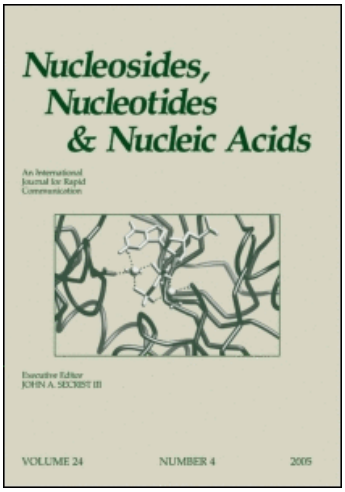

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Ruifang Wang[a]; Xinchao Chen[a]; John C. Drach[b]; Earl R. Kern[c]; Jiri Zemlicka[ad]
[a] Developmental Chemotherapy Program, Department of Chemistry, Barbara Ann Karmanos Cancer Institute, Detroit, Michigan, USA [b] Department of Biologic and Materials Science, School of Dentistry, Ann Arbor, Michigan, USA [c] Department of Pediatrics, The University of Alabama at Birmingham, Birmingham, Alabama, USA [d] Developmental Chemotherapy Program, Department of Chemistry, Barbara Ann Karmanos Cancer Institute, Detroit, MI, USA

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Synthesis and Biological Activity of 2-Aminopurine Methylenecyclopropane Analogues of Nucleosides

Ruifang Wang,[1] Xinchao Chen,[1] John C. Drach,[2] Earl R. Kern,[3] and Jiri Zemlicka[1,*]

[1]Developmental Chemotherapy Program, Department of Chemistry, Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, Michigan, USA
[2]Department of Biologic and Materials Science, School of Dentistry, University of Michigan, Ann Arbor, Michigan, USA
[3]Department of Pediatrics, The University of Alabama at Birmingham, Birmingham, Alabama, USA

ABSTRACT

Synthesis and biological activity of racemic 2-aminopurine methylenecyclopropane analogues of nucleosides **4**, **5**, **10** and **11** is described. One-pot alkylation-elimination of 2-aminopurine (**6**) with dibromide **7** gave a mixture of four isomeric methylenecyclopropanes. The (*E, Z*)-N^9 and (*E, Z*)-N^7 isomers **8** and **9** were resolved by chromatography on silica gel. Deacetylation of **8** afforded the respective (*Z*)-N^9 and (*E*)-N^9 isomers **4** and **10** which were separated by chromatography on silica gel. In a similar fashion, (*E, Z*)-N^7 mixture **9** furnished (*Z*)-N^7 and (*E*)-N^7 isomers **5** and **11**. The *S*-(+)-enantiomer **4** was obtained by desulfurization of (*S*)-(+)-6-thiosynguanol (**13**) with Raney Ni. Compound **13** was obtained from (*S*)-(+)-2-amino-6-chloro derivative **12** and NaSH in methanol. Racemic analogues **4**, **5, 10** and **11** were inactive against HCMV, HSV-1,

*Correspondence: Jiri Zemlicka, Developmental Chemotherapy Program, Department of Chemistry, Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI 48201-1379, USA; Fax: (313) 832-7294.

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HSV-2, EBV and VZV. Enantiomer (*S*)-(+)-**4** inhibited replication of HSV-1 in BSC-1 cells (ELISA) with EC_{50} 35 μM and it was non-cytotoxic in KB cells ($CC_{50} > 100$ μM). Compound (*S*)-(+)-**4** was also moderately effective against VZV in HFF culture with EC_{50}/CC_{50} (μM) $60/>460$ and it was a substrate for xanthine oxidase.

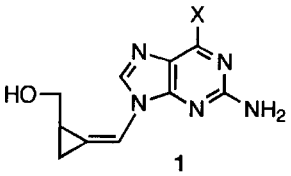
Key Words: Nucleoside analogues; Methylenecyclopropanes; 2-aminopurine; Prodrugs; Alkylation-elimination; Xanthine oxidase.

INTRODUCTION

Purine *Z*-methylenecyclopropane analogues of nucleosides are broad-spectrum antiviral agents strongly effective against human cytomegalovirus (HCMV).[1,2] The anti-CMV activity is associated with the *S*-(+) enantiomeric forms of these analogues.[3] Synguanol (**1a**) and its cyclopropylamino analogue **1b** are effective in vivo in various mouse models of CMV infection.[4,5] Efficacy of compound **1b**, a potential prodrug of synguanol (**1a**), is equal or superior to current drug ganciclovir.

