A Series of Novel Acyclic Nucleosides. IV.[1] Synthesis of N^1-Sulfur Analogues of Acyclovir, Directed toward Improved Antiviral Activities

Chisato KANEKO*,[a] Sumiko HARA,[a] Hiroatsu MATSUMOTO,[a] Tadao TAKEUCHI,[a] Takeo MORI,[a] Kazuyoshi IKEDA,[b] and Yoshihisa MIZUNO[a]

Research Laboratory, Minophagen Pharmaceutical Co.,[a] 2–5233, Komatsubara, Zama, Kanagawa 228 and The Center for Instrumental Analysis of Hokkaido University,[b] Kita 11, Nishi 8, Kita-ku, Sapporo, Hokkaido 060, Japan. *Received October 8, 1990*

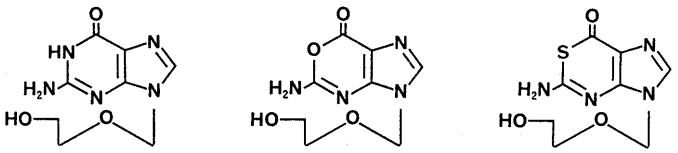
Novel imidazothiazine acyclic nucleoside analogues (9a—d, 12a—d and 3c, d) in which N^1 of the purine base is replaced by a sulfur atom were synthesized. 5-Substituted imidazo[4,5-*d*][1,3]thiazine-7(3*H*)-thiones (7a—d) were prepared from 5(4)-substituted amino-4(5)-ethoxycarbonyl-1(3*H*)-imidazoles with Lawesson reagent and then 7a—d were alkylated with 2-oxa-1,4-butanediol diacetate or with 2-acetoxyethoxymethyl halide to give 9a—d and 10a, d in moderate yields. Compounds 9a—d were led to the corresponding 7-one derivatives (12a—d) by $KMnO_4$ oxidation. Deprotection of the acetyl group in 9a—d and 12c, d was achieved by means of the Zemplen procedure.

Keywords antiviral agent; acyclonucleoside; oxidative desulfuration; imidazo[4,5-*d*][1,3]thiazin-7(3*H*)-one; Lawesson reagent

Some acyclic nucleosides such as Acyclovir (**1**),[2] and 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG),[3] modified in the carbohydrate portion of the ribonucleosides, exhibit selective and potent antiviral activity against herpes viruses. These acyclic nucleosides are viewed as prodrugs in terms of the mode of action, because they are initially phosphorylated by virus-encoded thymidine kinase, not by a kinase originated from the host, and are further phosphorylated to the corresponding triphosphates, which are specific inhibitors of DNA-polymerase (deoxyribonucleic acid-polymerase), associated with the multiplication of viruses.

There have been only a few papers[4] dealing with synthesis of acyclic nucleosides having modified purine rings. Some of the products showed antiviral activities.

We have been concerned with acyclic nucleosides in which N^1 of purine bases is replaced by O, S, Se or sp^2 carbon because of our interest in the relationship between structure and antiviral activity, and to examine the substrate specificity of viral thymidine kinases. As part of this program, we recently reported the synthesis of acyclic oxanosine (**2**), and it was found that the replacement of N^1 of acyclovir with an oxygen atom resulted in a dramatic reduction in antiviral activity against herpes simplex virus (HSV-I).[5] Compound **2** also showed no activity against human immunodeficiency virus (HIV-I).[5]

