Synthesis and Cyclic AMP Phosphodiesterase 4 Isoenzyme Inhibitory Activity of Heterocycle Condensed Purines

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To reverse the adverse reactions of alkylxanthines and to develop novel inhibitors of cyclic AMP phosphodiesterase 4 (PDE4), a series of heterocycle [*a*]-, [*b*]-, [*c*,*d*]-, and [*i*]-condensed purines were designed and synthesized. Although all compounds did not display PDE1 and PDE3 inhibitory activities, several heterocycle [*i*]-condensed purines strongly inhibited PDE4. Especially, *dl*-3,4-dipropyl-8-methyl-4,5,7,8-tetrahydro-1*H*-imidazo[2,1-*i*]purin-5-one (*dl*-7c) exhibited comparable PDE4 inhibitory activity (IC_{50}=1.9 μM) to rolipram and denbufylline (DBF).

Key words PDE4 inhibitor; heterocycle condensed purine; tetrahydro-imidazo[2,1-*i*]purine

cAMP-phosphodiesterase 4 (PDE4) inhibitors have relaxation effects on bronchochial smooth muscle and anti-inflammatory activities, and have attracted attention as a remedy for asthmatic patients.[1,2] Our investigations on the structure–activity relationships of alkylxanthines as PDE4 inhibitors have shown that 1-, 3- and 7-substituents on the xanthine nucleus are important for PDE4 inhibitory activity.[3—5] Although denbufylline (DBF) and XT-44, among compounds prepared by us, were effective against osteoporosis animal models,[6,7] two compounds caused emesis as an undesirable side effect, comparable to several prototype PDE4 inhibitors such as rolipram and its analogs.[8]

Previous work in this series has shown that heterocycle condensed purines, namely tetrahydro- imidazo[2,1-*i*]purine (**1**)[9] and (**2**),[10] were effective for reducing the side effects of xanthines, and it became desirable to determine the effect of other condensed purines on PDE4 inhibitory activity.

As a continuation of studies on [*g*,*h*]-condensed purines (**3**),[11] we have designed and synthesized a series of heterocycles [*a*]- (**4**), [*b*]- (**5**), [*c*,*d*]- (**6**), and [*i*]-condensed purines (**7**, **8**) fixing the propyl group[12] as a substituent on the imidazole *N* atom, and examined their *in vitro* effects on PDE isoenzymes.

Chemistry

[*a*]-Condensed purines (**4**) were prepared according to the method of Nagamatsu *et al*.[13] Treatment of **9** with propanal and sodium cyanoborohydride gave 5-(propylamino)imidazole (**10**), which was treated with benzoylisothiocyanate to give **11**. Cyclization of **11** in aq. NaOH yielded **12**. Successive *S*-methylation of **12**, treatment of **13** with aminoalcohol, and ring closure of **14** with thionyl chloride gave the [*a*]-condensed purines (**4a**, **b**). *N*-Propylation of **4a**, **b** afforded **4c** and **4d**, respectivery (Chart 3).

[*b*]-Condensed purines (**5**) were prepared according to the method of Ahn *et al*.[14] 7-Benzyl-1-propylxanthine (**17**), which was obtained from regioselective benzylation[15] of 5,6-diamino-3-propyluracil (**15**)[16] and ring closure of **16** with diethoxymethyl acetate, was treated with excess phosphorus oxychloride to give 7-benzyl-2-chloropurine (**18**). By treatment of **18** with aminoalcohols and subsequent ring closure of **19a**, **b** with thionyl chloride, the corresponding [*b*]-condensed purines (**20a**, **b**) were obtained. Debenzylation of **20** by catalytic hydrogenation afforded the desired **5a**, **b**, which were alkylated with *n*-propyl bromide in the presence of potassium carbonate to give **5c**, **d** (Chart 4).

[*c*,*d*]-Condensed purines (**6**) were prepared according to the method of Simo *et al*.[17] Catalytic hydrogenation of nitropyrimidines (**21a**, **b**)[18] gave diamines (**22a**, **b**), which were treated with ethyl orthoformate without purification to give the [*c*,*d*]-condensed purines (**6a**, **b**), respectively. *N*-propylation of **6a**, **b** with *n*-propyl bromide in the presence of potassium carbonate yielded **6c**, **d** (Chart 5).