The 6-deoxyanalogues of acyclovir and penciclovir (**2a** and **2b**) are efficient inhibitors of herpesviruses in vivo although they exhibit little activity in cell culture.[6,7] Both analogues act in vivo as prodrugs that are converted to guanine analogues **2c** and **2d** by the action of xanthine oxidase. More recently, the N^7-isomer of 6-deoxyganciclovir **3** was found to exhibit a potent activity against herpesviruses in vitro and in vivo.[8–11] Unlike the N^9-isomers **2a** and **2b**, analogue **3** does not require oxidation in vivo for activity.

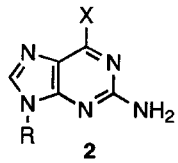
Therefore, it was of interest to synthesize and investigate the N^9- and N^7-isomers of methylenecyclopropane analogues **4** and **5**.



1

1a: X = OH

1b: X =



2

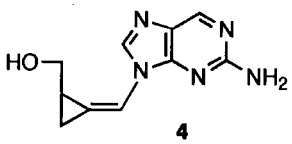
2a: X = H, R = $CH_2OCH_2CH_2OH$

2b: X = H, R = $CH_2CH_2CH(CH_2OH)_2$

2c: X = OH, R = $CH_2OCH_2CH_2OH$

2d: X = OH, R = $CH_2CH_2CH(CH_2OH)_2$

3



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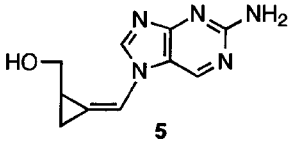

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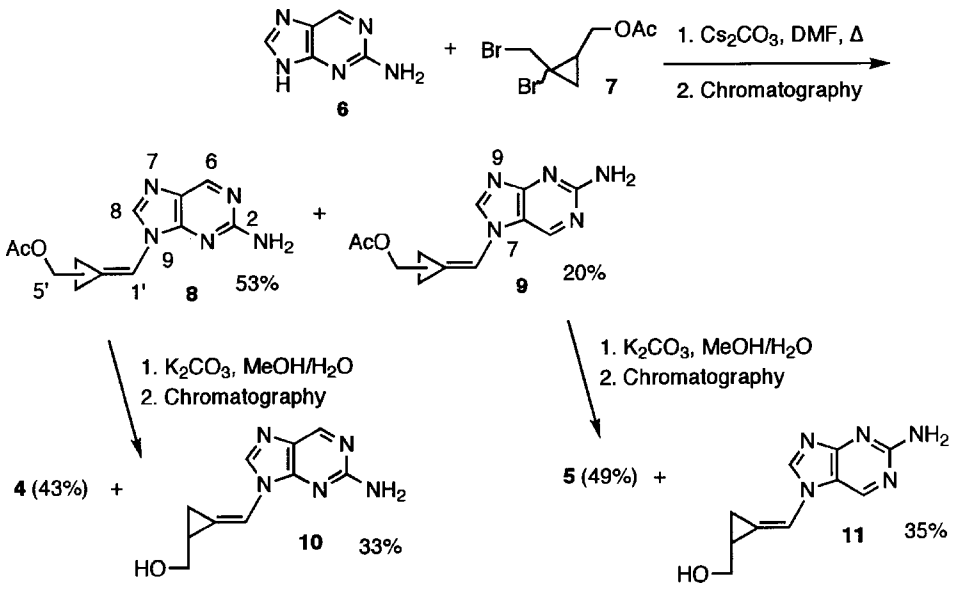
RESULTS AND DISCUSSION

A. Synthesis

The N^7- and N^9-isomers of 2-aminopurine nucleoside analogues are usually synthesized from the corresponding guanine derivatives.[12] For our purpose, it was considered advantageous to prepare both isomers **4** and **5** directly from commercially available 2-aminopurine (**6**) in a one-pot reaction (Sch. 1) by alkylation-elimination procedure employed previously with other nucleic acid bases.[1,13,14] Reaction of 2-aminopurine (**6**) with dibromide **7** and Cs_2CO_3 in DMF at 65°C and chromatographic separation gave (*E, Z*)-N^9-isomers **8** (53%) and (*E, Z*)-N^7-isomers **9** (20%). The N^9/N^7 ratio (2.7/1) is significantly lower than that observed in simple alkylations of 2-aminopurine (**6**) (5/1 – 11/1).[15] Deprotection of **8** using K_2CO_3 in aqueous methanol gave, after chromatographic separation, compound **4** (43%) and the *E*-isomer **10** (33%). A similar treatment of **9** afforded analogue **5** (49%) and the *E*-isomer **11** (35%).

