, the reaction mixture was warmed to room temperature and stirred at this temperature for 12 h. The solvent was removed under reduced pressure and the residue purified by column chromatography (hexanes/EtOAc, 3:1) to afford **19**–**23** and **28**–**30**, which are contaminated with DIAD byproducts.

Products **19**–**22** and **28**–**30**, were dissolved in a mixture of MeOH (5 mL) and 2 N HCl (4 mL) and the resulting solution was brought to reflux for 2 h and then cooled to room temperature. After addition of basic resin (Amberlite IR67) for neutralization of the solution and filtration, the solvent was removed under vacuum and the residue purified by column chromatography (EtOAc/MeOH, 10:1) to give **7a**, **7b**, **8a**, **8b** and **9a**–**c**.

3.1.3. (1*R*,4*R*,5*S*)-3-(Hydroxymethyl)-4,5-dihydroxy-2-cyclopenten-l-yl]-4-amino-6-fluoroimidazo[4,5-*c*]pyridine (7a)

Yield: 62% (for two steps), white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 1H), 6.60 (br, 2H), 6.28 (d, J = 1.6 Hz, 1H), 5.78 (m, 1H), 5.25 (d, J = 7.6 Hz, 1H), 5.20 (m, 1H), 5.09 (d, J = 5.6 Hz, 1H), 5.04 (t, J = 5.6 Hz, 1H), 4.37, (t, J = 5.2 Hz, 1H), 4.13 (m, 2H), 4.01 (dd, J = 13.2, 6.0 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 150.4 (d, J = 157 Hz), 142.1, 141.5, 140.5, 129.4, 127.3 (d, J = 11 Hz), 125.8 (d, J = 21 Hz), 123.8, 78.4, 72.6, 67.2, 59.0. Anal. Calcd for $C_{12}H_{13}FN_4O_3$: C, 51.43; H, 4.68; N, 19.99. Found: C, 51.16; H, 4.60; N, 19.76.

3.1.4. (1*R*,4*R*,5*S*)-3-(2-Hydroxyethyl)-4,5-dihydroxy-2-cyclopenten-l-yl]-4-amino-6-fluoroimidazo[4,5-*c*]pyridine (7b)

Yield: 65% (for two steps), white solid. ^{1}H NMR (600 MHz, CD_3OD) δ 8.05 (s, 1H), 6.24 (s, 1H), 6.05 (d, J = 1.8 Hz, 1H), 5.30 (d, J = 5.4 Hz, 1H), 4.59 (m, 1H), 4.35 (t, J = 5.4 Hz, 1H), 3.61 (t, J = 6.6 Hz, 2H), 2.19 (m, 1H), 1.97 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.9 (d, J = 185 Hz), 148.8, 141.5, 140.2, 129.5, 127.2 (d, J = 12 Hz), 125.8 (d, J = 21 Hz), 125.5, 79.0, 78.0, 74.8, 59.4, 33.0. Anal. Calcd for $C_{13}H_{15}FN_4O_3$: C, 53.06; H, 5.14; N, 19.04. Found: C, 53.40; H, 5.21; N, 18.75.

3.1.5. (1*R*,4*R*,5*S*)-3-(Hydroxymethyl)-4,5-dihydroxy-2-cyclopenten-l-yl]-4-amino-7-fluoroimidazo[4,5-*c*]pyridine (8a)

Yield: 55% (for two steps), white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (s, 1H), 7.61 (d, J = 3.6 Hz, 1H), 5.92 (dd, J = 2.0, 4.0 Hz, 1H), 5.60 (m, 1H), 4.62 (m, 1H), 4.32 (m, 2H), 4.26 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 150.3, 142.9, 141.2, 125.0, 124.8, 123.9, 78.4, 77.4, 72.7, 67.4, 61.5, 58.8. Anal. Calcd for $C_{12}H_{13}FN_4O_3$: C, 51.43; H, 4.68; N, 19.99. Found: C, 51.67; H, 4.70; N, 20.01.