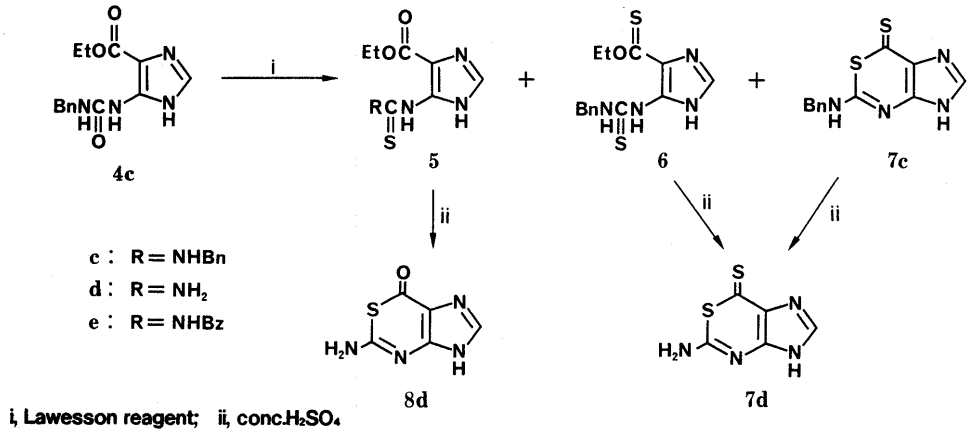


1 2 3d

Chart 1

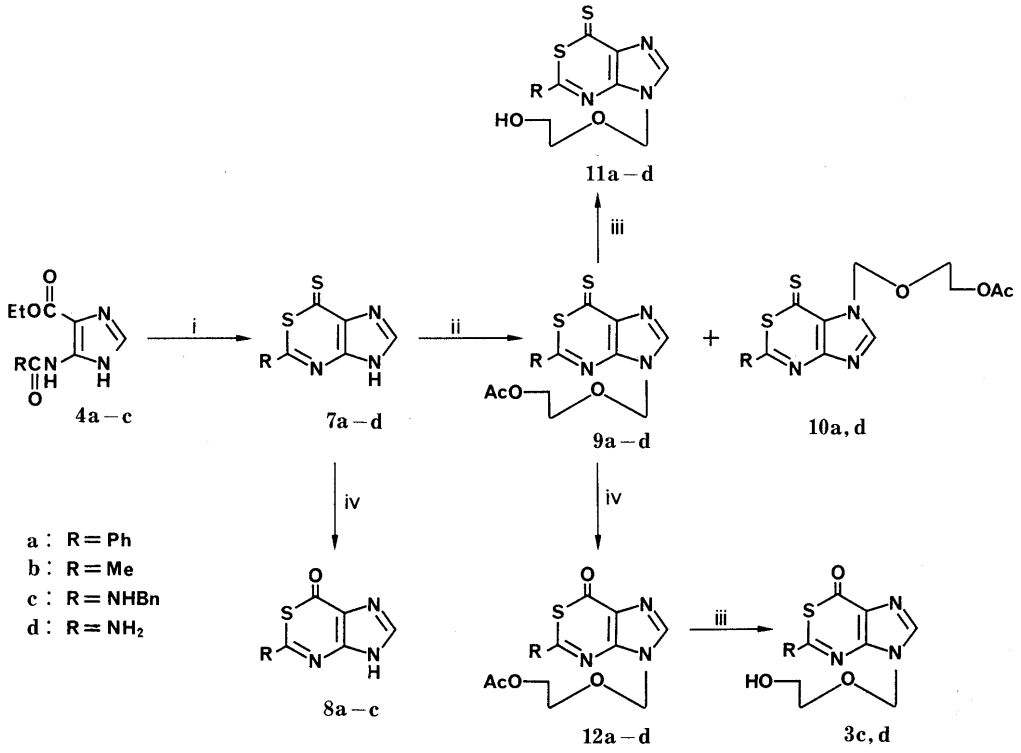
This paper describes syntheses of acyclic 5-substituted (amino, benzylamino, methyl, and phenyl) imidazo [4,5-*d*]-[1,3]thiazine-7(3*H*)-thiones (**9a—d**) and also their 7(3*H*)-one derivatives (**12a—d**), that is, the N^1-sulfur analogues of acyclovir.[6]

5(4)-Substituted amino-4(5)-ethoxycarbonyl-1(3*H*)-imidazoles (**4a—c**) were synthesized from 5(4)-amino-4(5)-ethoxycarbonyl-1(3*H*)-imidazole by the use of acetic anhydride, benzoyl chloride, and benzyl isocyanate, respectively. They were treated with an excess amount of Lawesson reagent[7] in refluxing xylene to give the thiazine derivatives (**7a—c**) in good yields. It was found that the cyclization yield depended on the reaction time. For example, when the mixture was refluxed for 8 h, **4c** gave **5c**, **6**, and **7c** in 15%, 64%, and 9% yields, respectively, and when refluxing was continued for another 8 h, **7c** was the predominant product (86% yield). Treatment of the pu-



4c 5 6 7c 8d 7d

Chart 2



i, Lawesson reagent; ii, $AcOCH_2CH_2OCH_2X$, X=Cl or OAc; iii, NaOMe/MeOH; iv, $KMnO_4$/acetone

Chart 3

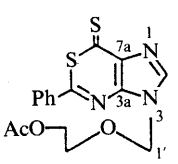
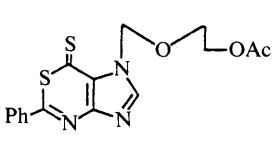
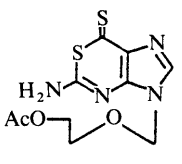
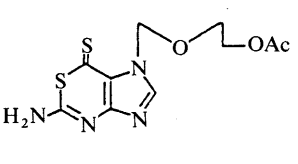
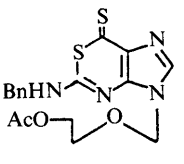
rified dithione compound (**6**) with more Lawesson reagent in refluxing xylene afforded **7c** in 60% yield. These results suggested that 5(4)-thioureido-4(5)-ethoxycarbonyl-1(3*H*)-imidazole (**5c**) was initially formed and this further reacted with Lawesson reagent to give the dithione derivative (**6**), which cyclized to form the thiazine ring either spontaneously or by catalysis of the reagent. On treatment with concentrated sulfuric acid, **6** was also cyclized, with simultaneous debenzylation to give **7d**; debenzylation of **7c** was effected with concentrated sulfuric acid to give **7d** in 75% yield. Compounds **7a**—**c** were oxidatively desulfurized by the use of potassium permanganate to afford **8a**—**c** without damage to the imidazothiazine ring. Compounds **5d**, **e** could be directly cyclized to **8d** on treatment with concentrated sulfuric acid. This procedure, however, has the following drawbacks; the yields of these products were quite poor and the purification was difficult because of instability.

These thiazine compounds (**7a**, **b**, and **7c**) were converted to the corresponding (2-acetoxyethoxymethyl)imidazothiazine derivatives (**9a**, **b**, **c** and **10a**) by fusion with 2-oxa-1,4-butanediol diacetate in the absence of a catalyst. The 5-phenyl derivative (**7a**) gave a mixture of positional isomers, whereas **7b** and **7c** gave only the 3-substituted derivatives as isolable products. Compounds **9d** and **10d** were synthesized via silylation that is, **7d** was firstly trimethylsilylated using hexamethyldisilazane and then alkylated with 2-acetoxyethoxymethyl chloride in the presence of cesium iodide according to Kim and coworkers[8] in moderate yield (33%). The alkylation of **7a** and **7d** took place on both N^1 and N^3 in the imidazole ring. In the cases of **7b** and **7c**, the N^3-alkylated compounds **9b** and **9c** were isolated as the only products (99% and 56%).