The *S*-(+)-enantiomer of **4** was prepared as follows (Sch. 2). The (*S*)-(+)-2-amino-6-chloro derivative (**12**)[14] was converted to 6-thiosynguanol (**13**) by reaction with NaSH in methanol in 67% yield. Desulfurization of **13** with Raney Ni in aqueous methanol gave *S*-(+)-**4** (46%). The isomeric assignments were confirmed by UV and NMR spectroscopy (Table 1). As expected,[12] the long wavelength UV maximum of the N^7-isomers **5** and **11** is bathochromically shifted relative to N^9-isomers **4** and **10**. Also, the patterns of chemical shifts δH_8 (N^9) < δH_8 (N^7), δNH_2 (N^9) > δNH_2 (N^7) and C_8 (N^9) < C_8 (N^7) follow an empirical rule postulated for N^9- and N^7-alkyl purines.[16] The *Z*, *E*-isomeric assignment of N^9-isomers then



Scheme 1.

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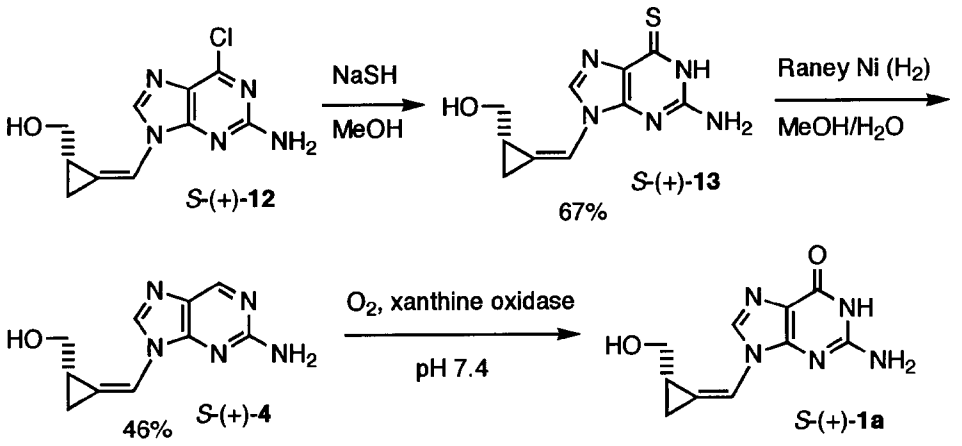

Scheme 2.

agreed with those of other purine methylenecyclopropane analogues:[1] Deshielding of the H_8, OH and shielding of the $H_{1'}$ in the *Z*-isomer **4** relative to the *E*-isomer **10**. Non-equivalency of the H_5 protons in the *Z*-isomer **4** as opposed to *E*-isomer **10** is also an important feature found generally in the purine series.[1,2] Interestingly, these relationships were closely followed by N^7 isomers **5** and **11**. It should be noted that in an *anti* conformation of both *Z*-isomers **4** and **5** the CH_2OH is juxtaposed to the H_8 which explains a significant downfield shift of the latter resonance relative to the respective *E*-isomers **10** and **11**.

B. Biological Activity

Compounds **4**, **5**, **10** and **11** were inactive ($EC_{50} > 100\,\mu M$) in the following assays: HCMV, HSV-1, HSV-2, EBV, HBV and VZV. Enantiomer *S*-(+)-**4** was moderately effective against HSV-1/BSC-1 (ELISA), cytotoxicity in KB cells, EC_{50}/CC_{50} (μM) 35/ > 100 and VZV/HFF /EC_{50}/CC_{50} (μM) 35/ > 100.

Compound (*S*)-(+)-**4** was a substrate for xanthine oxidase (Figs. 1 and 2). The reaction lacks stereoselectivity because racemic *Z*- and *E*-isomers **4** and **10** were also oxidized (data not shown). The assays were perfomed under conditions close to those

Table 1. UV maxima and some relevant NMR chemical shifts of compounds **4**, **5**, **10**, and **11**.

