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Synthesis of 5′-methylenearisteromycin and its 2-fluoro derivative with potent antimalarial activity due to inhibition of the parasite *S*-adenosylhomocysteine hydrolase[1]

Chieko Takagi,[a] Makoto Sukeda,[a] Hye-Sook Kim,[b] Yusuke Wataya,[b] Saori Yabe,[c] Yukio Kitade,[c] Akira Matsuda[a] and Satoshi Shuto*[a]

[a] *Graduate School of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo, 060-0812, Japan. E-mail: shu@pharm.hokudai.ac.jp; Fax: +81-11-706-4980; Tel: +81-11-706-3229*

[b] *Faculty of Pharmaceutical Sciences, Okayama University, Tsushima, Okayama, 700-8530, Japan*

[c] *Faculty of Engineering, Gifu University, Yanagido 1-1, Gifu, 501-1193, Japan*

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5′-Methylenearisteromycin (**5**) and its 2-fluoro derivative **6**, which were designed as antimalarial agents because of their AdoHcy hydrolase inhibition, were synthesized from D-ribose, using a stereoselective intramolecular radical cyclization as the key step to construct the carbocyclic structure. These compounds were evaluated as AdoHcy hydrolase inhibitors with the recombinant human and malarial parasite enzymes. Although **5** and **6** were both potent inhibitors of the malarial parasite AdoHcy hydrolase, the 2-fluoro derivative **6** proved to be superior due to its lower inhibitory effect on the human enzyme. In addition, **6** was identified as a potent antimalarial agent using an *in vitro* assay system with *Plasmodium falciparum*.

Introduction

The spreading resistance of *Plasmodium falciparum* (*P. falciparum*) to currently available drugs such as chloroquine, underscores the urgent need for the development of new, more effective antimalarial agents.[2] *S*-Adenosyl-L-homocysteine (AdoHcy) hydrolase, which is responsible for the hydrolysis of AdoHcy to adenosine (Ado) and L-homocysteine (Hcy),[3] has been recognized as a new target for antimalarial agents.[4] Since the parasite has its own AdoHcy hydrolase,[4d] a drug, which inhibits this hydrolase to increase the parasite AdoHcy level, would be highly useful in the treatment of malaria. AdoHcy is a potent feedback inhibitor of cellular transmethylation; consequently, inhibition of AdoHcy hydrolase increases the levels of AdoHcy thereby preventing transmethylation reactions using *S*-adenosyl-L-methionine (AdoMet) as the methyl donor, *e.g.*, mRNA methylations, which are essential for the proliferation of the parasite.

Naturally occurring carbocyclic adenine nucleosides (Fig. 1) such as aristeromycin (**1**) and neplanocin A (**2**) are known to inhibit AdoHcy hydrolase.[3] In recent years, we have been engaged in the synthetic study of novel carbocyclic adenine nucleosides in the hope of finding potent inhibitors to the enzyme,[5,6] and we have shown that these AdoHcy hydrolase inhibitors actually exhibit antimalarial activity both *in vitro* and *in vivo*.[4e,6]

For clinical use, such chemotherapeutic drugs should be selectively toxic to eliminate the target pathogens without untoward side effects. Unfortunately, the enzyme AdoHcy hydrolase is essential not only for the proliferation of the parasite, but also for the proliferation of mammalian cells.[3] Accordingly, the most desirable antimalarial drugs are those which inhibit the malarial parasite AdoHcy hydrolase without affecting the enzyme of the human cells.

A recent study suggested that introduction of a fluorine atom at the 2-position of a carbocyclic adenine nucleoside derivative might improve the selectivity index between human and malarial parasite AdoHcy hydrolase inhibition.[6] Thus, the IC_{50} values of the dehydroxymethylated 2-fluoroaristeromycin derivative **4** against the human and the *P. falciparum* AdoHcy hydrolases were 63 and 13 μM, respectively (selectivity index (human/*P. falciparum*) = 4.8), while its non-fluoro derivative **3** showed a lower IC_{50} value for the human enzyme compared with that for the parasite enzyme (human, IC_{50} = 1.1 μM; *P. falciparum*, IC_{50} = 3.1 μM; selectivity index = 0.35).[6b]

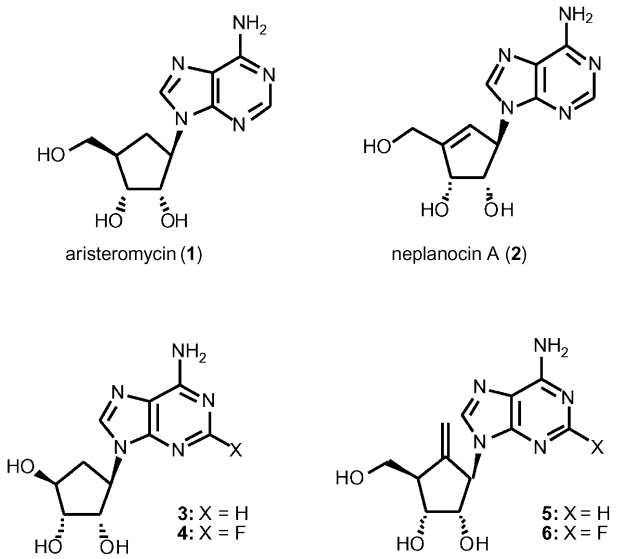

Fig. 1 Carbocyclic adenine nucleosides as AdoHcy hydrolase inhibitors.

On the other hand, it has been recognized that adenine nucleoside derivatives can be rapidly deaminated by adenosine deaminase to a chemotherapeutically inactive inosine congener. Introduction of a halogen atom at the 2-position of adenine nucleosides allowed resistance to the adenosine deaminase.[5c,7] From this metabolic viewpoint, the 2-fluoro-modification of AdoHcy hydrolase inhibitors could bring about an improvement of therapeutic potency.

Prisbe and co-workers synthesized a series of 5′-substituted aristeromycin derivatives in racemic forms, and found that (±)-5′-methylenearisteromycin [(±)-**5**] was an inhibitor of rabbit erythrocyte AdoHcy hydrolase.[8] We were interested in the

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enantioselective synthesis of the eutomer (bioactive enantiomer) **5**, the stereochemistry of which should be the same as that of naturally occurring aristeromycin (**1**), in order to clarify its inhibitory effect on both the human and the *P. falciparum* AdoHcy hydrolases as well as to confirm its antimalarial potency. The 2-fluoro derivative **6** might be superior to the eutomer **5** as an antimalarial agent, particularly in the selectivity index and the metabolic stability for the reasons mentioned above.