The alkylated sites of the isomers (**9** and **10**) were determined by proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectrometry. Chemical shift values are listed in Table I, together with long-range (two or three bonds) ^{1}H–^{13}C-connectivity. Namely, the ^{1}H-NMR signals of 1′-methylene protons in the N^1-isomers were always observed at lower field than those of the N^3-isomers, because the N^1-isomers are exposed to the anisotropic effect of thiocarbonyl groups at the peri-position. Further, the ^{13}C chemical shifts for C-3a or C-7a were shifted upfield by 10 ppm in most cases, when the adjacent nitrogen in the imidazole ring was alkylated. Similarly, compounds **10a** and **10d** having the substituent at position N^1 caused a shielding of carbon 7a by the same order of magnitude. These shift values are in agreement with reported values in imidazole ring systems.[9] Compound **9a** and **9d** also exhibited a connectivity between 1′-methylene protons and two carbons (C-3a and C-2) in ^{1}H–^{13}C-heteronuclear multiple bond connectivity (HMBC).[10] Protons of the 1′-methylene group in **10a** and **10d** showed a connectivity with C-7a and C-2 carbons, respectively. No connectivity was observed between carbon 3a and the 1′-methylene group in **10a** and **10d**, or between carbon 7a and the methylene protons in **9a** and **9d**. These results support the conclusion that the acyclic side chain in **9a** and **9d** is attached to N^3 of the imidazole ring, whereas **10a** and **10d** are alkylated at the N^1 position.

Compounds **9a**—**d** were then desulfurized with potassium permanganate in acetone to give colorless products (**12a**—**d**) (46—85% yields). These products showed a new carbonyl absorption band at around 1690 cm^{-1} in the infrared (IR) spectra, and the absorption maxima in the ultraviolet (UV) spectra of the former were shifted hypsochro-

TABLE I. ^{1}H- and ^{13}C-NMR Chemical Shifts of Acyclic Imidazo[4,5-*d*][1,3]thiazines

	 **9a**	 **10a**		 **9d**	 **10d**		 **9c**
^{1}H-NMR H-1′	5.73	(0.54)[a]	6.27	5.48	(0.72)	6.20	5.38
δ: ppm H-2	8.09	(0.20)	8.29	8.04	(0.24)	8.28	7.75
$CDCl_3$							
^{13}C-NMR C-2	141.94		146.69	140.17		148.25	139.40
δ: ppm C-3a	142.04	(11.29)	153.33	147.51	(9.99)	157.50	146.82
$CDCl_3$ C-7a	134.60	(9.62)	124.98	129.51	(7.34)	122.17	131.07
or							
DMSO-d_6 C-1′	73.52	(4.22)	77.74	72.93	(3.92)	76.85	72.45
^{1}H–^{13}C-NMR HMBC							
1′-CH_2: C-2	+		+	+		+	+
1′-CH_2: C-3a	+		−	+		−	+
1′-CH_2: C-7a	−		+	−		+	−

a) Values in parentheses are differences of NMR chemical shift values between N^1- and N^3-alkylated derivatives. +, connectivity; −, no connectivity.

mically by *ca.* 85 nm compared with those of the latter. Attempts at direct formation of **12a—c** from **8a—c** were abandoned because of the low yields of **8a—c** from **7a—c**, respectively.

Deprotection of the acetyl group in **9a—d** and **12c, d** was achieved by treatment with a catalytic amount of sodium methoxide in methanol at low temperature (Zemplen procedure)[11] to afford **11a—d** and **3c, d** in good yields, though these compounds were unstable on prolonged treatment with a strongly alkaline medium. New sulfur analogues of acyclovir and their thione derivatives were successively prepared in moderate yields through several reaction steps.

These new compounds (**3d, 9c, 11a, b, d,** and **12a, b**) were found to be inactive against HIV and HSV-I. Details of the bioassay will be the subject of a separate paper.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were obtained on a JEOL GX-270 spectrometer using tetramethylsilane as an internal standard. Unless otherwise stated, deuteriodimethyl sulfoxide (DMSO-d_6) was used as a solvent. Chemical shifts are given on the δ scale (ppm). ArH-*o*, *p* and ArH-*m* refer to *ortho*, *para*, and *meta* aromatic hydrocarbon atoms. Mass and high resolution mass spectra (MS and HR-MS) measurements were run on a JMS-DX303 spectrometer. IR spectra were recorded with a JASCO IRA-1 spectromerer in KBr disks. UV spectra were measured on a Hitachi 200-20 spectrophotometer. Column chromatography was performed on Silica gel 60 (E. Merck, 70–230 mesh).

5-Phenylimidazo[4,5-*d*][1,3]thiazine-7(3*H*)-thione (7a) Lawesson reagent (5.24 g, 13.0 mmol) was added to a solution of **4a** (2.80 g, 10.8 mmol) in xylene (80 ml), and the reaction mixture was refluxed for 1.5 h, then allowed to cool. Yellow-colored precipitates were collected by filtration and then washed with MeOH to give **7a** (1.58 g, 60%), mp 250—260 °C. MS *m/z*: 245 (M^+). ^{1}H-NMR: 7.62—7.66 (3H, m, ArH-*m*, *p*), 8.04—8.07 (2H, m, ArH-*o*), 8.56 (1H, s, 2-H). UV $\lambda_{max}^{H_2O}$ nm: 261, 290 (sh), 340, 405.