Compound	λ_{max} (nm)	δH_8	$\delta H_{1'}$	δOH	δNH_2	$\delta H_{5'}$	C_8
4, *Z*-N^9	310	8.60	7.25	5.07	6.63	3.73 & 3.28	140.1
5, *Z*-N^7	330	8.81	7.51	5.08	6.35	3.63 & 3.31	145.6
10, *E*-N^9	310	8.45	7.35	4.80	6.78	3.40	139.6
11, *E*-N^7	330	8.57	7.58	4.91	6.37	3.41	146.4

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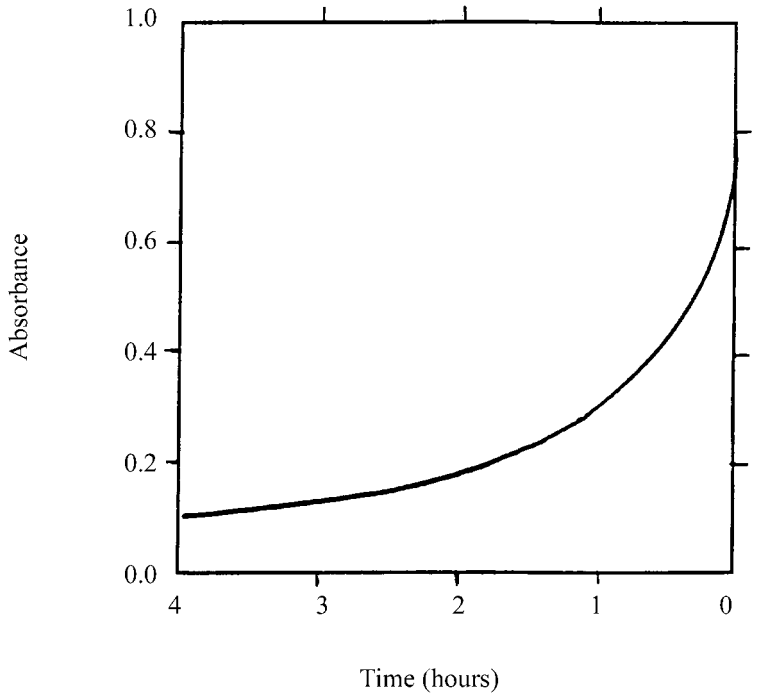

Figure 1. Time-course of oxidation of (*S*)-(+)-6-deoxysynguanol (**4**) to (*S*)-(+)-synguanol [(*S*)-(+)-**1a**] catalyzed by xanthine oxidase. *Conditions:* 0.07 mM (*S*)-(+)-**4** in 0.05 M Na_2HPO_4 (pH 7.4, 1.2 mL) plus xanthine oxidase from cow milk (20 units/mL, 20 μL, 0.4 units), room temperature, continuous monitoring at 304 nm.

reported for 6-deoxypenciclovir (**2b**).[7] These results have indicated that (*S*)-(+)-6-deoxysynguanol (**4**) is a viable candidate for in vivo testing as a prodrug of (*S*)-(+)-synguanol (**1a**).

EXPERIMENTAL SECTION

General Methods

The ^1H and ^{13}C NMR spectra were determined at 400 and 100 MHz, respectively, in CD_3SOCD_3 unless stated otherwise. UV spectra were measured in ethanol. Mass spectra were performed in an electrospray ionization mode (ESI-MS) using aqueous MeOH and NaCl.

(*Z*, *E*)-2-Amino-9-[(2-acetoxymethyl)cyclopropylidenemethyl]purine (8) and (*Z*, *E*)-2-Amino-7-[(2-acetoxymethyl)cyclopropylidenemethyl]purine (9). A mixture of 2-aminopurine (**6**, 600 mg, 4.44 mmol) and dibromide **7** (1.52 g, 5.33 mmol) in DMF (30 mL) was stirred with Cs_2CO_3 (7.24 g, 22.2 mmol) at room temperature for 2 h and then at 65°C for 6 h. The solids were filtered off, the filtrate was evaporated in

