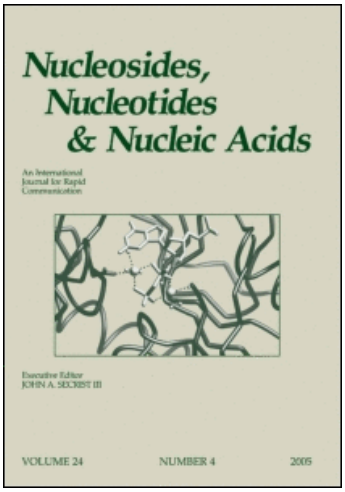

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Zulfiqar, Fazila , Kojima, Hiroharu , Nakanishi, Masayuki , Ando, Takayuki and Kitade, Yukio(2008) 'Synthesis of Carbocyclic 2-Substituted Adenine Nucleoside and Related Analogs', Nucleosides, Nucleotides and Nucleic Acids, 27: 10, 1153 — 1157
To link to this Article: DOI: 10.1080/15257770802341459
URL: http://dx.doi.org/10.1080/15257770802341459

Nucleosides, Nucleotides and Nucleic Acids, 27:1153–1157, 2008

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770802341459

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SYNTHESIS OF CARBOCYCLIC 2-SUBSTITUTED ADENINE NUCLEOSIDE AND RELATED ANALOGS

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□ *2-Iodonoraristeromycin, 2-iodoaristeromycin and related analogs were synthesized to investigate their inhibitory activities against human and Plasmodium falciparum S-adenosyl-L-homocysteine hydrolases.*

Keywords 2-Iodonoraristeromycin; 2-Iodoaristeromycin; *S*-adenosyl-L-homocysteine hydrolase 2-modified carbocyclic nucleoside; enzyme inhibitor

INTRODUCTION

S-Adenosyl-L-homocysteine hydrolase (SAHH) is the enzyme that catalyzes the breakdown of *S*-adenosylhomocysteine (SAH) to homocysteine and adenosine.[1] SAH is a strong inhibitor of numerous methyltransferases that transfer methyl groups from *S*-adenosylmethionine to nucleic acids, proteins, lipids and other small molecules.[2] Since methylation reactions are required for the proliferation of viruses and tumor cells, the accumulation of SAH leads to anti-virus/anti-tumor effects.[3,4]

We previously reported that the introduction of fluorine to the 2-position of noraristeromycin (**1**) and aristeromycin (**7**) increases the selective inhibition of *Plasmodium falciparum* SAHH (PfSAHH) in comparison with human SAHH (HsSAHH).[5,6] PfSAHH has additional space near the 2-position of the adenine-ring in the substrate binding pocket compared

Received 10 March 2008; accepted 26 June 2008.
This research was in part supported by Grants-in-Aid for Scientific Research on Priority Area No. 16017239 (to Y. K) and Japan Society for the Promination of Science No P-02184 (to Z. F).
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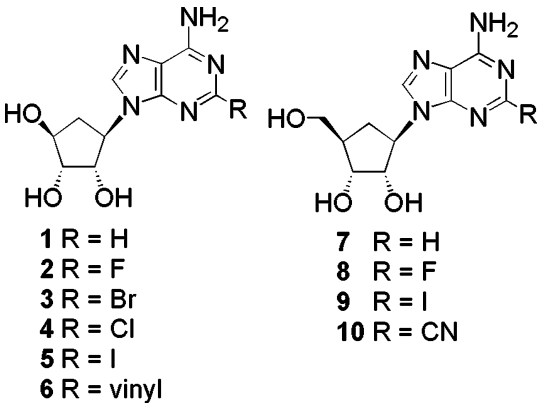
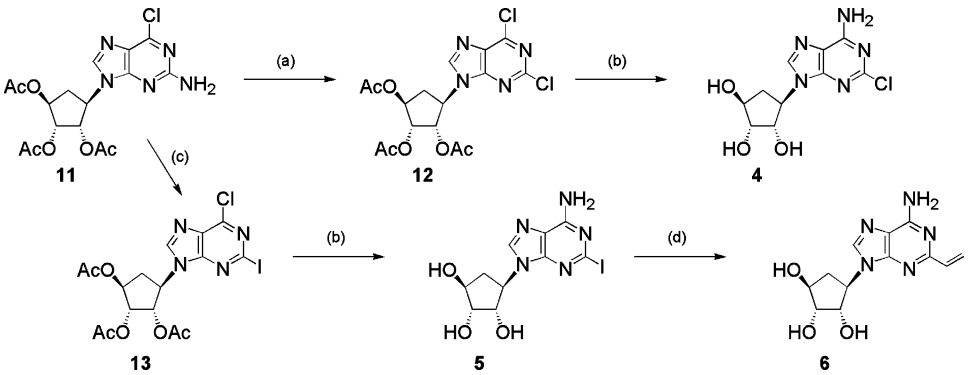