Substituted [*i*]-condensed purines (**7**, **8**) were prepared according to our reported method.[9] 6-(Hydroxyethylamino)-purines (*dl*-**24**, *dl*-**25**, *dl*-**27** and *dl*-**28**) were obtained respec-

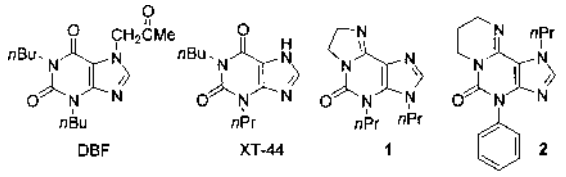

Chart 1

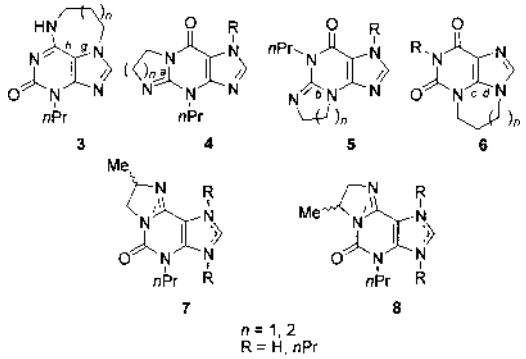

Chart 2

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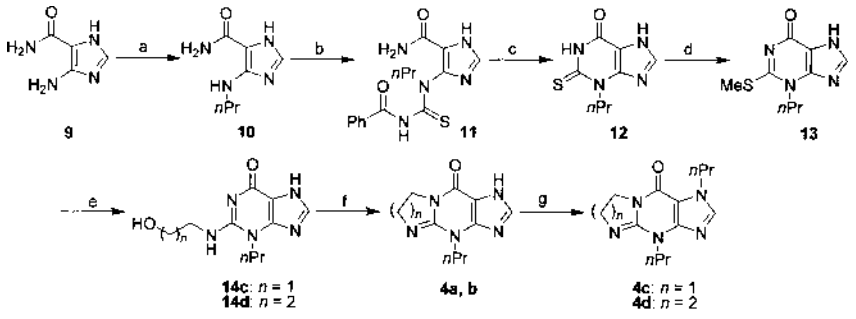
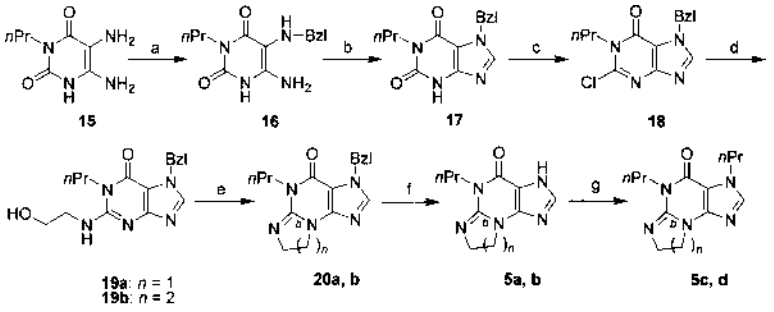


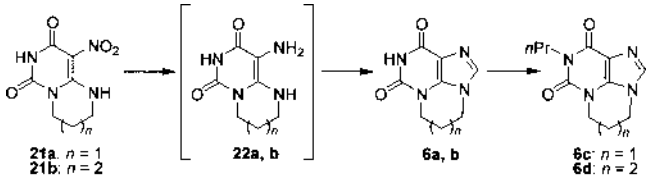
Reagents: (a) EtCHO, $NaBH_3CN$, MeOH; (b) PhCONCS, CH_2Cl_2; (c) 1M NaOH; (d) Me_2SO_4, 2M NaOH; (e) 2-amino-1-ethanol or 3-amino-1-propanol, pyridine, (f) $SOCl_2$, CH_2Cl_2; (g) nPrBr, K_2CO_3, DMF