5-Methylimidazo[4,5-*d*][1,3]thiazine-7(3*H*)-thione (7b) Lawesson reagent (4.90 g, 12.0 mmol) was added to a solution of **4b** (1.96 g, 10.0 mmol) in xylene (80 ml), and the reaction mixture was worked up as above to give **7b** (1.38 g, 76%), mp 276—277 °C (dec). MS *m/z*: 183 (M^+) HR-MS Calcd for $C_6H_5N_3S_2$: 182.9925. Found *m/z*: 182.9921. ^{1}H-NMR: 2.66 (3H, s, CH_3), 8.46 (1H, br s, 2-H), 13.86 (1H, br s, NH). UV $\lambda_{max}^{H_2O}$ nm: 270, 313, 383.

5-Benzylaminoimidazo[4,5-*d*][1,3]thiazine-7(3*H*)-thione (7c) Lawesson reagent (2.48 g, 6.4 mmol) was added to a solution of **4c** (885 mg, 3.1 mmol) in xylene (60 ml), and the reaction mixture was refluxed for 16 h, then allowed to cool. Yellow-colored precipitates were collected by filtration, and purified by silica gel column chromatography using 3% MeOH–$CHCl_3$ as an eluant to give **7c** (725 mg, 86%), mp 245–246 °C. MS *m/z*: 274 (M^+). HR-MS Calcd for $C_{12}H_{10}N_4S_2$: 274.0347. Found *m/z*: 274.0331. ^{1}H-NMR (20% DMSO-d_6–$CDCl_3$): 4.66 (2H, d, CH_2, J=4.95 Hz), 7.85 (1H, br s, 2-H), 7.28—7.35 (5H, m, ArH). UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon \times 10^3$): 238 (22.4), 300 (3.3), 412 (10.2). When the refluxing time was only 8 h, the reaction mixture gave **5c** (15%), **6** (64%) and **7c** (9%) after purification by silica gel column chromatography using 3% MeOH–$CHCl_3$ as an eluant. **5c**: mp 198—200 °C. MS *m/z*: 304 (M^+). ^{1}H-NMR (10% DMSO-d_6–$CDCl_3$): 1.44 (3H, t, CH_3, J=7.14 Hz), 4.39 (2H, q, CH_2, J=7.15 Hz), 4.96 (2H, d, $ArCH_2$, J=5.49 Hz), 7.24—7.41 (6H, m, ArH and 2-H), 9.02 (1H, s $NHCH_2$), 11.00 (1H, s, NHC=S), 12.71 (1H, br s, 1H, NH). UV λ_{max}^{MeOH} nm: 252, 293. **6**: mp 147—148 °C. MS *m/z*: 320 (M^+). ^{1}H-NMR ($CDCl_3$): 1.52 (3H, br t, CH_3), 4.67 (2H, q, CH_2, J=7.14 Hz), 4.96 (2H, d, $ArCH_2$, J=5.49 Hz), 7.26—7.41 (6H, m, ArH and 2-H), 9.86 (1H, br s, $NHCH_2$), 10.89 (1H, br s, NHC=S).

5-Aminoimidazo[4,5-*d*][1,3]thiazine-7-(3*H*)-thione (7d) a) Compound **7c** (282 mg, 1.0 mmol) was added to cooled, concentrated H_2SO_4 (3 ml) at 0 °C, and the reaction mixture was kept overnight at 60 °C. After neutralization with aqueous NaOH solution, the reaction mixture was concentrated to dryness under reduced pressure. The residue was triturated with EtOH (100 ml) and salts were filtered off. The filtrate was evaporated and the residue was purified by silica gel column chromatography using 6% MeOH–$CHCl_3$ as an eluant to give **7d** (114 mg, 75%), mp > 300 °C. MS *m/z*: 184 (M^+). HR-MS Calcd for $C_5H_4N_4S_2$: 183.9877. Found *m/z*: 183.9862. ^{1}H-NMR: 8.11 (1H, s, 2-H), 8.27 (2H, s, NH_2). UV $\lambda_{max}^{H_2O}$: 232, 255, 290 (sh), 408. b) **6** (100 mg, 0.3 mmol) was added to concentrated H_2SO_4 (1 ml) at 0 °C and the reaction mixture was kept overnight at 60 °C. After work-up as above, the title compound (**7d**) was obtained (50 mg, 95%).

5-Phenylimidazo[4,5-*d*][1,3]thiazin-7-(3*H*)-one (8a) $KMnO_4$ (160 mg) was added slowly to a solution of **7a** (60 mg, 0.3 mmol) in acetone (2 ml) at 60 °C in a water bath until the color of the reaction mixture became violet, and the excess $KMnO_4$ was decomposed with MeOH. The solution was filtered, the filtrate was evaporated, and the residue was recrystallized from MeOH to give **8a** (12 mg, 21%), mp > 300 °C. MS *m/z*: 229 (M^+). ^{1}H-NMR: 7.55—7.62 (3H, q, ArH-*m*, *p*), 8.00—8.03 (2H, t, ArH-*o*), 8.33 (1H, s, 2-H), 13.90 (1H, br s, NH). UV λ_{max}^{MeOH} nm: 280 (sh), 300 (sh), 330. IR (KBr): 1676 cm^{-1} (C=O).

5-Methylimidazo[4,5-*d*][1,3]thiazin-7(3*H*)-one (8b) $KMnO_4$ (172 mg)

was added slowly to a solution of **7b** (67 mg, 0.4 mmol) in acetone (2 ml) at 60 °C in a water bath, and the reaction mixture was worked up as above to give **8b** (29 mg, 47%, viscous oil). MS *m/z*: 167 (M^+). ^{1}H-NMR: 2.60 (3H, s, CH_3), 7.96 (1H, s, 2-H). UV λ_{max}^{MeOH} nm: 265 (sh), 302. IR (KBr): 1688 cm^{-1} (C=O).