3.1.6. (1*R*,4*R*,5*S*)-3-(2-Hydroxyethyl)-4,5-dihydroxy-2-cyclopenten-l-yl]-4-amino-7-fluoroimidazo[4,5-*c*]pyridine (8b)

Yield: 58% (for two steps), white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 5.80 (dd, J = 1.6, 3.2 Hz, 1H), 5.56 (m, 1H), 4.55 (d, J = 5.2 Hz, 1H), 4.23 (dt, J = 1.6, 5.2 Hz, 1H), 3.81 (m, 2H), 2.52 (t, J = 6.4 Hz, 2H) ^{13}C NMR (100 MHz, CD_3OD) δ 150.6, 149.6, 143.3 (d, J = 241 Hz), 142.8, 130.5, 129.3 (d, J = 12 Hz), 126.5 (d, J = 23 Hz), 79.6, 76.4, 69.2, 60.9, 49.2, 33.7. Anal. Calcd for $C_{13}H_{15}FN_4O_3$: C, 53.06; H, 5.14; N, 19.04. Found: C, 52.99; H, 5.14; N, 18.87.

3.1.7. (1*R*,2*S*,3*R*,5*R*)-3-(4-Amino-6-fluoro-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-5-(hydroxymethyl)cyclopentane-1,2-diol (9a)

Yield: 59% (for two steps), white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.12 (s, 1H), 6.58 (br, 2H), 6.43 (s, 1H), 5.00 (d, J = 7.0 Hz, 1H), 4.87 (t, J = 5.0 Hz, 1H), 4.74 (d, J = 5.0 Hz, 1H), 4.52 (dd, J = 7.0, 19.2 Hz, 1H), 4.15 (m, 1H), 3.80 (m, 2H), 3.40 (m, 1H), 2.26 (m, 1H), 2.06 (m, 1H), 1.69 (m, 1H). ^{13}C NMR (150.9 MHz, DMSO-d_6) δ 158.7 (d, J = 220 Hz), 150.1 (d, J = 22 Hz), 141.3, 141.2, 124.6, 78.6 (d, J = 46 Hz), 75.2, 72.2, 62.8, 60.7, 45.2, 28.4. Anal. Calcd for $C_{12}H_{15}FN_4O_3$: C, 51.06; H, 5.36; N, 19.85. Found: C, 50.88; H, 5.50; N, 19.65.

3.1.8. (1*R*,2*S*,3*R*,5*R*)-3-(4-Amino-6-fluoro-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-5-(2-hydroxyethyl)cyclopentane-1,2-diol (9b)

Yield: 63% (for two steps), white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (s, 1H), 6.46 (s, 1H), 4.58 (m, 1H), 5.77 (m, 1H), 4.25 (dd, J = 6.0, 7.6 Hz, 1H), 3.84 (t, J = 6.0 Hz, 1H), 3.68 (m, 2H), 2.46 (m, 1H), 2.15 (m, 1H), 1.93 (m, 1H), 1.68 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 160.9 (d, J = 225 Hz), 151.2 (d, J = 20 Hz), 143.5, 142.3, 125.4, 80.4 (d, J = 45 Hz), 76.8, 76.6, 63.0, 61.6, 41.9, 38.2, 33.5. Anal. Calcd for $C_{13}H_{17}FN_4O_3$: C, 52.70; H, 5.78; N, 18.91. Found: C, 52.60; H, 5.70; N, 18.78.

3.1.9. (1*S*,2*R*,3*S*,4*R*)-4-(4-Amino-6-fluoro-1*H*-imidazo[4,5-*c*]pyridin-1-yl)cyclopen-tane-1,2,3-triol (9c)

Yield: 62% (for two steps), white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (s, 1H), 6.68 (s, 1H), 4.71 (m, 1H), 5.57 (dd, J = 4.4, 8.4 Hz, 1H), 4.14 (m, 1H), 3.94 (d, J = 4.4 Hz, 1H), 2.83 (m, 1H), 1.94 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.2 (d, J = 225 Hz), 149.7 (d, J = 21 Hz), 142.0, 141.1, 124.2, 79.2 (d, J = 45 Hz), 76.9, 75.9, 73.7, 60.6, 35.3. Anal. Calcd for $C_{11}H_{13}FN_4O_3$: C, 49.25; H, 4.89; N, 20.89. Found: C, 49.43; H, 4.96; N, 20.85.