Chart 3



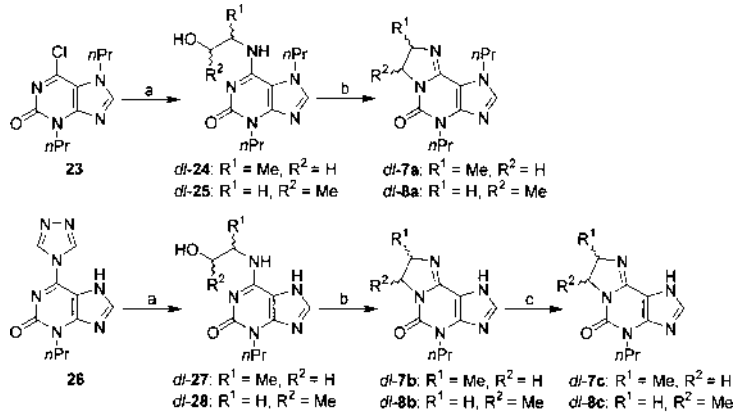
Reagents: (a) 1) PhCHO, H_2O 2)Raney-Ni / H_2; (b) $MeCO_2CH(OEt)_2$, DMF; (c) $POCl_3$; (d) 2-amino-1-ethanol or 3-amino-1-propanol, pyridine; (e) $SOCl_2$, CH_2Cl_2; (f) $Pd(OH)_2$-C / H_2, MeOH; (g) *n*PrBr, K_2CO_3, DMF

Chart 4



Reagents: (a) Pd-C, H_2 / H_2O; (b) $HC(OEt)_3$, DMF; (c) nPrBr, K_2CO_3, DMF

Chart 5



Reagents: (a) *dl*-1-amino-2-propanol or *dl*-2-amino-1-propanol, pyridine. (b) MsCl, Et_3N, DMF; (c) *n*PrBr, K_2CO_3, DMF

Chart 6

tively from reaction between 6-chloro-3,7-dipropylxanthine (**23**) or 3-propyl-6-(1,2,4-triazol-4-yl)purine (**26**) with each of *dl*-1-amino-2-propanol and *dl*-2-amino-1-propanol. *dl*-**24**, *dl*-**25**, *dl*-**27** and *dl*-**28** were reacted with methanesulfonyl chloride in the presence of triethylamine to give *dl*-**7a**, *dl*-**8a**, *dl*-**7b** and *dl*-**8b**, respectively. *N*-Propylation of *dl*-**7b** and *dl*-**8b** with *n*-propyl bromide in the presence potassium carbonate afforded *dl*-**7c** and *dl*-**8c**, respectively (Chart 6).

Results and Discussion

The inhibitory activities of the heterocycle condensed purines (**4**—**8**) against PDE1 and PDE4 isoenzymes from guinea-pig brain and PDE3 from guinea-pig heart were measured according to the published methods.[9] The results are shown in Table 1 together with the PDE inhibitory activities of **1**, **2**, **3**, XT-44, DBF and rolipram, reported already.[19]

All newly prepared condensed purines showed no or only weak inhibitory activities against PDE1 and PDE3 isoenzymes. Against the PDE4 isoenzyme, the conclusions shown below were drawn.

1. The PDE4 inhibitory activities of heterocycle [*a*]- (**4**), [*b*]- (**5**), [*c*,*d*]- (**6**) and [*g*,*h*]-condensed purines (**3**) were weak. Compounds **4a**, **4c**, **5a** and **5b** inhibited selectively PDE4, but were weak compared with the [*i*]-condensed purines (**1**, **2**, **7**, **8**).

2. All of the heterocycle fused purines (**4**, **5**, **7**, **8**), except **6**, substituted with a propyl group at the *N*-position of the imidazole ring inhibited PDE4 more strongly than the corresponding unsubstituted compounds. **4c**, **4d** *vs.* **4a**, **4b**; **5c**, **5d** *vs.* **5a**, **5b**; *dl*-**7a**, *dl*-**7c** *vs*. *dl*-**7b**; *dl*-**8a**, *dl*-**8c** *vs.* *dl*-**8b**.