5-Benzylaminoimidazo[4,5-*d*][1,3]thiazin-7(3*H*)-one (8c) $KMnO_4$ (53 mg) was added slowly to a solution of **7c** (37 mg, 0.14 mmol) in acetone (20 ml) at room temperature, and the reaction mixture was kept for 1.5 h, then concentrated. The residue was purified by silica gel column chromatography using 5% MeOH–$CHCl_3$ as an eluant to give **8c** (5 mg, 14%), mp 195 °C. MS *m/z*: 258 (M^+). HR-MS Calcd for $C_{12}H_{10}N_4OS$ 258.0575. Found *m/z*: 258.0565. ^{1}H-NMR: 4.57 (2H, d, $ArCH_2$, J=5.49 Hz), 7.21—7.35(5H, m, ArH), 7.73 (1H, s, 2-H), 9.07 (1H, t, CH_2NH), 12.83 (1H, s, NH). UV $\lambda_{max}^{H_2O}$ nm: 220 (sh), 264, 332.

5-Aminoimidazo[4,5-*d*][1,3]thiazin-7(3*H*)-one (8d) a) **5d** (50 mg, 0.23 mmol) was added to concentrated H_2SO_4 (0.5 ml) at 0 °C and the solution was kept at 60 °C for 2 d. After cooling, the reaction mixture was poured onto ice, then neutralized with aqueous NaOH solution and evaporated. The residue was purified by silica gel column chromatography using 5% MeOH–$CHCl_3$ as an eluant to give **8d** (3 mg, 8%), mp > 280 °C. MS *m/z*: 168 (M^+). ^{1}H-NMR: 7.72 (1H, s, 2-H), 7.91 (2H, s, NH_2), 12.66 (1H, br s, NH). UV $\lambda_{max}^{H_2O}$ nm: 275, 330. IR (KBr): 1643 cm^{-1} (C=O). b) **5e** (100 mg, 0.31 mmol) was added to concentrated H_2SO_4 (1 ml) at 0 °C and the reaction mixture was kept overnight at 60 °C. Work-up as above gave **8d** (12 mg, 23%).

3-(2-Acetoxyethoxymethyl)-5-phenylimidazo[4,5-*d*][1,3]thiazine-7(3*H*)-thione (9a) and 1-(2-Acetoxyethoxymethyl)-5-phenylimidazo-[4,5-*d*][1,3]-thiazine-7-(1*H*)-thione (10a) A mixture of **7a** (167 mg, 0.68 mmol) and 2-oxa-1,4-butanediol diacetate (1 ml, 2.5 mmol) was fused at 150 °C for 20 min. The reaction mixture was purified by silica gel column chromatography using $CHCl_3$ as an eluant to give **9a** (406 mg, 55%) and **10a** (276 mg, 38%). **9a**: mp 100—105 °C. MS *m/z*: 361 (M^+). ^{1}H-NMR ($CDCl_3$): 2.05 (3H, s, $COCH_3$), 3.80–3.83 (2H, m, 4′-CH_2), 4.21—4.25 (2H, m, 3′-CH_2), 5.73 (2H, s, 1′-CH_2), 7.51—7.64 (3H, m, ArH-*m*, *p*), 8.02—8.05 (2H, m, ArH-*o*), 8.09 (1H, br s, 2-H). ^{13}C-NMR ($CDCl_3$): 73.5 (C-1′), 134.6 (C-7a), 141.9 (C-2), 142.0 (C-3a). UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon \times 10^3$): 262 (33.49), 339 (12.77), 405 (11.56). *Anal.* Calcd for $C_{16}H_{15}N_3O_3S_2$: C, 53.17; H, 4.18; N, 11.63; S, 17.74. Found: C, 52.93; H, 4.17; N, 11.61; S, 17.50. **10a**: mp 95–100 °C. MS *m/z*: 361 (M^+). ^{1}H-NMR ($CDCl_3$): 2.08 (3H, s, $COCH_3$), 3.87—3.90 (2H, m, 4′-CH_2), 4.22—4.26 (2H, m, 3′-CH_2), 6.27 (2H, s, 1′-CH_2), 7.58—7.59 (3H, m, ArH-*m*, *p*), 8.09—8.12 (2H, m, ArH-*o*), 8.29 (1H, br s, 2-H). ^{13}C-NMR ($CDCl_3$): 77.7 (C-1′), 125.0 (C-7a), 153.3 (C-3a), 146.7 (C-2). UV λ_{max}^{MeOH} nm ($\varepsilon \times 10^3$): 410, 340, 280. *Anal.* Calcd for $C_{16}H_{15}N_3O_3S_2$: C, 53.17; H, 4.18; N, 11.63; S, 17.74. Found: C, 52.93; H, 4.17; N, 11.61; S, 17.50.

3-(2-Hydroxyethoxymethyl)-5-phenylimidazo[4,5-*d*][1,3]thiazine-7(3*H*)-thione (11a) A catalytic amount of sodium methoxide was added to a solution of **9a** (90 mg, 0.25 mmol) in absolute MeOH (30 ml), and the reaction mixture was kept for 5 min at room temperature. The precipitates were collected by filtration and washed with EtOAc to give **11a** (79 mg, 99%), mp 209—210 °C. MS *m/z*: 319. ^{1}H-NMR: 3.61—3.71 (4H, m, 3′ and 4′-CH_2), 4.61 (1H, t, OH), 5.80 (2H, s, 1′-CH_2), 7.53—7.64 (3H, m, ArH-*m*, *p*), 8.06—8.09 (2H, m, ArH-*o*), 8.40 (1H, s, 2-H). UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon \times 10^3$): 261 (12.10), 338 (4.59), 403 (4.24).