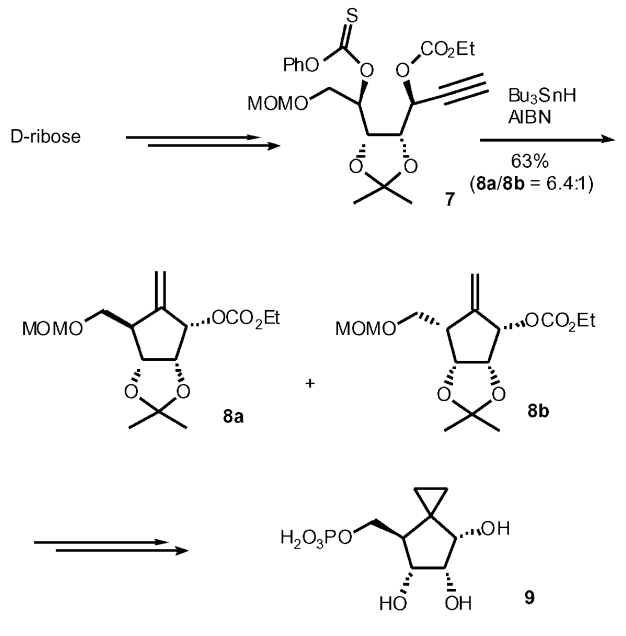
In this report, we describe the enantioselective synthesis and biological effect of 5′-methylenearisteromycin (**5**) and its 2-fluoro derivative **6**.

Results and discussion

Synthetic plan

In the synthesis of carbocyclic nucleosides, construction of the carbocycles (particularly in an optically active form) is often troublesome. We thought that the enantioselective construction of the desired exomethylenecarbocyclic moiety would be accomplished using a radical reaction as the key step.

Gaudino and Wilcox synthesized the carbocyclic analogue **9** of D-ribose 5-phosphate, using a key radical reaction of the heptyne derivative **7**, prepared from D-ribose, to give a mixture of the *trans*-product **8a** and the *cis*-product **8b** in a ratio of 6.4 : 1 in 63% yield (Scheme 1).[9] The major product **8a** preserves the proper functional groups with the desired stereochemistry at the 2′, 3′, and 4′-positions for our target 5′-exomethylenecarbocyclic nucleosides **5** and **6**. Therefore, we decided to employ this kind of radical reaction in this study. Based on the following consideration, we expected that the stereoselectivity might be improved. Stereoselectivity of the radical 5-*exo*-cyclizations has been explained by a chair-like transition state model (Beckwith–Houk model).[10] Using this model, the radical reaction of **7** could be interpreted, as shown in Fig. 2, where the cyclization could occur *via* the two chair-like transition states **Ia** and **Ib**. Due to steric repulsion between the isopropylideneoxy and the adjacent methoxymethyloxymethyl moieties in **Ib**, **Ia** seemed to be more advantageous than **Ib**, and accordingly the *trans*-cyclized product **8a** might be formed as the major product. We speculated that if the steric repulsion in the transition state **Ib** was greater, the reaction might produce the desired *trans*-product with higher selectivity. Thus, we designed the 5-*O*-monomethoxytrityl (MMTr) -2,3-*O*-*p*-methoxybenzylidene–protected substrate **10** (Fig. 3), the *p*-methoxyphenyl (PMP)



Scheme 1

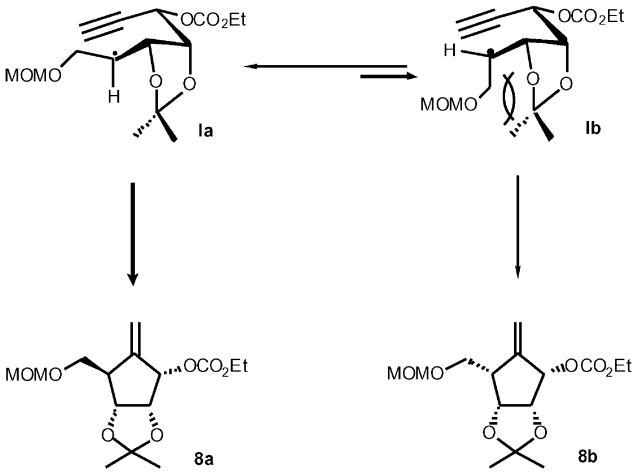


Fig. 2 Conceivable radical intermediates **1a** and **1b** derived from **7**.

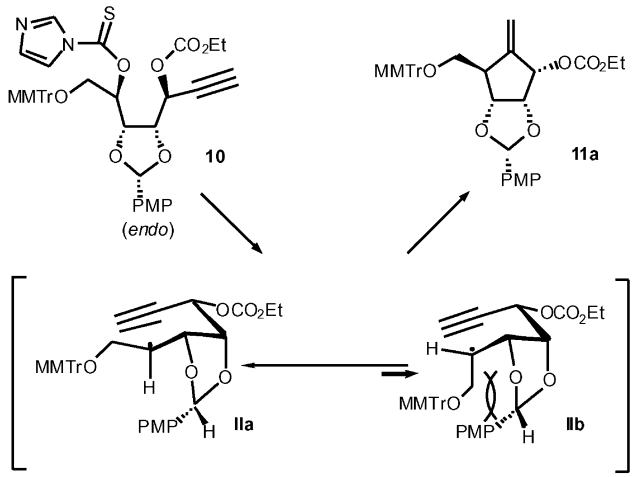
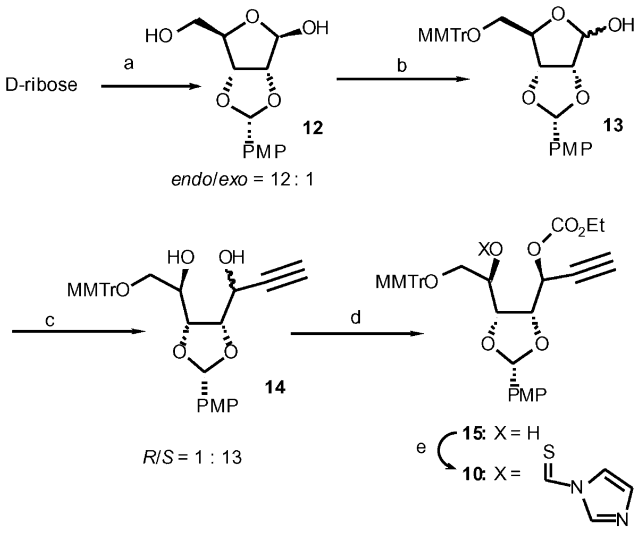


Fig. 3 Expected radical cyclization pathway selectively forming **11a**.

group of which should be in the *endo* orientation. We expected that the transition state **IIa** could be even more favored, because the *endo*-oriented PMP group would exert steric repulsion in the other transition state **IIb**, to give the desired *trans*-cyclization product **11a** selectively *via* **IIa**. From the *trans*-cyclization product **11a**, the target 5-methylenecarbocyclic nucleosides **5** and **6** would be synthesized *via* a stereo-inverted introduction of adenine or 2-fluoroadenine at the allylic 1-position. In addition, the MMTr and *p*-methoxybenzylidene groups were preferred due to their easy and simultaneous removal under mild acidic conditions, since the target compounds **5** and **6** might be unstable because of the constrained exomethylene-carbocyclic ring system.