FIGURE 1 Structure of carbocyclic 2-substituted adenine nucleosides.

with HsSAHH.[7] Mutagenic analysis of the amino acid residue forming the additional space confirmed that selective inhibition is due to a difference in only one amino acid residue.[8] In fact, 2-bromonoraristeromycin[9] showed less inhibitory activity against both SAHHs. To confirm the size dependence of 2-substituente against both SAHH, we designed and synthesized 2-iodonoraristeromycin, 2-iodoaristeromaycin, and their related vinyl- and cyano-derivatives (Figure 1).

RESULTS AND DISCUSSION

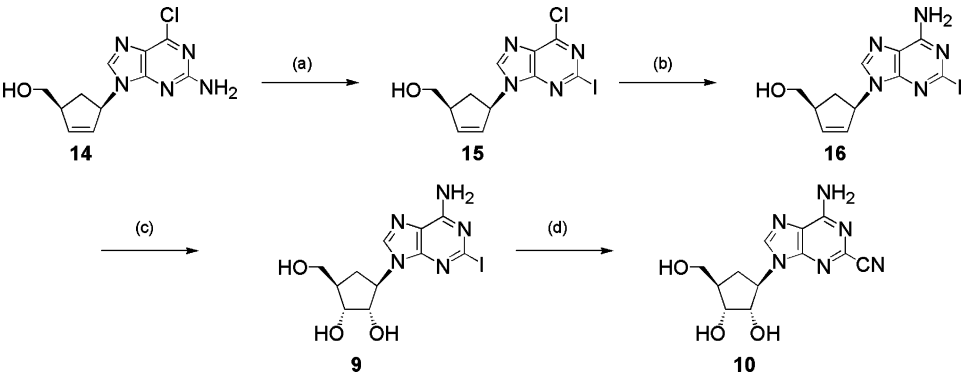
We selected compound **11**[9] as a starting material, which was previously synthesized from the coupling product of 2-amino-6-chloropurine and a cyclopenten derivative. Although 2-chloronoraristeromycin (**4**) has been synthesized by Siddiq et al.,[10] we used a different synthetic pathway choosing the common starting compound **11** for systematic synthesis of 2-chloro, 2-iodo-, and 2-vinylnoraristeromycine (Scheme 1). The 2-amino



SCHEME 1 Reagents and conditions: (a) isoamyl nitrite, CCl_4, 80°C, 1 hour, 48%; (b) NH_3/MeOH (28%, w/w) 60°C in sealed tube, 4 hours, 60% (for **4**) and 68% (for **5**); (c) isoamyl nitrite, CH_2I_2, CH_3CN, reflux, 3 hours, 68%; (d) tributyl(vinyl)tin, bis(acetonitrile)palladium (II), DMF, 80°C, 1 hour, 56%.

group of **11** was converted to a chloro group by treatment with isoamyl nitrite and CCl_4[11] at 80°C to give **12** in 68% yield. Subsequent deacetylation and selective amidation of **12** afforded 2-chloronoraristeromycin (**4**) in 60% yield. Similarly, treatment of **11** with isoamyl nitrite and CH_2I_2[12] afforded the 2-iodo compound **13** (68%) and thereafter deacetylation and selective amidation yielded the desired 2-iodonoraristeromycin (**5**) in 68% yield. Further substitution of the iodo group by using tributyl(vinyl)tin and bis(acetonitrile)palladium(II) afforded 2-vinylnoraristeromycin (**6**) in 56% yield.

In the meantime, the 2-amino group of compound **14**[13] was converted to an iodo group as described. Selective amination of **15** produced compound **16** in 82% yield, and then osmium oxidation[14] with *N*-methylmorpholine-*N*-oxide afforded the desired 2-iodoaristeromycin (**9**) and 2′ and 3′ epimer of **9** (62% and 32%). Further substitution of the iodo group by a cyano group was performed by using Bu_3SnCN and $(Ph_3P)_4Pd$ to give 2-cyanoaristeromycin (**10**) in 76% yield (Scheme 2).