3. *N*-propyl substituted [*i*]-condensed purines (*dl*-**7a**, **c** and *dl*-**8a**, **c**) having a methyl group at the 7- or 8-position, although they caused a decline in selectivity, exert more influence on the PDE4 inhibitory activities than **1** and **2**.

In conclusion, *dl*-3,4-dipropyl-8-methyl-4,5,7,8-dihydro-1*H*-imidazo[2,1-*i*]purine-5-one (*dl*-**7c**) exhibited comparable PDE4 inhibitory activity to the known PDE4 inhibitors, rolipram and DBF. An earlier paper[9] has shown that the intramolecular interaction between the alkyl group at the 1-position and the carbonyl group at the 6-position of the xanthine skeleton may be important to elicit selectivity. This observation also suggests that the dihydroimidazole ring moiety of [*i*]-condensed purine may be important for PDE4 inhibitory activity. Currently, we are investigating the synthesis and PDE4 inhibitory activity of enantiomers of racemic heterocycle [*i*]-condensed purines (*dl*-**7a**, **c**).

Table 1. PDE Inhibitory Activities of Heterocycle Condensed Purines (**4**—**8**)

Compd. No.	IC_{50} (μM)		
	PDE1	PDE3	PDE4
4a	>100	>100	>100
4b	>100	>100	>100
4c	>100	>100	24
4d	>100	>100	70
5a	>100	>100	>100
5b	>100	>100	>100
5c	>100	>100	30
5d	>100	>100	58
6a	>100	>100	>100
6b	>100	>100	>100
6c	>100	>100	>100
6d	92	>100	>100
dl-**7a**	41	94	4.7
dl-**7b**	>100	>100	88
dl-**7c**	35	92	1.9
dl-**8a**	77	>100	19
dl-**8b**	>100	>100	>100
dl-**8c**	98	>100	15
1	>100	53	7.0
2	>100	>100	5.7
3a (n=1)	>100	>100	>100
3b (n=2)	>100	>100	>100
XT-44	>100	>100	5.7
DBF	78	>100	1.5
Rolipram	>100	>100	2.9

Data are mean of three experiments.

Experimental

Melting points were measured on a Yanagimoto micro melting point hot stage apparatus and are uncorrected. Infrared spectra (IR) were determined with a Horiba FT-720 spectrometer or a Hitachi 270-30 spectrometer. Mass spectra (MS) were measured with JEOL-DX300 instrument. Nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a JEOL EX 90A spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethyl silane as an internal standard. Microanalyses were performed in the Micro Analytical Laboratory of this faculty. Yield and physicochemical data for the heterocycles [*a*]- (**4**), [*b*]- (**5**), [*c*,*d*]- (**6**) and [*i*]-condensed purines (**7**, **8**) are summarized in Tables 2 and 3, respectively.

5-Propylaminoimidazole-4-carboxamide (10) To a solution of 5-aminoimidazole-4-carboxamide hydrochloride **9** (1.0 g, 6.2 mmol) in MeOH (10 ml) was added sodium cyanoborohydride (0.31 g, 4.9 mmol) and propional (0.43 g, 7.4 mmol), the reaction mixture was stirred for 24 h at room temperature (rt), then filtered, and evaporated *in vacuo*. The residue was chromatographed on silica gel using $CHCl_3$–MeOH (6 : 1) as an eluent to give **10** (0.66 g, 64%)), which was recrystallized from $CHCl_3$–MeOH. mp 155—156 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.88 (3H, t, J=7.1 Hz), 1.49 (2H, sext., J=7.1 Hz), 3.14 (2H, t, J=7.1 Hz), 6.00 (1H, br s), 6.64 (2H, br s), 7.20 (1H, s), 11.57 (1H, br s). IR (KBr) ν_{max}: 3413, 3351, 3302, 1651, 1631 cm^{-1}. *Anal.* Calcd for $C_7H_{12}N_4O$: C, 49.99; H, 7.19; N, 33.31. Found: C, 50.13; H, 7.40; N, 33.47.