Synthesis of the target compounds

The synthesis of the radical reaction substrate **10** is summarized in Scheme 2. We found that the desired *endo*-2,3-*O*-*p*-methoxybenzylidene-β-D-ribose (**12**) was obtained as the major product (*endo*/*exo* = 12 : 1), when D-ribose was treated with *p*-MeOPhCH(OMe)$_2$–pyridinium *p*-toluenesulfonate (PPTS) in DMF at 0 °C. The *endo*-stereochemistry of the benzylidene moiety was determined by an NOE (2.2%) observed between the 3-proton and the benzylidine-methyne proton. Since the *endo*/*exo*-mixture could not be separated at this stage, after protection of the 5-hydroxyl of **12** with MMTr group, nucleophilic addition of acetylide to the resulting **13** was examined. When **13** was treated with CH≡CMgBr in THF at −78 °C, the corresponding addition products **14** was obtained in 96% yield. At this point, the minor *exo*-benzylidene isomer was successfully removed by silica gel column chromatography. The Grignard reaction selectively



Scheme 2 Reagents: (a) *p*-MeOPhCH(OMe)$_2$, PPTS, DMF, 60%; (b) MMTrCl, py, 98%; (c) CH≡CMgBr, THF, 96%, (d) ClCO$_2$Et, py, CH$_2$Cl$_2$, 86%; (e) TCDI, CH$_2$Cl$_2$, 87%.

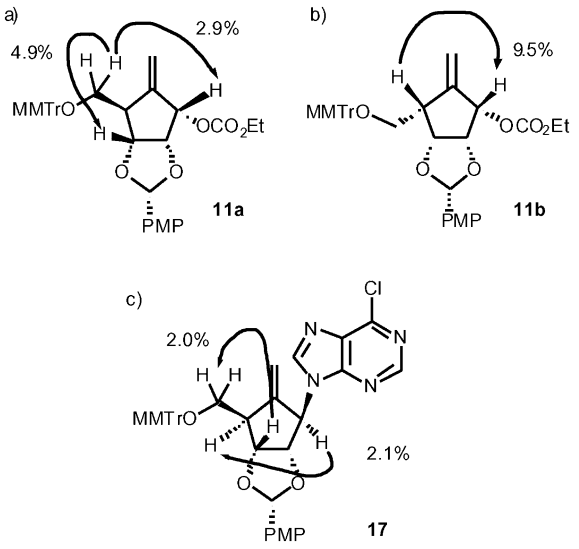


Fig. 4 NOE experimental results of (a) **11a**; (b) **11b**; and (c) **17**.

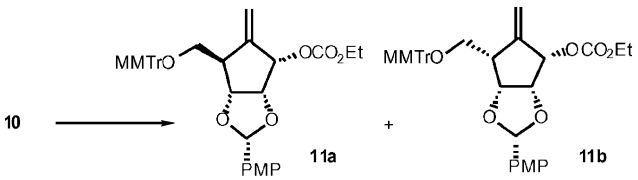
gave the desired *S*-product (*R*/*S* = 1 : 13),[8] the stereochemistry of which was determined after radical cyclization, as described below. The hydroxyl at the propargyl position of **14** (*R*/*S*-mixture) was selectively protected by an ethoxycarbonyl group to give **15**, which was obtained in a diastereomerically pure form after silica gel column chromatography. Treatment of **15** with *N*,*N*′-thiocarbonyldiimidazole (TCDI) in CH$_2$Cl$_2$ produced the radical reaction substrate **10**.

The radical reaction of **10** was investigated with Bu$_3$SnH (1.1 eq.) as the reductant under various conditions, and the results are summarized in Table 1. The reaction was first carried out with AIBN as a radical initiator in benzene under reflux to give a mixture of the desired *trans*-product **11a** and the *cis*-product **11b** in 63% yield in a ratio of 3.0 : 1 (entry 1). The stereochemistry of the products **11a** and **11b** was confirmed by NOE experiments, shown in Fig. 4a and 4b. The reaction was next examined at lower temperature using V-70L[11] as an initiator. Although the radical reaction did not occur at 0 °C (entry 2), the radical cyclization proceeded efficiently at rt (entry 3). However, the yield and the ratio did not improve, compared with those at higher temperature (entry 1). The effect of Lewis acids as an additive on the reaction was next investigated, since Lewis acids sometimes improve stereoselectivity in radical reactions.[12] Methylaluminum bis(2,4,6-tri-*t*-butylphenoxide) (MAT) completely inhibited the radical reaction (entry 4), and MgBr$_2$ did not affect the reaction in terms of either yield or *cis*/*trans*-ratio (entry 5). However, when the radical reaction with V-70L was performed in the presence of Me$_3$Al at rt, the stereoselectivity was significantly improved, but an unknown product was formed and the yield was not sufficient (entry 6). The stereoselectivity of the reaction with Me$_3$Al as the additive was decreased at higher temperature (entry 7).

Although the stereoselectivity of the radical cyclization was not very high, the procedure efficiently provided the key intermediate **11a** in six reaction steps from D-ribose. Thus, with **11a** in hand, we next tried to synthesize the target carbocyclic nucleosides **5** and **6** (Schemes 3 and 4).

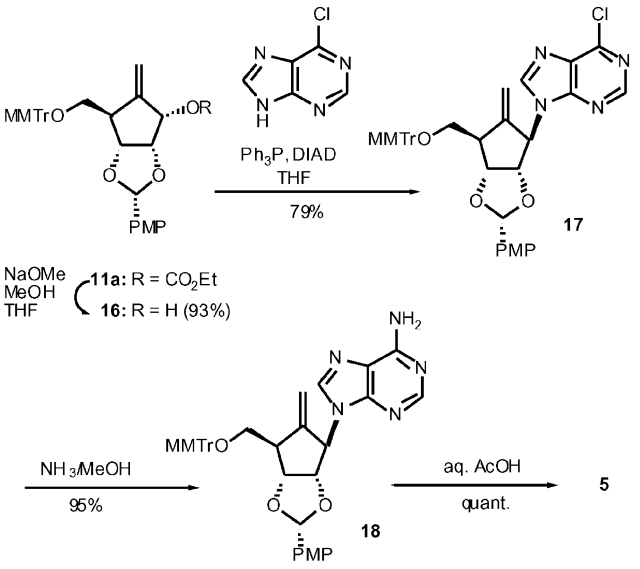
After removal of the ethoxycarbonyl group of **11a**, introduction of a nucleobase to the resulting **16** was examined under Mitsunobu reaction conditions (Scheme 3). When **16** and 6-chloropurine was treated with diisopropyl azodicarboxylate (DIAD) and Ph$_3$P in DMF at 0 °C and then at rt, the condensation occurred regio- and stereoselectively to afford the desired carbocyclic nucleosidic product **17** with β-stereochemistry in 79% yield. An NOE observed between the H-1′ and H-4′ (Fig. 4c) showed the β-stereochemistry of **17**, and the N9-regiochemistry was confirmed by UV spectral data.[13] After treatment of **17** with NH$_3$–MeOH to produce the corresponding adenine derivative **18**, the protecting groups were simultaneously removed with