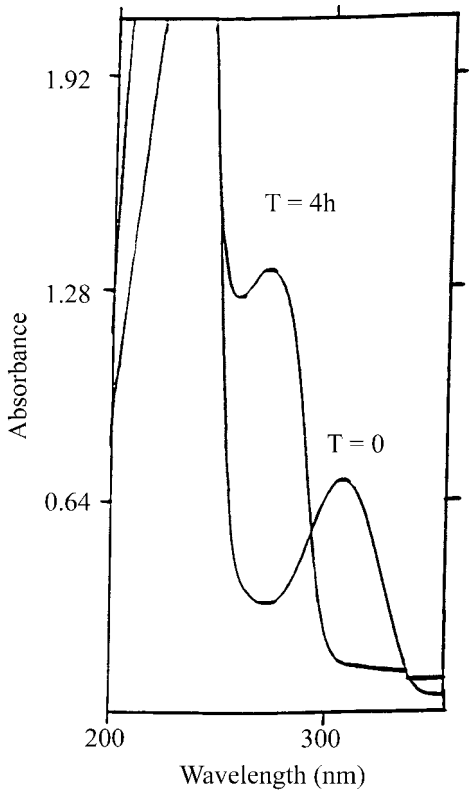

Figure 2. UV spectra of (*S*)-(+)-**4** (pH 7.4, T = 0, before addition of enzyme) and after incubation with enzyme (T = 4 h). The latter spectrum corresponded to authentic (*S*)-(+)-synguanol [(*S*)-(+)-**1a**].

vacuo and the residue was chromatographed on a silica gel column using CH_2Cl_2 : MeOH = 98 : 2) as an eluent. The (*E, Z*)-9-isomers **8** (610 mg, 53%) were eluted first followed by (*E, Z*)-7-isomers **9** (230 mg, 20%).

(*E, Z*)-9-isomers **8**: Mp 120–124°C; UV max 310 nm (ε 6,000), 232 (ε 24,600); ^{1}H NMR ($CDCl_3$) δ 8.70 and 8.68 (s, 1H), 8.29 and 8.21 (s, 1H), 7.48 and 7.36 (dd, 1H, J = 4.0 and 2.4 Hz), 5.30 (brs, 2H), 4.33–3.95 (m, 2H), 2.29–2.13 (m, 1H), 2.10 and 2.05 (s, 3H), 1.80–1.76 and 1.68–1.63 (m, 1H), 1.47–1.43 and 1.36–1.32 (m, 1H); ^{13}C NMR 171.3, 171.1, 160.4, 160.3, 152.0, 150.2, 150.1, 140.0, 139.1, 128.2, 113.9, 113.1, 111.6, 111.5, 67.0, 66.3, 21.2, 21.1, 16.4, 14.4, 10.3, 8.0; ESI-MS 260 (M + H, 12.0), 282 (M + Na, 100.0).

(*E, Z*)-7-isomers **9**: Mp 176–180°C; UV max 326 nm (ε 4,800), 250 (ε 14,100), 211 (ε 22,600); ^{1}H NMR δ 8.83 and 8.76 (s, 1H), 8.53 and 8.51 (s, 1H), 7.62 and 7.53 (d, 1H, J = 1.6 Hz), 6.30 (brs, 2H), 4.16–3.80 (m, 2H), 2.43–2.39 and 2.13–2.09 (m, 1H), 2.03 and 1.77 (s, 3H), 1.92–1.88 and 1.66–1.62 (m, 1H), 1.64–1.60 and 1.37–1.33 (m, 1H); ^{13}C NMR ($CDCl_3$) 170.9, 170.5, 163.1, 163.0, 161.8, 146.5, 146.0, 143.4, 143.2, 118.1, 115.0, 114.5, 114.3, 113.3, 66.6, 66.2, 21.4, 21.0, 16.7, 14.8, 11.6, 8.2; ESI-MS 260 (M + H, 10.8), 282 (M + Na, 100.0).

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(*Z*)-2-Amino-9-[(2-hydroxymethyl)cyclopropylidenemethyl]purine (4) and (*E*)-2-Amino-9-[(2-hydroxymethyl)cyclopropylidenemethyl]purine (10). The isomeric mixture **8** (520 mg, 2.0 mmol) was stirred with K_2CO_3 (304 mg, 2.2 mmol) in MeOH-H_2O (15 : 1, 30 mL) at room temperature for 3 h. The pH was adjusted to 7 with AcOH, volatile components were evaporated and the residue was chromatographed on a silica gel column using CH_2Cl_2:MeOH = 19 : 1 as an eluent to give the *Z*-isomer **4** (185 mg, 43%) followed by *E*-isomer **10** (145 mg, 33%) as white solids.