3-(2-Acetoxyethoxymethyl)-5-methylimidazo[4,5-*d*][1,3]thiazine-7(3*H*)-thione (9b) A mixture of **7b** (120 mg, 0.66 mmol) and 2-oxa-1,4-butanediol diacetate (1 ml, 2.5 mmol) was fused at 150 °C for 20 min. The reaction mixture was purified by silica gel column chromatography using 0.2% MeOH–$CHCl_3$ as an eluant to give **9b** (194 mg, 94%), mp 80—81 °C. MS *m/z*: 299 (M^+). ^{1}H-NMR ($CDCl_3$): 2.11 (3H, s, $COCH_3$), 2.65 (3H, s, CH_3), 3.75 (2H, m, 4′-CH_2), 4.21 (2H, m, 3′-CH_2), 5.62 (2H, s, 1′-CH_2), 8.02 (1H, s, 2-H). UV λ_{max}^{MeOH} nm: 222, 261, 318, 380. *Anal.* Calcd for $C_{11}H_{13}N_3O_3S_2$: C, 44.10; H, 4.38; N, 14.04; S, 21.42. Found: C, 43.99; H, 4.33; N, 13.97; S, 21.46.

3-(2-Hydroxyethoxymethyl)-5-methylimidazo[4,5-*d*][1,3]thiazine-7(3*H*)-thione (11b) A catalytic amount of sodium methoxide was added to a solution of **9b** (100 mg, 0.3 mmol) in absolute MeOH (3 ml), and the reaction mixture was kept for 5 min at room temperature. The precipitates were collected by filtration and washed with EtOAc to give **8b** (48 mg, 56%), mp 217—217.5 °C. MS *m/z*: 257 (M^+). ^{1}H-NMR: 2.68 (2H, s, CH_3), 3.46—3.66 (4H, m, 3′ and 4′-CH_2), 4.65 (1H, br t, OH), 5.62 (2H, s, 1′-CH_2), 8.49 (1H, s, 2-H). UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon \times 10^3$): 224 (14.71), 262 (10.43), 318 (6.85), 378 (10.62).

3-(2-Acetoxyethoxymethyl)-5-benzylaminoimidazo[4,5-*d*][1,3]-thiazine-7(3*H*)-thione (9c) A mixture of **7c** (50 mg, 0.2 mmol) and 2-oxa-1,4-butanediol diacetate (1 ml) was fused at 160 °C for 20 min. The reaction mixture was worked up as above to give **9c** (40 mg, 56%), mp 147—148 °C. MS *m/z*: 390 (M^+). HR-MS Calcd for $C_{17}H_{18}N_4O_3S_2$ 390.0802. Found *m/z*: 390.0801. ^{1}H-NMR ($CDCl_3$): 2.02 (3H, s, $COCH_3$), 3.51 (2H, m, 4′-CH_2), 4.04 (2H, m, 3′-CH_2), 4.65 (2H, d, $ArCH_2$, J=5.49 Hz), 5.38 (2H, s, 1′-CH_2), 7.32—7.33 (5H, m, ArH), 7.55 (1H, s, 2-H), 8.86 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$): 46.1 ($ArCH_2$), 62.5 (C-4′), 67.2 (C-3′), 72.5 (C-1′), 131.1 (C-7a), 139.4 (C-2), 146.8 (C-3a), 166.8 (C-5), 214.8 (C=S). UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon \times 10^3$): 240 (28.92), 296 (8.23), 410 (24.86).

5-Benzylamino-3-(2-hydroxyethoxymethyl)imidazo[4,5-*d*][1,3]thiazine-7-(3*H*)-thione (11c) A catalytic amount of sodium methoxide was added to a solution of **9c** (0.01 g, 0.03 mmol) in absolute MeOH (8 ml), and the reaction mixture was kept for 90 min at 0 °C. It was neutralized with 1.4% AcOH and evaporated. The residue was purified by silica gel column chromatography using 1% MeOH–$CHCl_3$ as an eluant to give **11c** (3.8 mg, 43%), mp 173—174 °C. MS *m/z*: 348 (M^+). HR-MS Calcd for $C_{15}H_{16}N_4O_2S_2$ 348.0715. Found *m/z*: 348.0704. ^{1}H-NMR: 3.42—3.47 (4H, m, 3′ and 4′-CH_2), 4.63 (2H, m, $ArCH_2$), 5.43 (2H, s, 1′-CH_2), 7.25—7.39 (5H, m, ArH), 8.25 (1H, s, 2-H), 9.71 (1H, br NH). UV λ_{max}^{MeOH} nm: 253, 296, 390 (sh), 410.