Table 1 Radical cyclization of **10**[a]

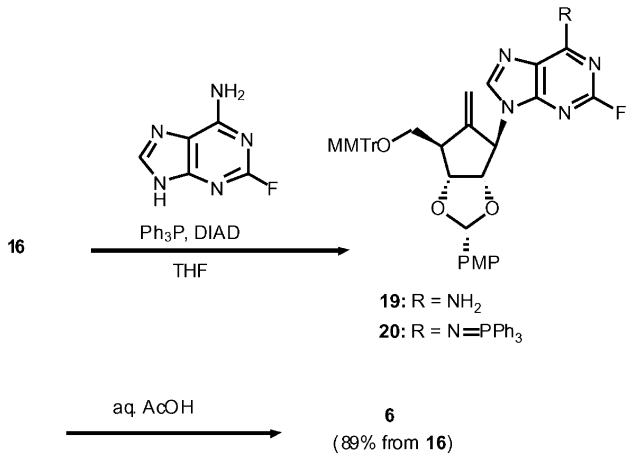


Entry	Initiator	Additive	Solvent	Temperature	Yield (%)	**11a** : **11b**
1	AIBN	—	Benzene	80 °C	63	3.0 : 1
2	V-70L	—	CH$_2$Cl$_2$	0 °C	0	—
3	V-70L	—	CH$_2$Cl$_2$	Rt	60	3.0 : 1
4	V-70L	MAT	CH$_2$Cl$_2$	Rt	0	—
5	V-70L	MgBr$_2$	CH$_2$Cl$_2$	Rt	66	2.9 : 1
6	V-70L	Me$_3$Al	CH$_2$Cl$_2$	Rt	40	1.0 : 0[b]
7	AIBN	Me$_3$Al	Benzene	80 °C	40	1.6 : 1

[a] Reaction was carried out with Bu$_3$SnH (1.1 eq.) and an initiator (1.0 eq.) in the absence or the presence of an additive (2.0 eq.). [b] An unknown product was obtained in about 40% yield.



Scheme 3



Scheme 4

aqueous AcOH to furnish the desired 5′-methylenearisteromycin (**5**), as shown in Scheme 3.

The 2-fluoro derivative **6** was similarly synthesized from **16** (Scheme 4). When the Mitsunobu reaction of **16** was performed with 2-fluoroadenine, instead of 6-chloropurine, the desired carbocyclic nucleoside **19** was obtained along with its derivative **20**, which was formed by the condensation of Ph_3P at the N^6-position of **19**. However, the N=P bond was found to be easily hydrolyzed under mild acidic conditions. Thus, after the Mitsunobu reaction of **16** and 2-fluoroadenine, the resulting mixture of **19** and **20**, without purification, was treated with aqueous AcOH to afford the target 2-fluoro-5′-methylenearisteromycin (**6**) in high yield.

Inhibitory effect on human and *P. falciparum* AdoHcy hydrolases

In order to identify effective antimalarial agents, the activity of which is due to the AdoHcy hydrolase inhibition, it is essential to examine the inhibitory potency of the compounds with both the malarial parasite and the human enzymes. Consequently, we expressed the recombinant *P. falciparum* and also the human AdoHcy hydrolases in *E. coli* and developed a method for the evaluation of the inhibitors using these enzymes.[14] Thus, the inhibitory effect of the newly synthesized carbocyclic nucleosides **5** and **6** on the *P. falciparum* and human AdoHcy hydrolases were evaluated by this method, and the results are shown in Table 2.

5′-methylenearisteromycin (**5**) significantly but non-selectively inhibited both the parasite and the human AdoHcy hydrolases with IC_{50} values of 0.61 and 0.52 μM, respectively, and with a selectivity index of 0.85. Thus, chiral 5′-methylenearisteromycin (**5**) proved to be a potent AdoHcy hydrolase inhibitor in this evaluation system, as suggested by the previous results of the racemic compound with the rabbit enzyme,[8] even though the selectivity index was low.

Table 2 Inhibitory effect of 5′-exomethylenecarbocyclic nucleosides **5** and **6** on *P. falciparum* and human AdoHcy hydrolases

	AdoHcy hydrolase, IC_{50}/μM		
Compound	*P. falciparum*	Human	Selectivity index[a]
5	0.61	0.52	0.85
6	2.1	15.7	7.5
4[b]	13	63	4.8

[a] IC_{50} (human)/IC_{50} (*P. falciparum*). [b] Data were taken from ref. 6*b*

On the other hand, the 2-fluoro derivative **6** effectively inhibited the parasite enzyme with an IC_{50} value of 2.1 μM and only weakly inhibited the human enzyme (IC_{50} = 15.7 μM), where the selectivity index improved to 7.5. These results showed that introduction of a fluorine atom at the 2-position of **5** improved the efficacy, particularly, in regard to the selectivity index, as we had expected.[15]

Antimalarial effect

The antimalarial activity of **5** and **6** against *P. falciparum* (FCR-3 strain) was evaluated *in vitro*, and the inhibitory effect of these compounds on cell proliferation was also evaluated with mouse FM3A cells in the growing phase.[16] These results are summarized in Table 3. While 5′-methylenearisteromycin (**5**) was clearly cytotoxic to FM3A cells with an IC_{50} value of 0.31 μM, it had only a weak antimalarial effect (IC_{50} = 16 μM). The 2-fluoro derivative **6** showed significant antimalarial activity with an IC_{50} value of 0.40 μM, and was demonstrated to exert lower cytotoxicity against proliferation of FM3A cells (IC_{50} = 1.5 μM) compared with **5**. The selectivity indexes of **5** and **6** were 0.019 and 3.8, respectively.