3.1.10. (1*R*,4*R*,5*S*)-3-(Hydroxymethyl)-4,5-dihydroxy-2-cyclopenten-l-yl]-4-amino-7-methylimidazo[4,5-*c*]pyridine (10)

To a solution **23** (obtained in Section 3.1.2) in dry THF (20 mL) was added $Pd(Ph_3P)_4$ (100 mg, 0.087 mmol). To this mixture, $AlMe_3$ (1.25 mL, 2.0 M in THF, 2.5 mmol) was added dropwise at room temperature. The reaction mixture was then stirred at room temperature for 1 h followed by heating at reflux for 12 h. The reaction mixture was allowed to cool to room temperature and was then diluted with Et_2O (30 mL); this was washed with H_2O and brine and dried (anhydrous $MgSO_4$). Concentration of the solution *in vacuo* gave **24** as a dark solid, which was used in the next step without further purification.

Crude **24** was subjected to the hydrolysis procedure as with **19**–**22** and **28**–**30** to give **10**: yield: 43% (for three steps), white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (s, 1H), 7.44 (s, 1H), 5.95 (dd, J = 2.0 Hz, 3.6 Hz, 1H), 5.77 (m, 1H), 4.62 (dd, J = 0.8 Hz, 5.6 Hz, 1H), 4.34 (dd, J = 2.0 Hz, 4.0 Hz, 2H), 4.12 (dd, J = 4.8 Hz, 5.6 Hz, 1H), 2.58 (s, 3H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 151.2, 151.0, 140.5, 140.4, 139.1, 137.6, 123.4, 106.7, 78.9, 72.5, 65.4, 58.6, 15.2. Anal. Calcd for $C_{13}H_{16}N_4O_3{\cdot}0.1\ H_2O$: C, 56.15; H, 5.87; N, 20.15. Found: C, 55.91; H, 5.91; N, 19.85. HRMS calcd for $C_{13}H_{17}N_4O_3$ $[M+H]^+$, 277.1301, found 277.1292.

3.2. X-ray data for compounds 8a, 8b, and 13

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre with the following deposition numbers CCDC 1063211 (**13**), 1063212 (**8a**), and 1063213 (**8b**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.

3.3. Antiviral assays

These assays are presented in Ref. 14.

3.4. *S*-Adenosylhomocysteine (AdoHcy) hydrolase assay

This assay is described in Ref. 14.

Acknowledgements

We are grateful to the Molette Fund and Auburn University for support and to Gloria Kozamin of Microbiotix, Inc. Worcester, MA for the AdoHcy hydrolase assays. We are also indebted to the NIAID in vitro assay team for the viral data presented herein.[5]