3-(2-Acetoxyethoxymethyl)-5-aminoimidazo[4,5-*d*][1,3]thiazine-7(3*H*)-thione (9d) A solution of **7d** (90 mg, 0.49 mmol) in 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (20 ml) and CH_3CN (5 ml) was refluxed in the presence of a catalytic amount of $(NH_4)_2SO_4$ for 3 h. The reaction mixture was concentrated under vacuum with exclusion of moisture and the silylated base was treated with 2-acetoxyethoxymethyl chloride (149 mg, 1.0 mmol) in the presence of CsI (141 mg, 0.5 mmol) in CH_3CN (25 ml) under reflux for 4 h. After cooling of the reaction mixture, pyridine (2 ml) was added and the whole was evaporated. The residue was purified by silica gel column chromatography using $CHCl_3$ to give **9d** (27 mg, 18%) and **10d** (23 mg, 15%). **9d**: mp 170—171 °C. MS *m/z*: 300 (M^+). HR-MS Calcd for $C_{10}H_{12}N_4O_3S_2$: 300.0351. Found *m/z*: 300.0321. ^{1}H-NMR: 2.03 (3H, s, $COCH_3$), 3.75—3.79 (2H, m, 4′-CH_2), 4.16—4.20 (2H, m, 3′-CH_2), 5.48 (2H, m, 1′-CH_2), 8.04 (1H, s, 2-H), 8.14 (1H, s, NH_2). ^{13}C-NMR: 20.7 (CH_3), 62.7 (C-4′), 67.4 (C-3′), 72.9 (C-1′), 129.5 (C-7a), 40.2 (C-2), 147.5 (C-3a). UV λ_{max}^{MeOH} nm ($\varepsilon \times 10^3$): 232, 251, 295, 407. **10d**: mp 163—165 °C. MS *m/z*: 300 (M^+). HR-MS Found *m/z*: 300.0372. ^{1}H-NMR: 2.04 (3H, s, $COCH_3$), 3.83—3.85 (2H, m, 4′-CH_2), 4.16—4.18 (2H, m, 3′-CH_2), 6.20 (2H, s, 1′-CH_2), 7.88 (2H, s, NH_2), 8.28 (1H, s, 2-H). ^{13}C-NMR: 76.9 (C-1′), 122.2 (C-7a), 148.3 (C-2), 157.8 (C-3a). UV λ_{max}^{MeOH} nm: 229, 252, 320 (sh), 418.

5-Amino-(2-hydroxyethoxymethyl)imidazo[4,5-*d*][1,3]thiazine-7(3*H*)-thione (11d) A catalytic amount of sodium methoxide was added to a solution of **9d** (12.5 mg, 0.04 mmol) in absolute MeOH (10 ml) at 0 °C. The reaction mixture was kept for 1 h at 0 °C and worked up as above give **11b** (11 mg, 99%), mp 211 °C. MS *m/z*: 258 (M^+). HR-MS Calcd for $C_8H_{10}N_4O_2S_2$: 258.0245. Found *m/z*: 258.0240. ^{1}H-NMR: 3.50 (4H, m, 3′ and 4′-CH_2), 4.66 (1H, t, OH), 5.39 (2H, s, 1′-CH_2), 8.12 (1H, s, 2-H), 8.62 (2H, s, NH_2). UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon \times 10^3$): 233 (2.2), 254 (16.5), 296 (6.8), 406 (22.9).

3-(2-Hydroxyethoxymethyl)-5-phenylimidazo[4,5-*d*][1,3]thiazin-7(3*H*)-one (12a) $KMnO_4$ (57 mg) was added gradually to a solution of **9a** (40 mg, 0.1 mmol) in acetone (8 ml) at room temperature until the color of the reaction mixture changed to violet. Silica gel column chromatography of the mixture using 5% MeOH–$CHCl_3$ gave **12a** (31 mg, 81%), mp 144—145 °C. MS *m/z*: 345 (M^+). ^{1}H-NMR ($CDCl_3$): 2.05 (3H, s, $COCH_3$), 3.79—3.83 (2H, t, 4′-CH_2), 4.20—4.24 (2H, t, 3′-CH_2), 5.74 (2H, s, 1′-CH_2), 7.26—7.59 (3H, m, ArH-*m*, *p*), 8.00—8.02 (2H, t, ArH-*o*), 8.05 (1H, s, 2-H). UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon \times 10^3$): 228 (25.18), 239 (sh) (20.80), 270 (10.44), 337 (12.80). *Anal.* Calcd for $C_{16}H_{15}O_4N_3S$: C, 55.64; H, 4.38; N, 12.17; S, 9.28. Found: C, 55.48; H, 4.36; N, 12.27, S; 9.36.

3-(2-Acetoxyethoxymethyl)-5-methylimidazo[4,5-*d*][1,3]thiazin-7(3*H*)-one (12b) $KMnO_4$ (325 mg) was added gradually to a solution of **9b** (100 mg, 0.3 mmol) in acetone (2 ml) at room temperature until the color of the reaction mixture changed to violet. Work-up as above gave **12b** as an amorphous powder (80 mg, 85%). mp 217—217.5 °C. MS *m/z*: 283 (M^+). ^{1}H-NMR ($CDCl_3$): 2.05 (3H, s, $COCH_3$), 2.71 (3H, s, CH_3), 3.77 (2H, m, 4′-CH_2), 4.21 (2H, m, 3′-CH_2), 5.64 (2H, s, 1′-CH_2), 7.94 (1H, s, 2-H). UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon \times 10^3$): 303 (4.08), 266 (4.50), 258 (4.41), 228 (23.70).

3-(2-Acetoxyethoxymethyl)-5-benzylaminoimidazo[4,5-*d*][1,3]thiazin-7(3*H*)-one (12c) $KMnO_4$ (58 mg) was added gradually to a solution of **9c** (0.25 g, 0.06 mmol) in acetone (8 ml) at room temperature until the color of the reaction mixture changed to violet. Work-up as above gave **12c** (11 mg, 46%), mp 146—148 °C. MS *m/z*: 374 (M^+). HR-MS Calcd for $C_{17}H_{18}N_4O_4S$: 374.1049. Found *m/z*: 374.1030. ^{1}H-NMR ($CDCl_3$): 2.03

(3H, s, $COCH_3$), 3.56 (2H, t, 4′-CH_2), 4.09 (2H, q, 3′-CH_2), 4.69 (2H, d, $ArCH_2$, $J=5.5$ Hz), 5.42 (2H, s, 1′-CH_2), 7.26—7.37 (5H, m, ArH), 7.67 (1H, s, 2-H). UV λ_{max}^{MeOH} nm: 264, 272 (sh), 330.