Therefore, 2-fluoro-5′-methylenearisteromycin (**6**) was shown to be an effective antimalarial agent, and more potent than the previously reported dehydroxymethylated 2-fluoroaristeromycin derivative **4**.[6b] Although the inhibitory effect of the 2-fluoro compound **6** on the parasite AdoHcy hydrolase was weaker than that of the non-fluoro derivative **5**, its antimalarial activity was superior to that of **5**. A possible reason for the increased efficacy of **6** might be that the compound is resistant to Ado deaminase, keeping its concentration at a relatively higher level in the assay system compared with the non-fluoro derivative **5**.

In summary, 2-fluoro-5′-methylenearisteromycin (**6**), synthesized from D-ribose, with the key step being a stereoselective intramolecular radical cyclization to construct the carbocyclic structure, was identified as a potent antimalarial agent, which selectively inhibits the malaria parasite AdoHcy hydrolase. Therefore, compound **6** appears to be a promising drug candidate for the treatment of malaria parasite infections.

Table 3 *In vitro* antimalarial activity of 5′-exomethylenecarbocyclic nucleosides **5** and **6**

	IC_{50}/μM		
Compound	*P. falciparum*	FM3A (growing)	Selectivity index[a]
5	16	0.31	0.019
6	0.4	1.5	3.8
4[b]	7.4	7.2	0.97

[a] IC_{50} (FM3A)/IC_{50} (*P. falciparum*). [b] Data were taken from ref. 6*b*

Experimental

General methods

NMR spectra were recorded at 400 (^{1}H) and 100 (^{13}C) MHz, and are reported in ppm downfield from Me_4Si. The ^{1}H NMR assignments indicated were in agreement with COSY spectra. Mass spectra were obtained by the fast atom bombardment (FAB) method. Thin-layer chromatography was performed on Merck coated plate $60F_{254}$. Silica gel chromatography was performed with Merck silica gel 5715. Reactions were carried out under an argon atmosphere.

2,3-*O*-(*p*-Methoxybenzylidene)-β-D-ribofuranose (12)

A mixture of D-ribose (750 mg, 5.0 mmol), *p*-MePhCH(OMe)$_2$ (3.4 mL, 20 mmol), and PPTS (6.3 g, 25 mmol) in DMF (50 mL) was stirred at 0 °C for 24 h. After neutralization with $NaHCO_3$, the resulting mixture was filtered through Celite, and the filtrate was evaporated. The residue was purified by column chromatography (silica gel, 30–50% AcOEt in hexane) to give **12** (800 mg, 60%) as a white solid. The *endo*/*exo* ratio was 12 : 1 based on the ^{1}H NMR spectrum; δ_H (400 MHz, $CDCl_3$, Me_4Si) for *endo*-isomer 7.43 (d, 2 H, *J* 8.7 Hz), 6.91 (d, 2 H, *J* 8.7 Hz), 5.74 (s, 1 H), 5.58 (d, 1 H, *J* 6.8 Hz), 4.92 (d, 1 H, *J* 6.2 Hz), 4.68 (d, 1 H, *J* 6.0 Hz), 4.60 (m, 1 H), 4.01 (d, 1 H, *J* 7.0 Hz), 3.85–3.76 (m, 5 H), 3.06 (dd, 1 H, *J* 2.8, 7.3 Hz); NOE irradiate H-3/observed *p*-MeOPhC*H* (2.2%); for *exo*-isomer δ 7.39 (d, 2 H, *J* 8.5 Hz), 6.91 (d, 2 H, *J* 8.7 Hz), 5.93 (s, 1 H, CH_3OPhCH), 5.54 (d, 1 H, *J* 7.0 Hz), 5.02 (d, 1 H, *J* 5.6 Hz), 4.71 (d, 1 H, *J* 5.7 Hz), 4.53 (m, 1 H), 4.11 (d, 1 H, *J* 7.0 Hz), 3.85–3.76 (m, 5 H), 2.93 (dd, 1 H, *J* 4.5, 5.7 Hz); *m*/*z* (FAB) 269.1014 (MH^+. $C_{13}H_{17}O_6$ requires 269.1025).

2,3-*O*-(*p*-Methoxybenzylidenedioxy)-5-*O*-[(4-methoxyphenyl)diphenylmethyl]-D-ribofuranose (13)

A mixture of **12** (537 mg 2.0 mmol), MMTrCl (695 mg, 2.25 mmol) in pyridine (17 mL) was stirred at rt for 12 h. After addition of MeOH, the resulting mixture was evaporated, and the residue was partitioned between AcOEt and aqueous HCl (1 N). The organic layer was washed with H_2O and then with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, 25% AcOEt in hexane) to give **13** (1.07 g, 98%, α/β = 4.5 : 1) as a white foam; δ_H (400 MHz, $CDCl_3$, Me_4Si) for β-anomer (*endo*/*exo* = 7.8 : 1) 7.47–7.24 (m, 14 H), 6.94–6.84 (m, 4 H), 5.91 (s, 0.11 H), 5.77 (s, 0.89 H), 5.48 (d, 0.89 H, *J* 9.6 Hz), 5.44 (d, 0.11 H, *J* 9.2 Hz), 5.05 (d, 0.11 H, *J* 6.2 Hz), 4.93 (d, 0.89 H, *J* 6.2 Hz), 4.82 (d, 1 H, *J* 6.2 Hz), 4.46 (m, 0.11 H), 4.53 (m, 0.89 H), 4.14 (d, 1 H, *J* 9.6 Hz), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.46 (dd, 1 H, *J* 3.4, 10.4 Hz), 3.37 (dd, 1 H, *J* 2.8, 7.3 Hz); for α-anomer (*endo*/*exo* = 12 : 1) 7.47–7.24 (m, 14 H), 6.94–6.84 (m, 4 H), 6.02 (s, 0.08 H), 5.88 (s, 0.92 H), 5.82 (dd, 1 H, *J* 4.5, 11.7 Hz), 4.86 (dd, 1 H, *J* 4.3, 6.6 Hz), 4.72 (d, 1 H, *J* 6.6 Hz), 4.40 (m, 1 H), 3.96 (d, 1 H, *J* 11.5 Hz), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.48 (dd, 1 H, *J* 2.8, 9.6 Hz), 3.06 (dd, 1 H, *J* 2.9, 9.8 Hz); *m*/*z* (FAB) 541.2245 (MH^+. $C_{33}H_{33}O_7$ 541.2227 requires 541.2227).