Z-isomer **4**: Mp 186–188°C; UV max 310 nm (ε 7,800), 233 (ε 33,100); ^{1}H NMR δ 8.68 (s, 1H, H_6), 8.60 (s, 1H, H_8), 7.25 (d, 1H, J = 1.6 Hz, $H_{1'}$), 6.63 (s, 2H, NH_2), 5.07 (dd, 1H, J = 6.2 and 5.2 Hz, OH), 3.73 (m, 1H) and 3.28 (m, overlapped with H_2O, $H_{5'}$), 2.11 (m, 1H, $H_{4'}$), 1.48 (dt, 1H) and 1.20 (m, 1H, $H_{3'}$); ^{13}C NMR 161.5 (C_2), 152.0 (C_4), 150.1 (C_6), 140.1 (C_8), 127.2 (C_5), 115.7 ($C_{2'}$), 110.3 ($C_{1'}$), 63.6 ($C_{5'}$), 19.9 ($C_{4'}$), 6.9 ($C_{3'}$); ESI-MS 218 (M + H, 95.8), 240 (M + Na, 100.0). Anal. Calcd for $C_{10}H_{11}N_5O{\cdot}0.5H_2O$: C, 53.09; H, 5.35; N, 30.96. Found: C, 53.38; H, 5.40; N, 31.12.

E-isomer **10**: Mp 124–126°C; UV max 310 nm (ε 7,500), 233 (ε 30,600); ^{1}H NMR δ 8.65 (s, 1H, H_6), 8.45 (s, 1H, H_8), 7.35 (dd, 1H, J = 4.2 and 2.4 Hz, $H_{1'}$), 6.78 (s, 2H, NH_2), 4.80 (brs, 1H, OH), 3.40 (d, overlapped with H_2O, J = 6.8 Hz, $H_{5'}$), 1.96 (m, 1H, $H_{4'}$), 1.70 (dt, 1H) and 1.36 (m, 1H, $H_{3'}$); ^{13}C NMR 161.5 (C_2), 152.2 (C_4), 150.2 (C_6), 139.6 (C_8), 127.2 (C_5), 116.4 ($C_{2'}$), 110.5 ($C_{1'}$), 63.9 ($C_{5'}$), 18.3 ($C_{4'}$), 10.0 ($C_{3'}$); ESI-MS 218 (M + H, 100.0), 240 (M + Na, 66.8). Anal. Calcd for $C_{10}H_{11}N_5O$: C, 55.29; H, 5.10; N, 32.24. Found: C, 55.13; H, 5.19; N, 32.13.

(*Z*)-2-Amino-7-[(2-hydroxymethyl)cyclopropylidenemethyl]purine (5) and (*E*)-2-Amino-7-[(2-hydroxymethyl)cyclopropylidenemethyl]purine (11). A mixture of 7-isomers **9** (230 mg, 0.88 mmol) was deacetylated as described for acetates **8** to give the *Z*-isomer **5** (95 mg, 49%) followed by *E*-isomer **11** (65 mg, 35%) as white solids.

Z-isomer **5**: Mp 211–213°C; UV max 330 nm (ε 5,100), 253 (ε 16,400), 210 (ε 22,700); ^{1}H NMR δ 8.84 (s, 1H, H_6), 8.81 (s, 1H, H_8), 7.51 (d, 1H, J = 1.6 Hz, $H_{1'}$), 6.35 (s, 2H, NH_2), 5.08 (brs, 1H, OH), 3.63 (dd, 1H, J = 11.2, 6.4 Hz) and 3.31 (dd, 1H, J = 11.4, 7.6 Hz, $H_{5'}$), 2.19 (m, 1H, $H_{4'}$), 1.49 (poorly resolved dt, 1H) and 1.20 (m, 1H, $H_{3'}$); ^{13}C NMR 162.8 (C_2), 161.8 (C_4), 145.6 (C_8), 143.1 (C_6), 118.2 (C_5), 115.4 ($C_{2'}$), 113.2 ($C_{1'}$), 63.5 ($C_{5'}$), 20.4 ($C_{4'}$), 7.1 ($C_{3'}$); ESI-MS 218 (M + H, 89.8), 240 (M + Na, 78.4), 457 (2M + Na, 100.0). Anal. Calcd for $C_{10}H_{11}N_5O$: C, 55.29; H, 5.10; N, 32.24. Found: C, 55.41; H, 5.16; N, 32.23.