SCHEME 2 Reagents and conditions: (a) isopentyl nitrite, CH_2I_2, CH_3CN, 85°C, 12 hours, 74%; (b) NH_3/MeOH (28%, w/w) 55°C, 24 hours, 82%; (c) OsO_4, *N*-methylmorphorine-*N*-oxide, THF-H_2O (10–1), room temperature, 3 hours, 62%; (d) Bu_3SnCN, $(Ph_3P)_4Pd$, 120°C, 24 hours, 76%.

The inhibitory activities against HsSAHH and PfSAHH[15] of the typical compounds are summarized in Table 1. Clearly, 2-chloronoraristeromycin (**4**), 2-iodonoraristeromycin (**5**), 2-iodoaristeromycin (**9**), and 2-cyanoaristeromycin (**10**) showed complete loss of inhibitory activity compared with the corresponding carbocyclic adenine nucleosides. The introduction of a large halogen atom to the 2-position did not produce effective inhibition of PfSAHH. The results indicate that the size of the fluorine atom (van der Waals radius; 1.47 Å) is a suitable fit for the binding site of PfSAHH to produce selective inhibition. Thus, in the development of a potent and selective inhibitor, the H at the 2-position was too small to selectively inhibit PfSAHH, and Br, Cl and I and the other molecules were too large.

TABLE 1 Inhibitory activities against HsSAHH and PfSAHH

Compound	HsSAHH IC_{50}, μM	PfSAHH IC_{50}, μM	Selective index[a]	2-position X
1	1.1[b]	3.1[b]	0.35[b]	H
2	63[b]	13[b]	4.8[b]	F
3	nd	>500	—	Br
4	nd	nd	—	Cl
5	nd	nd	—	I
6	nd	nd	—	vinyl
7	47.2[b]	1.98[b]	0.085[b]	H
8	90.7[b]	4.51[b]	24[b]	F
9	nd	nd	—	I
10	nd	nd	—	CN

[a]Selective index: mean of IC_{50} value for HsSAH/mean of IC_{50} value for PfSAHH.
[b]See the literature.[5,6]
nd: no inhibitory activity showed at 1000 μM.

In conclusion, we synthesized various carbocyclic 2-modified adenine nucleosides and confirmed the fitness of a halogen atom and cyano group at the 2-position in the additional space of PfSAHH. Further multi-modifications of carbocyclic adenine nucleoside are now under investigation and additional potent analogs will be reported in due course.

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16. Selective physical datas : For **5** ^{1}H-NMR (DMSO-d_6, 400MHz) δ 8.12 (1H, s, H-8), 7.63 (2H, s, NH_2), 5.20 (1H, d, J = 4.4 Hz, OH-4′), 5.03 (1H, d, J = 6.8 Hz, OH-2′), 4.90 (1H, d, J = 4.0 Hz, OH-3′), 4.62 (1H, q, J = 8.4 Hz, H-1′), 4.41 (1H, q, J = 6.4 Hz, H-2′), 3.89 (1H, t, J = 2.0 Hz, H-4′), 3.74 (1H, s, H-3′), 2.59 (1H, m, H-5′β), 1.68 (1H, m, H-5′α); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 155.91, 150.18, 139.52, 120.49, 118.86, 76.65, 75.78, 73.60, 57.98, 48.63; HREIMS Calcd for $C_{10}H_{12}IN_5O_3$ 376.9985 Found 376.9981. For **6** ^{1}H-NMR (DMSO-d_6, 400MHz) δ 8.15 (1H, s, H-8), 7.21 (2H, s, NH_2), 6.58 (1H, q, J = 10.8 Hz, vinyl), 6.33 (1H, dd, J = 2.0 and 17.0 Hz, vinyl), 5.51 (1H, dd, J = 2.0 and 10.8 Hz, vinyl), 5.45 (1H, d, J = 4.8 Hz, OH-4′), 5.04 (1H, d, J = 6.4 Hz, OH-2′), 4.90 (1H, d, J = 3.2 Hz, OH-3′), 4.69 (1H, q, J = 8.4 Hz, H-1′), 4.50 (1H, q, J = 6.0 Hz, H-2′), 3.89 (1H, s, H-4′), 3.76 (1H, s, H-3′), 2.62 (1H, m, H-5′β), 1.78 (1H, m, H-5′α); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 157.35, 155.68, 149.95, 140.39, 137.45, 120.73, 118.45, 76.79, 75.60, 73.71, 58.24, 36.80; HREIMS calud for $C_{12}H_{15}N_5O_3$ 277.1175 found 277.1170.