(4*S*,5*R*,6*R*)-3,6-Dihydroxy-4,5-(*p*-methoxybenzylidenedioxy)-7-[(4-methoxyphenyl)diphenylmethoxy]heptyne (14)

To a solution of **13** (13.5 g, 25 mmol) in THF (50 mL) was added CH≡CMgBr (0.5 M in THF, 200 mL, 100 mmol) slowly over 2 h at −78 °C, and the mixture was stirred at rt for 14 h. The resulting mixture was partitioned between AcOEt and aqueous saturated NH_4Cl, and the organic layer was washed with H_2O and then with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, 30–35% AcOEt in hexane) to give **14** (13.4 g, 96%) as a white foam. The *R*/*S* ratio was 1 : 13 based on the ^{1}H NMR spectrum; δ_H (400 MHz, $CDCl_3$, Me_4Si) 7.42–721 (m, 14 H), 690–6.80 (m, 4 H), 5.75 (s, 1 H), 4.83 (m, 0.07 H), 4.75 (m, 0.93 H), 4.43 (dd, 0.07 H, *J* 3.2, 7.2 Hz), 4.35 (dd, 0.93 H, *J* 6.2, 8.5 Hz), 4.21 (m, 2 H), 4.04 (m, 1 H, H-6), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.62 (d, 0.07 H, *J* 10.0), 3.51 (dd, 0.93 H, *J* 3.0, 10.0 Hz), 3.53 (dd, 0.07 H, *J* 6.0, 9.9 Hz), 3.32 (dd, 0.93 H, *J* 7.0, 9.8 Hz), 3.19 (d, 0.93 H, *J* 3.6 Hz), 2.92 (d, 0.07 H, *J* 4.9 Hz), 2.52 (d, 0.93 H, *J* 2.3 Hz), 3.10 (d, 0.07 H, *J* 2.3 Hz); *m*/*z* (FAB) 566.2309 (M^+. $C_{35}H_{34}O_7$ requires 566.2305).

(3*S*,4*R*,5*R*,6*R*)-3-Ethoxycarbonyloxy-6-hydroxy-7-[(4-methoxyphenyl)diphenylmethoxy]-4,5-(*p*-methoxybenzylidenedioxy)heptyne (15)

A mixture of **14** (566 mg, 1.0 mmol), pyridine (243 μL, 3.0 mmol), and $ClCO_2Et$ (143 μL, 1.5 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C for 2 h. After addition of MeOH, the resulting mixture was evaporated, and the residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$. The organic layer was washed with H_2O and then with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, 25% AcOEt in hexane) to give **15** (549 mg, 86%) as a white foam; δ_H (400 MHz, $CDCl_3$, Me_4Si) 7.46–7.20 (m, 14 H), 6.87–6.81 (m, 4 H), 5.81 (dd, 1 H, *J* 2.3, 3.6 Hz), 5.76 (s, 1 H), 4.52 (dd, 1 H, *J* 3.8, 6.8 Hz), 4.28–4.19 (m, 4 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.47 (dd, 1 H, *J* 2.7, 9.7 Hz), 3.38 (dd, 1 H, *J* 5.3, 9.6 Hz), 2.59 (d, 1 H, *J* 5.3 Hz), 2.57 (d, 1 H, *J* 2.3 Hz), 1.31 (t, 3 H, *J* 7.1 Hz); *m*/*z* (FAB) 638.2524 (M^+. $C_{38}H_{38}O_9$ requires 638.2516).

(3*S*,4*R*,5*S*,6*R*)-3-Ethoxycarbonyloxy-7-[(4-methoxyphenyl)-diphenylmethoxy]-4,5-(*p*-methoxybenzylidenedioxy)-6-(imidazolylthiocarbonyloxy)heptyne (10)

A mixture of **15** (128 mg, 0.20 mmol) and *N*,*N*′-thiocarbonyldiimidazole (356 mg, 2.0 mmol) in CH_2Cl_2 (2 mL) was stirred at rt for 2 d. The resulting mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, 15–30% AcOEt in hexane) to give **10** (130 mg, 87%) as a white foam (Found C, 67.24; H, 5.35; N, 3.82. $C_{42}H_{40}N_2O_9S$ requires C, 67.36; H, 5.38; N, 3.74%); δ_H (400 MHz, $CDCl_3$, Me_4Si) 8.27 (m, 1 H), 7.58 (m, 1 H), 7.42–7.16 (m, 14 H), 7.05 (m, 1 H), 6.86 (m, 2 H), 6.69 (m, 2 H), 5.91 (s, 1 H), 5.82 (m, 1 H), 5.37 (dd, 1 H, *J* 2.1, 5.2 Hz), 5.01 (dd, 1 H, *J* 6.2, 8.3 Hz), 4.57 (dd, 1 H, *J* 6.2, 6.2 Hz), 4.08 (m, 1 H), 3.96 (m, 1 H), 3.83 (s, 3 H), 3.79 (m, 1 H) 3.75 (s, 3 H), 3.61 (dd, 1 H, *J* 3.6, 11.5 Hz), 2.44 (d, 1 H, *J* 2.3 Hz), 1.21 (t, 3 H, *J* 7.2 Hz); δ_X (100 MHz, $CDCl_3$, Me_4Si) 182.0, 160.5, 158.5, 153.5, 144.3, 143.9, 143.8, 136.8, 136.8, 134.8, 130.7, 130.3, 130.2, 128.3, 128.1, 128.1, 128.0, 127.9, 127.9, 127.7, 126.8, 126.8, 117.9, 117.8, 113.6, 113.5, 113.0, 103.7, 103.7, 86.5, 79.3, 77.5, 77.4, 46.5, 75.2, 65.7, 64.8, 60.5, 55.3, 55.2, 14.1; *m*/*z* (FAB) 749 (MH^+)

(1*S*,2*R*,3*R*,4*R*)-1-Ethoxycarbonyloxy-2,3-(*p*-methoxybenzylidenedioxy)-4-{[(4-methoxyphenyl)diphenylmethoxy]methyl}-5-methylenecyclopentane (11a) and (1*S*,2*R*,3*R*,4*S*)-1-ethoxycarbonyloxy-2,3-(*p*-methoxybenzylidenedioxy)-4-{[(4-methoxyphenyl)diphenylmethoxy]methyl}-5-methylenecyclopentane (11b)

A mixture of **10** (150 mg, 0.2 mmol), Bu_3SnH (59 μL, 0.22 mmol), AIBN (16 mg, 0.02 mmol) in benzene (10 mL) was heated under reflux for 3 h. The resulting mixture was evaporated, and the residue was purified by column chromatography (silica gel, 8–10% AcOEt in hexane) to give **11a** (59 mg, 47%) and **11b** (20 mg, 16%) as white forms. Compound **11a**; δ_H (400 MHz, $CDCl_3$, Me_4Si) 7.44–7.19 (m, 14 H, Ph), 6.87–6.77 (m, 4 H, Ph), 5.71 (s, 1 H, CH_3OPhCH), 5.57 (m, 1 H, H-1), 5.41 (s, 1 H, C=CH), 5.27