5-[*N*-(Benzoylthiocarbamoyl)-*N*-propylamino]imidazole-4-carboxamide (11) To a suspension of **10** (0.66 g, 3.9 mmol) in CH_2Cl_2 (15 ml) was added dropwise benzoylisothiocyanate (0.77 g, 4.7 mmol), the reaction mixture was stirred for 6 h at rt. The precipitate was filtered and recrystallized from MeOH to give **11** (0.88 g, 68%). mp 185—186 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.82 (3H, t, J=7.2 Hz), 1.59 (2H, sext., J=7.2 Hz), 3.16 (2H, t, J=7.2 Hz), 6.00 (1H, br s), 6.64 (2H, br s), 7.52—8.00 (8H, m), 11.13 (1H, br s). IR (KBr) ν_{max}: 3344, 3284, 3234, 1658 cm^{-1}. *Anal.* Calcd for $C_{15}H_{17}N_5O_2S$: C, 54.37; H, 5.17; N, 21.13. Found: C, 54.33; H, 5.40; N, 20.97.

3-Propyl-2-thioxanthine (12) A solution of **11** (2.7 g, 8.2 mmol) in 1 M NaOH (30 ml) was heated to reflux for 3 h. The reaction mixture was neutralized with hydrochloric acid and the precipitate was collected by filtration and recrystallized from MeOH to give **12** (1.4 g, 79%). mp >290 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.91 (3H, t, J=7.2 Hz), 1.78 (2H, sext., J=7.2 Hz), 4.42 (2H, t, J=7.2 Hz), 8.16 (1H, s), 12.37 (1H, br s). IR (KBr) ν_{max}: 3471, 1654, 1620 cm^{-1}. *Anal.* Calcd for $C_8H_{10}N_4OS$: C, 45.70; H, 4.79; N, 26.65. Found: C, 45.88; H, 4.98; N, 26.69.

2-Methylthio-3-propylpurin-6-one (13) To a solution of **12** (0.64 g, 3.1 mmol) in 2 M NaOH (15 ml) was added dimethyl sulfate (0.46 g, 3.7 mmol), and the reaction mixture was stirred for 1 h at rt, then neutralized with acetic acid. The precipitate was collected by filtration and recrystallized from AcOEt–MeOH to give **13** (0.41 g, 60%). mp 257—258 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, t, J=7.2 Hz), 1.80 (2H, sext., J=7.2 Hz), 2.56 (3H, s), 4.18 (2H, t, J=7.2 Hz), 8.10 (1H, s), 13.50 (1H, br s). IR (KBr) ν_{max}: 3467, 1630, 1618 cm^{-1}. *Anal.* Calcd for $C_9H_{12}N_4OS$: C, 48.20; H, 5.39; N, 24.98. Found: C, 48.31; H, 5.18; N, 24.83.

2-(Hydroxyethylamino)-3-propylpurin-6-one (14a) and 2-(Hydroxypropylamino)-3-propylpurin-6-one (14b) A mixture of **13** (0.41 g, 1.8 mmol) and aminoalcohol (5 ml) in pyridine (10 ml) was heated at reflux overnight and then concentrated *in vacuo*. The residue was recrystallized from AcOEt–MeOH to give **14**.

14a: Yield: 83%. mp 253—254 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.88 (3H, t,

Table 2. Physicochemical Data for Heterocycle Condensed Purines (**4**— **8**)