References and notes

1. Campian, M.; Putala, M.; Sebesta, R. *Curr. Org. Chem.* **2014**, *18*, 2808.
2. Curran, A.; Ribera, E. *Expert Opin. Drug Saf.* **2011**, *10*, 389.
3. Wang, J.; Rawal, R. K.; Chu, C. K. *Med. Chem. Nucleic Acids* **2011**, 1.
4. Cooperwood, J. S.; Gumina, G.; Boudinot, G.; Chu, C. K. Nucleoside and Nucleotide Prodrugs. In *Recent Advances in Nucleosides: Chemistry and Chemotherapy*; Chu, C. K., Ed.; Elsevier Science B.V: Amsterdam, 2002; pp 127–128.
5. For example, (a) Das, S. R.; Schneller, S. W. *Nucleosides Nucleotides Nucleic Acids* **2014**, *33*, 668; (b) Ye, W.; Schneller, S. W. *Bioorg. Med. Chem.* **2014**, *22*, 5315; (c) Chen, Q.; Liu, C.; Shulyak, T. S.; Schneller, S. W. *Tetrahedron* **2014**, *70*, 892; (d) Liu, C.; Chen, Q.; Yang, M.; Schneller, S. W. *Bioorg. Med. Chem.* **2013**, *21*, 359; (e) Liu, C.; Chen, Q.; Schneller, S. W. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5182; (f) Liu, C.; Chen, Q.; Schneller, S. W. *Tetrahedron Lett.* **2011**, *52*, 4931; (g) Chen, C.; Ye, W.; Liu, C.; Schneller, S. W. *Tetrahedron* **2012**, *68*, 3908.
6. De Clercq, E. *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, 1395.
7. De Clercq, E. *Nucleosides Nucleotides* **1998**, *17*, 625.
8. (a) Herdewijn, P.; Balzarini, J.; De Clercq, E.; Vanderhaeghe, H. *J. Med. Chem.* **1985**, *28*, 1385; (b) Borchardt, T.; Keller, T.; Patel-Thombre, U. *J. Biol. Chem.* **1984**, *259*, 4353; (c) De Clercq, E. *Antimicrob. Agents Chemother.* **1985**, *28*, 84.
9. Wolfe, S.; Borchardt, T. *J. Med. Chem.* **1991**, *34*, 1521.
10. (a) Montgomery, J.; Clayton, S.; Thomas, J.; Shannon, W.; Arnett, G.; Bodner, A.; Kion, I.; Cantoni, G.; Chiang, P. *J. Med. Chem.* **1982**, *25*, 626; (b) Tseng, C.; Marquez, V.; Fuller, R.; Goldstein, B.; Haines, D.; McPherson, H.; Parsons, J.; Shannon, W.; Arnett, G. *J. Med. Chem.* **1989**, *32*, 1442; (c) Bray, M.; Paragas, J. *Antiviral Res.* **2002**, *54*, 1; (d) Schneller, S. W.; Yang, M. *S*-Adenosylhomocysteine Hydrolase Inhibitors as a Source of Antifilovirus Agents. In *Antiviral Drug Discovery for Emerging Diseases and Bioterrorism Threats*; Terrence, P. F., Ed.; John Willey and Sons: New York, 2005; pp 139–152.
11. Chiang, K.; Richards, H.; Cantoni, L. *Mol. Pharmacol.* **1977**, *13*, 939.
12. (a) Yang, M.; Zhou, J.; Schneller, S. W. *Tetrahedron* **2006**, *62*, 1295; (b) Yang, M.; Zhou, J.; Schneller, S. W. *Tetrahedron Lett.* **2004**, *45*, 8981.
13. Obara, T.; Shuto, S.; Saiyo, Y.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1996**, *39*, 3847.
14. Chen, Q.; Liu, C.; Komazin, G.; Bowlin, T. L.; Schneller, S. W. *Bioorg. Med. Chem.* **2014**, *22*, 6961.
15. Ando, T.; Iwata, M.; Zulfiqar, F.; Miyamoto, T.; Nakanishi, M.; Kitade, Y. *Bioorg. Med. Chem.* **2008**, *16*, 3809.
16. (a) Yang, M.; Schneller, S. W.; Korba, B. *J. Med. Chem* **2005**, *48*, 5043; (b) Yang, M.; Schneller, S. W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 149.
17. Liu, M.; Luo, M.; Mozdziesz, D. E.; Lin, T.; Dutschman, G. E.; Gullen, E. A.; Cheng, Y.; Sartorelli, A. C. *Nucleosides Nucleotides Nucleic Acids* **2001**, *20*, 1975.
18. There was no activity by the target compounds for (host cell): Compounds **8a**, **8b** and **10** were inactive towards WNV (Vero 76), cowpox (HFF), vaccinia (HEL), rhinovirus (Hela Ohio-1), adenovirus (A-549), respiratory syncytial virus (Hela/MA-104), influenza A (H1N1) (MDCK), influenza A (H3N2) (MDCK), Venezuelan equine encephalitis virus (Vero), PIV (MA-104), and SARS corona (Vero E6);

Compounds **7a** and **b** were inactive when assayed against rift valley fever (Vero 76), dengue (Vero), West Nile (Vero 76), vaccinia (HEL), hepatitis C (Ava5), Venezuelan equine encephalitis virus (Vero), respiratory syncytial virus (Hela/MA104), herpes virus 1 and 2 (HEL), influenza A (H1N1) (MDCK), polio (LLC-MK_2 clone 7.1), SARS corona (Vero E6). Compounds **9a**, **9b**, and **9c** were inactive towards Rift Valley fever (Vero 76), Tacaribe (Vero 76), dengue (Vero), West Nile (Vero 76), vaccinia (HEL), hepatitis C (Ava5), Venezuelan equine encephalitis virus (Vero), and respiratory syncytial virus (Hela/MA-104). Target **9c** was also inactive versus herpes virus 1 and 2 (HEL), influenza A (H1N1) (MDCK), polio (LLC-MK_2 clone 7.1), SARS corona (Vero E6), cowpox (HFF), chikungunya (Vero 76), entero-71 (LLC-MK_2), cytomegalovirus (HEL), pinchinde (Vero), and human papilloma virus (HEK 293).

19. Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.