(s, 1 H, C=CH), 4.93 (dd, 1 H, H-2, *J* 5.8, 5.8 Hz), 4.53 (d, 1 H, H-3, *J* 5.6 Hz), 4.21 (m, 2 H, O*CH*$_2$CH$_3$), 3.79 (s, 3 H, OCH$_3$), 3.79 (s, 3 H, OCH$_3$), 3.20 (m, 2 H, 4-*CH*$_2$OMMTr), 2.63 (m, 1 H, H-4), 1.28 (t, 3 H, OCH$_2$*CH*$_3$, *J* 7.1 Hz); NOE irradiate 4-C*H*$_2$OTr/observed H-1 (2.9%), H-3 (4.9%); δ_C (100 MHz, $CDCl_3$, Me_4Si) 160.54, 158.51, 154.60, 146.92, 144.09, 143.94, 135.18, 130.26, 128.63, 128.57, 128.30, 128.27, 127.89, 127.80, 127.66, 126.91, 126.73, 113.56, 113.10, 112.98, 112.01, 105.21, 86.88, 82.57, 78.61, 65.47, 64.22, 55.29, 55.24, 48.72, 14.28; *m/z* (FAB) 621.2563 (M^+. $C_{38}H_{38}O_8$ requires 621.2567). Compound **11b**; δ_H (400 MHz, $CDCl_3$, Me_4Si) 7.48–7.17 (m, 14 H, Ph), 6.82–6.73 (m, 4 H, Ph), 5.72 (s, 1 H, CH$_3$OPh*CH*), 5.15 (s, 1 H, C=CH), 5.12 (m, 1 H, H-1), 4.86 (m, 2 H, C=CH, H-3), 4.81 (dd, 1 H, H-2, *J* 5.7, 5.8 Hz), 4.18 (m, 2 H, O*CH*$_2$CH$_3$), 3.80 (s, 3 H, OCH$_3$), 3.75 (s, 3 H, OCH$_3$), 3.63 (dd, 1 H, 4′-*CH*$_2$OMMTr, *J* 8.5, 8.5 Hz), 3.40 (dd, 1 H, 4-*CH*$_2$OMMTr, *J* 5.9, 8.8 Hz), 2.63 (m, 1 H, H-4), 1.26 (t, 3 H, OCH$_2$*CH*$_3$, *J* 7.2 Hz); NOE irradiate 4-H/observed H-1 (9.5%); *m/z* (FAB) 621.2580 (M^+. $C_{38}H_{38}O_8$ requires 621.2567).

9-{(1*R*,2*S*,3*R*,4*R*)-2,3-(4-Methoxybenzylidenedioxy)-4-{[(4-methoxyphenyl)diphenylmethoxy]methyl}-5-methylenecyclopentan-1-yl}-6-chloropurine (17)

To a solution of **16** (1.10 g, 2.0 mmol), 6-chloropurine (927 mg, 6.0 mmol), and Ph_3P (1.57 g, 6.0 mmol) in THF (20 mL) was slowly added a solution of DIAD (1.26 mL, 6.0 mmol) in THF (20 mL) at 0 °C, and the mixture was stirred at the same temperature for 3 h and then at rt for 18 h. After evaporation of the resulting mixture, to the residue was added AcOEt, and the resulting suspension was filtered. The filtrate was evaporated, and the residue was purified by column chromatography (silica gel, 15–20% AcOEt in hexane) to give **17** (1.07 g, 79%) as a white form; UV (MeOH) λ_{max} 266 nm; δ_H (400 MHz, $CDCl_3$, Me_4Si) 8.64 (s, 1 H, H-2), 8.08 (s, 1 H, H-8), 7.52–7.22 (m, 14 H, Ph), 6.97 (m, 2 H, Ph), 6.84 (m, 2 H, Ph), 5.97 (s, 1 H, CH$_3$OPh*CH*), 5.58 (m, 1 H, H-1′), 5.15 (dd, 1 H, H-2′, *J* 5.7, 5.7 Hz), 5.09 (br s, 1 H, C=CH), 4.88 (dd, 1 H, H-3′, *J* 2.3, 6.4 Hz,), 4.72 (br s, 1 H, C=CH), 3.84 (s, 3 H, OCH$_3$), 3.80 (s, 3 H, OCH$_3$), 3.52 (dd, 1 H, 4′-*CH*$_2$OMMTr, *J* 5.5, 9.2 Hz), 3.45 (dd, 1 H, 4′-*CH*$_2$OMMTr, *J* 5.9, 9.3 Hz), 3.31 (m, 1 H, H-4′); NOE irradiate H-3′/observed H-6′ (2.0%), irradiate H-1′/observed H-4′ (2.1%); δ_C (100 MHz, $CDCl_3$, Me_4Si) 160.7, 158.6, 151.9, 151.6, 151.1, 147.2, 144.4, 144.3, 144.0, 143.9, 135.0, 131.8, 130.3, 128.3, 128.1, 127.8, 127.0, 113.9, 113.3, 113.1, 106.6, 86.9, 83.8, 83.2, 65.4, 63.6, 55.4, 48.1, 21.8; *m/z* (FAB) 687.2372 (MH^+. $C_{40}H_{36}N_4O_5Cl$ requires 687.2374).

(1*S*,2*S*,3*R*,4*R*)-1-hydroxy-2,3-(4-methoxybenzylidenedioxy)-4-{[(4-methoxyphenyl)diphenylmethoxy]methyl}-5-methylenecyclopentane (16)

A mixture of **11a** (241 mg, 0.40 mmol) and NaOMe (28% in MeOH, 154 μL, 0.80 mmol) in THF (1 mL) and MeOH (4 mL) was stirred at rt for 5 h and then neutralized with Diaion WK-20 resin (H^+ form). After the resin was filtered off, the filtrate was evaporated, and the residue was purified by column chromatography (silica gel, 10–15% AcOEt in hexane) to give **16** (206 mg, 93%) as a white form; δ_H (400 MHz, $CDCl_3$, Me_4Si) 7.44–7.22 (m, 14 H), 6.90–6.80 (m, 4 H), 5.72 (s, 1 H), 5.43 (br s, 1 H), 5.24 (br s, 1 H), 4.75 (m, 1 H), 4.68 (dd, 1 H, *J* 6.0, 6.0 Hz), 4.54 (d, 1 H, *J* 6.0 Hz), 3.80 (s, 3 H), 3.80 (s, 3 H), 3.18 (d, 2 H, *J* 4.9 Hz), 2.88 (m, 1 H), 2.35 (d, 1 H, *J* 10.9 Hz); *m/z* (FAB) 551.2449 (MH^+. $C_{35}H_{35}O_6$ requires 551.2434).