E-isomer **11**: Mp 202–204°C; UV max 330 nm (ε 5,100), 254 (ε 16,200), 212 (ε 19,300); ^{1}H NMR δ 8.85 (s, 1H, H_6), 8.57 (s, 1H, H_8), 7.58 (s, 1H, $H_{1'}$), 6.37 (s, 2H, NH_2), 4.91 (brs, 1H, OH), 3.41 (m, 2H, $H_{5'}$), 1.96 (m, 1H, $H_{4'}$), 1.78 (poorly resolved dt, 1H) and 1.46 (m, 1H, $H_{3'}$); ^{13}C NMR 163.0 (C_2), 161.8 (C_4), 146.4 (C_8), 143.5 (C_6), 118.1 (C_5), 115.4 ($C_{2'}$), 113.9 ($C_{1'}$), 63.8 ($C_{5'}$), 18.6 ($C_{4'}$), 10.9 ($C_{3'}$); ESI-MS 218 (M + H, 9.0), 240 (M + Na, 77.3), 457 (2M + Na, 100.0). Anal. Calcd for $C_{10}H_{11}N_5O$: C, 55.29; H, 5.10; N 32.24. Found: C, 55.42; H, 5.12; N 32.03.

(*S*, *Z*)-(+)-2-Amino-6-thio-9-[(2-hydroxymethyl)cyclopropylidenemethyl]purine (13). A mixture of compound **12** (400 mg, 1.6 mmol) and sodium hydrosulfide hydrate (3.00 g, 53.5 mmol) in methanol (50 mL) was stirred at room temperature under N_2 for 24 h. The solvent was evaporated, the residue was dissolved in water

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(40 mL) and pH of the solution was adjusted to 6 with acetic acid. The precipitate was filtered off and it was washed with water. Recrystallization from methanol-water (1 : 1) gave compound **13** (265 mg, 67%). Mp. 240°C (decomp.); $[\alpha]_D^{20}$ 91.0° (c 0.26, DMF); UV max 346 nm (ε 24,000), 237 nm (ε 26,600); ^{1}H NMR δ 1.19 (ddd, 1H), 1.45–1.49 (dt, 1 H), 2.11 (m, 1H), 3.28 (m, overlapped with H_2O), 3.70 (m, 1H), 5.05 (t, 1H, J = 5.5 Hz), 6.85 (s, 2H), 7.09 (d, 1H, J = 2.0 Hz), 8.48 (s, 1H), 11.96 (s, 1H); ^{13}C NMR 6.9, 19.8, 63.4, 110.5, 116.8, 128.6, 137.9, 146.8, 153.9, 175.7. ESI-MS 521 (2M + Na, 50), 272 (M + Na, 100), 250 (M + H, 10). Anal. Calcd for $C_{10}H_{11}N_5OS$: C, 48.18; H, 4.45; N, 28.09; S, 12.86. Found: C, 48.10; H, 4.61; N, 28.25; S, 13.02.

(*S*, *Z*)-(+)-2-Amino-9-[(2-hydroxymethyl)cyclopropylidenemethyl]purine [(*S*)-(+)-4]. Raney Ni (200 mg) was added to a solution of compound **13** (166 mg, 0.67 mmol) in water: MeOH (1:1, 100 mL). The reaction mixture was stirred at room temperature for 16 h, catalyst was filtered off and filtrate was evaporated. The crude product was chromatographed on a silica gel column CH_2Cl_2 : MeOH (9 : 1) to give compound (*S*)-(+)-**4** (66 mg, 46%). Mp 185–187°C; $[\alpha]_D^{20}$ 77.7° (c 0.30, DMF); UV 310 nm (ε 7,900), 232 (ε 32,400); ^{1}H and ^{13}C NMR were identical with those of racemic compound **4**; ESI-MS 457 (2 M + Na, 21.2), 240 (M + Na, 100.0), 218 (M + H, 17.9). Anal. Calcd for $C_{10}H_{11}N_5O$: C, 55.29; H, 5.10; N, 32.24. Found: C, 55.40; H, 5.10; N, 32.19.

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