5-Benzylamino-3-(2-hydroxyethoxymethyl)imidazo[4,5-*d*][1,3]thiazin-7(3*H*)-one (3c) A catalytic amount of sodium methoxide was added to a solution of **12c** (0.01 g, 0.03 mmol) in absolute MeOH (6 ml) at 0 °C, and the reaction mixture was kept at 0 °C for 2 h. It was neutralized with 1.5% aqueous AcOH solution and evaporated to dryness. The residue was purified by silica gel column chromatography using 2% MeOH–$CHCl_3$ to give **3c** (6 mg, 68%) as a viscous oil. MS *m/z*: 332 (M^+). HR-MS Calcd for $C_{15}H_{16}N_4O_3S$: 332.0943. Found *m/z*: 332.0917. ^{1}H-NMR: 3.51 (2H, d, 4′-CH_2), 3.59 (2H, d, 3′-CH_2), 4.67 (2H, d, $ArCH_2$, $J=5.49$ Hz), 5.46 (2H, s, 1′-CH_2), 7.26 (3H, s, ArH-*m*, *p*), 7.33—7.38 (2H, q, ArH-*o*), 7.67 (1H, s, 2-H). UV $\lambda_{max}^{H_2O}$ nm: 266, 275 (sh), 332.

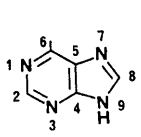
3-(2-Acetoxyethoxymethyl)-5-Aminoimidazo[4,5-*d*][1,3]thiazin-7(3*H*)-one (12d) $KMnO_4$ (47 mg) was added gradually to a solution of **9d** (0.014 g, 0.05 mmol) in acetone (3 ml) at room temperature until the color of the reaction mixture changed to violet. Work-up as above gave **12d** (11 mg, 83%), mp 112—113 °C. MS *m/z*: 284 (M^+). HR-MS calcd for $C_{10}H_{12}N_4O_4$: 284.0579. Found *m/z*: 284.0565. ^{1}H-NMR: 1.66 (3H, s, $COCH_3$), 3.67–3.71 (2H, m, 4′-CH_2), 4.07—4.10 (2H, m, 3′-CH_2), 5.40 (2H, s, 1′-CH_2), 7.97 (1H, s, 2-H), 8.33 (2H, s, NH_2). UV $\lambda_{max}^{H_2O}$ nm: 265, 274 (Sh), 322.

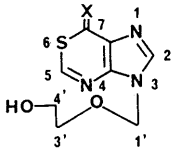
5-Amino-3-(2-hydroxyethoxymethyl)imidazo[4,5-*d*][1,3]thiazin-7(3*H*)-one (3d) A catalytic amount of sodium methoxide was added to a solution of **12d** (0.009 g, 0.03 mmol) in absolute MeOH (4 ml) at 0 °C, and the reaction mixture was kept for 40 min in an ice bath. The reaction mixture was neutralized with 1.5% aqueous AcOH solution and evaporated to dryness. The residue was purified by silica gel column chromatography using 8% MeOH–$CHCl_3$ as an eluant to give **3d** as colorless crystals (5 mg, 60%), mp 204—205 °C. MS *m/z*: 242 (M^+). HR-MS Calcd for $C_8H_{10}N_4O_3S$: 242.0473. Found *m/z*: 242.0480. ^{1}H-NMR: 3.51 (4H, s, 3′ and 4′-CH_2), 4.67 (1H, br s, OH), 5.39 (2H, s, 1′-CH_2), 7.96 (1H, s, 2-H), 8.31 (2H, s, NH_2). UV $\lambda_{max}^{H_2O}$ nm ($\varepsilon \times 10^3$): 265 (11.5), 326 (9.3).

Acknowledgement The authors are indebted to the staff of the Center for Instrumental Analysis of Hokkaido University for elemental analysis and measurements of MS and NMR spectra.

References and Notes

1) Paper III in this series, H. Matsumoto, C. Kaneko, T. Mori, and Y. Mizuno, *J. Heterocycl. Chem.*, **27**, 1307 (1990).
2) H. J. Schaeffer, L. M. Beauchamp, G. B. Miranda, D. J. Bauer, and P. Collins, *Nature* (London), **272**, 583 (1978).
3) K. O. Smith, K. S. Galloway, W. L. Kennell, K. K. Ogilvie, and R. K. Radatus, *Antimicrob. Agents Chemother.*, **22**, 55 (1982).
4) N. K. Saxana, L. A. Coleman, J. C. Drach, and L. B. Townsend, *J. Med. Chem.*, **33**, 1980 (1990); J. S. Pudlo, M. R. Nassiri, E. R. Kern, L. L. Wotring, J. C. Drach, and L. B. Townsend, *ibid.*, **33**, 1984 (1980).
5) H. Matsumoto, C. Kaneko, T. Mori, and Y. Mizuno, *Chem. Pharm. Bull.*, **37**, 229 (1989).
6) The numberings of the purine ring, imidazo [4,5-*d*] [1,3]thiazine and the acyclic side chain are as follows:





7) K. Klausen and S. O. Lawesson, *Bull. Soc. Chem. Belg.*, **88**, 305 (1979).
8) Y. H. Kim, J. Y. Kim, and C. H. Lee, *Chem. Lett.*, **1988**, 1045.
9) A. Parkin and M. R. Harnden, *J. Heterocycl. Chem.*, **19**, 33 (1982).
10) M. F. Summers, L. G. Marzilli, and A. Bax, *J. Am. Chem. Soc.*, **108**, 4285, (1985).
11) G. Zemplen and E. Pacsu, *Ber.*, **62**, 1613 (1929).