9-{(1*R*,2*S*,3*R*,4*R*)-2,3-(4-Methoxybenzylidenedioxy)-4-{[(4-methoxyphenyl)diphenylmethoxy]methyl}-5-methylenecyclopentan-1-yl}adenine (18)

A solution of **17** (34 mg, 0.05 mmol) in methanolic ammonia (saturated at 0 °C) was heated in a steel tube at 80 °C for 12 h. After cooling to rt, the resulting mixture was evaporated, and the residue was purified by column chromatography (silica gel, 2% MeOH in $CHCl_3$) to give **18** (32 mg, 95%) as a white form; UV (MeOH) λ_{max} 261 nm; δ_H (400 MHz, $CDCl_3$, Me_4Si) 8.26 (s, 1 H), 7.76 (s, 1 H), 7.53–7.21 (m, 14 H), 6.95 (m, 2 H), 6.84 (m, 2 H), 5.96 (s, 1 H), 5.75 (br s, 2 H), 5.11 (m, 1 H), 5.15 (dd, 1 H, *J* 5.8, 5.8 Hz), 5.04 (br s, 1 H), 4.85 (dd, 1 H, *J* 2.7, 6.5 Hz), 4.70 (br s, 1 H), 3.83 (s, 3H), 3.79 (s, 3 H), 3.48 (m, 2 H), 3.28 (m, 1 H); δ_C (100 MHz, $CDCl_3$, Me_4Si) 160.6, 158.5, 155.4, 152.9, 152.9, 150.0, 147.8, 144.1, 144.1 139.6, 139.6, 135.2, 130.3, 128.4, 128.3, 128.2, 127.8, 126.9, 119.7, 113.8, 113.1, 112.5, 106.5, 86.7, 83.8, 83.0, 64.6, 63.6, 55.3, 55.2, 48.2; *m/z* (FAB) 668.2863 (MH^+. $C_{40}H_{38}N_5O_5$ requires 668.2873).

9-[(1*R*,2*S*,3*R*,4*R*)-2,3,-Dihydroxy-4-hydroxymethyl-5-methylenecyclopentan-1-yl]adenine (5′-methylenearisteromycin, 5)

A solution of **18** (32 mg, 0.047 mmol) in aqueous AcOH (80%, 1 mL) was heated at 80 °C for 20 h. After cooling to rt, the resulting mixture was evaporated, and the residue was purified by column chromatography (silica gel, 5–20% MeOH in $CHCl_3$) to give **5** (13 mg, quant.) as a white form (Found C, 50.72; H, 5.47; N, 24.45. $C_{12}H_{16}N_5O_3\cdot0.4\ H_2O$ requires C, 50.66; H, 5.60; N, 24.62%); UV (MeOH) λ_{max} 260 nm; δ_H (400 MHz, DMSO-d_6, Me_4Si) 8.16 (s, 1H, H-2), 8.08 (s, 1H, H-8), 7.22 (br s, 2H, NH_2), 5.23 (dd, 1H, H-1′, $J_{1',2'} = 2.5$, $J_{1',C=CH} = 2.5$ Hz), 5.15 (d, 1H, 2′-OH, $J_{OH,2'} = 6.6$ Hz), 5.04 (dd, 1H, C=CH, $J_{C=CH,1'} = 2.4$, $J_{gem} = 2.4$ Hz), 4.99 (t, 1H, 4′-CH$_2$*OH*, $J_{OH,CH_2} = 5.6$ Hz), 4.85 (d, 1H, 3′-OH, $J_{OH,3'} = 3.0$ Hz), 4.54 (m, 1H, H-2′), 4.44(dd, 1H, C=CH, $J_{C=CH,4'} = 2.3$, $J_{gem} = 2.3$ Hz), 4.01 (m, 1H, H-2′), 3.58 (m, 2H, 4′-*CH*$_2$OH), 2.62 (m, 1H, H-4′); δ_C (100 MHz, DMSO-d_6, Me_4Si) 156.1, 152.1, 149.8, 148.2, 140.6, 120.0, 110.1, 74.3, 71.7, 63.4, 62.6, 51.8; *m/z* (FAB) 278.1261 (MH^+. $C_{12}H_{16}N_5O_3$ requires 278.1253). Anal. ($C_{12}H_{16}N_5O_3\cdot0.4\ H_2O$) C, H, N.

9-[(1*R*,2*S*,3*R*,4*R*)-2,3,-Dihydroxy-4-hydroxymethyl-5-methylenecyclopentan-1-yl]-2-fluoroadenine (2-fluoro-5′-methylenearisteromycin, 6)

To a solution of **16** (110 mg, 0.20 mmol), 2-fluoroadenine (92 mg, 0.60 mmol), and Ph_3P (157 mg, 0.60 mmol) in THF (2 mL) was slowly added a solution of DIAD (126 μL, 6.0 mmol) in THF (2 mL) at 0 °C, and the mixture was stirred at the same temperature for 3 h and then at rt for 18 h. After evaporation of the resulting mixture, to the residue was added AcOEt, and the resulting suspension was filtered. The filtrate was evaporated, and the residue was purified by column chromatography (silica gel, 0.1–2% MeOH in $CHCl_3$) to give a mixture of **19** and **20**. A solution of the mixture in aqueous AcOH (80%, 3 mL) was heated at 80 °C for 20 h. After cooling to rt, the resulting mixture was evaporated, and the residue was purified by column chromatography (silica gel, 1–20% MeOH in $CHCl_3$) to give **6** (53 mg, 89%) as a white form (Found C, 47.67; H, 4.76; N, 22.70. $C_{12}H_{14}FN_5O_3\cdot0.5\ H_2O$ requires C, 47.37; H, 4.97; N, 23.02); UV (MeOH) λ_{max} 262 nm; δ_H (400 MHz, DMSO-d_6, Me_4Si) 8.08 (s, 1 H, H-8), 7.71 (br s, 2 H, NH_2), 5.14 (br s, 1 H, 2′-OH), 5.08 (d, 1 H, H-1′), 5.00 (br s, 1 H, C=CH), 4.82 (br s, 2 H, 5′-OH, 3′-OH), 4.43 (br s, 1 H, C=CH), 4.40 (m, 1 H, H-2′), 3.95 (d, 1 H, H-3′, $J_{3',2'} = 4.0$ Hz), 3.49 (m, 2 H, 4′-*CH*$_2$OH), 2.55 (m, 1 H, H-4′); δ_C (100 MHz, DMSO-d_6, Me_4Si) 158.5 (d, *J* 202.3 Hz), 157.4 (d, *J* 21.6 Hz), 151.0 (d, *J* 20.2 Hz), 147.6, 140.7, 117.2, 110.0, 74.0, 71.2, 63.0, 62.3, 51.5; *m/z* (FAB) 296.1160 (MH^+. $C_{12}H_{15}N_5O_3F$ requires 296.1159).

Inhibitory effect on AdoHcy hydrolases

Assays were done according to previously reported methods.[14]

Antimalarial effect and cytotoxicity

Assays were done according to previously reported methods.[15]

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