Compd. No.	*n*	Yield[a] (%)	mp (°C)	Recryst. solv.	Formula	Analysis (%) Calcd (Found)		
						C	H	N
4a	2	70	256—257	AcOEt–MeOH	$C_{10}H_{13}N_5O$	54.78 (54.99)	5.98 (6.05)	31.94 (31.97)
4b	3	66	280—281	AcOEt–MeOH	$C_{11}H_{15}N_5O$	56.64 (56.91)	6.48 (6.59)	30.02 (30.56)
4c	2	63	108—109	Pet. Ether	$C_{13}H_{19}N_5O$	59.75 (59.90)	7.33 (7.31)	26.8 (26.89)
4d	3	62	105—106	Pet. Ether	$C_{14}H_{21}N_5O$	61.07 (61.21)	7.69 (7.78)	25.43 (25.53)
5a	2	87	242—243	AcOEt–MeOH	$C_{10}H_{13}N_5O$	54.78 (54.53)	5.98 (6.04)	31.94 (31.77)
5b	3	72	261—262	AcOEt–MeOH	$C_{11}H_{15}N_5O$	56.64 (56.45)	6.48 (6.47)	30.02 (29.97)
5c	2	63	60—61	Pet. Ether	$C_{13}H_{19}N_5O$	59.75 (57.91)	7.33 (7.32)	26.80 (25.85)
5d	3	30	Oil	—	$C_{14}H_{21}N_5O$		275.1746 257.1752[b]	
6a	3	51	>290	EtOH	$C_8H_8N_4O_2$	50.00 (49.81)	4.20 (4.18)	29.15 (28.99)
6b	4	56	>290	EtOH	$C_9H_{10}N_4O_2$	52.42 (52.33)	4.89 (4.95)	27.17 (26.95)
6c	3	45	248—249	AcOEt–MeOH	$C_{11}H_{14}N_4O_2$	56.40 (56.30)	6.02 (5.95)	23.92 (23.88)
6d	4	51	204—205	AcOEt–MeOH	$C_{12}H_{16}N_4O_2$	58.08 (57.92)	6.50 (6.34)	22.57 (22.56)
dl-**7a**	—	83	128—129	Pet. Ether	$C_{14}H_{21}N_5O$	61.07 (61.33)	7.69 (7.72)	25.43 (25.38)
dl-**7b**	—	71	248—249	AcOEt–MeOH	$C_{11}H_{15}N_5O$	56.64 (56.57)	6.48 (6.51)	30.02 (29.97)
dl-**7c**	—	85	111—112	Pet. Ether	$C_{14}H_{21}N_5O$	61.07 (61.33)	7.69 (7.84)	25.43 (25.50)
dl-**8a**	—	74	Oil	—	$C_{14}H_{21}N_5O$		275.1746 275.1744[b]	
dl-**8b**	—	77	272—273	AcOEt–MeOH	$C_{11}H_{15}N_5O$	56.64 (56.71)	6.48 (6.66)	30.02 (29.94)
dl-**8c**	—	83	Oil	—	$C_{14}H_{21}N_5O$		275.1746 275.1749[b]	

a) Yield of final step and for purified product. *b*) High resolution MS spectra data.

J=7.2 Hz), 1.70 (2H, sext., J=7.2 Hz), 3.38—3.62 (4H, m), 4.05 (2H, t, J=7.2 Hz), 4.90 (1H, br s), 6.97 (1H, br s), 7.84 (1H, s), 12.98 (1H, br s). IR (KBr) ν_{max}: 3448, 3288, 3164, 1630, 1606 cm^{-1}. *Anal.* Calcd for $C_{10}H_{15}N_5O_2$: C, 50.62; H, 6.37; N, 29.52. Found: C, 50.43; H, 6.40; N, 29.67.

14b: Yield: 71%. mp 194—195 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.88 (3H, t, J=7.2 Hz), 1.45—1.83 (4H, m), 4.04 (2H, t, J=7.3 Hz), 4.68 (1H, br s), 6.97 (1H, br s), 7.84 (1H, s), 12.69 (1H, br s). IR (KBr) ν_{max}: 3421, 3282, 3337, 1681 cm^{-1}. *Anal.* Calcd for $C_{11}H_{17}N_5O_2$: C, 52.58; H, 6.82; N, 27.87. Found: C, 52.73; H, 6.70; N, 27.77.

4-Propyl-4,5,6,7-tetrahydro-1*H*-imidazo[1,2-*a*]purin-9-one (4a) and 4-Propyl-4,5,6,7-tetrahydro-1*H*-pyrimido[1,2-*a*]purin-10-one (4b) A mixture of **14** (0.63 mmol) and $SOCl_2$ (0.23 g, 1.9 mmol) in CH_2Cl_2 (30 ml) was stirred for 24 h at rt. The reaction mixture was evaporated *in vacuo*, and the residue was chromatographed on silica gel using $CHCl_3$–MeOH (3 : 1) as an eluent to give **4**, which was recrystallized from AcOEt–MeOH.

1,4-Dipropyl-4,5,6,7-tetrahydro-1*H*-imidazo[1,2-*a*]purin-9-one (4c) and 1,4-Dipropyl-4,5,6,7-tetrahydro-1*H*-pyrimido[1,2-*a*]purin-10-one (4d) To a mixture of **4a** or **4b** (2.0 mmol) and anhydrous K_2CO_3 (0.41 g, 2.9 mmol) in *N*,*N*-dimethylformamide (DMF, 10 ml) was added propyl bromide (0.37 g, 3.0 mmol), and the mixture was stirred at rt for 10 h then concentrated *in vacuo*. The residue was chromatographed on silica gel using $CHCl_3$–MeOH (20 : 1) as an eluent to give **4c** and **4d**, which was recrystallized from petroleum ether.

6-Amino-5-(benzylamino)-3-propyluracil (16) A mixture of **15** (3.7 g, 20 mmol) and benzaldehyde (3.2 g, 30 mmol) in H_2O (150 ml) was stirred for 2 h at rt. The solution was cooled and the benzylidene was separated from the solution. The benzylidene was then hydrogenated over Raney-Ni (2.0 g) in 1 M NaOH (100 ml) at 3 atom for 12 h. After removal of catalyst and concentration the filtrate, then adjusting the pH to 6 with acetic acid, the crude product was recrystallized from EtOH to give **16** (4.10 g, 75%). mp 210—211 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.81 (3H, t, J=7.3 Hz), 1.48 (2H, sext., J=7.3 Hz), 3.65 (2H, t, J=7.3 Hz), 3.82 (2H, s), 5.73 (1H, br s), 7.20—7.38 (7H, s), 10.19 (1H, br s). IR (KBr) ν_{max}: 3332, 3268, 3196, 1698, 1662 cm^{-1}. *Anal.* Calcd for $C_{14}H_{18}N_4O_2$: C, 61.30; H, 6.61; N, 20.42. Found: C, 61.46; H, 6.60; N, 20.26.

7-Benzyl-1-propylxanthine (17) A mixture of **16** (2.7 g, 9.9 mmol) and diethoxymethyl acetate (6.4 g, 39 mmol) in DMF (15 ml) was stirred for 5 h at 80 °C. The reaction mixture was concentrated *in vacuo* and the residue was recrystallized from MeOH to give **17** (1.7 g, 61%). mp 177—178 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.84 (3H, t, J=7.3 Hz), 1.52 (2H, sext., J=7.3 Hz), 3.76 (2H, t, J=7.3 Hz), 5.45 (2H, s), 7.33 (5H, s), 8.15 (1H, s), 11.86 (1H, br s). IR (KBr) ν_{max}: 3504, 1709, 1657 cm^{-1}. *Anal.* Calcd for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71. Found: C, 63.41; H, 5.77; N, 19.67.

7-Benzyl-2-chloro-1-propylxanthine (18) A mixture of **17** (1.0 g, 3.7 mmol) and $POCl_3$ (20 ml) was refluxed for 5 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between $CHCl_3$ and sat. $NaHCO_3$ solution and the organic layer was washed with brine, dried and concentrated. The crude product was chromatographed on silica gel using $CHCl_3$–MeOH (20 : 1) as an eluent to give **18** (0.44 g, 40%), which was recrystallized from MeOH. mp 142—143 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.01 (3H, t, J=7.5 Hz), 1.80 (2H, sext., J= 7.5 Hz), 4.24 (2H, t, J=7.5 Hz), 5.61 (2H, s), 7.59 (5H, s), 7.84 (1H, s). IR (KBr) ν_{max}: 1707 cm^{-1}. MS *m*/*z*: 302 (M^+), 304 (M^++2). *Anal.* Calcd for $C_{15}H_{15}N_4OCl$: C, 59.51; H, 4.99; N, 18.51. Found: C, 59.52; H, 5.07; N, 18.53.

7-Benzyl-2-(hydroxyethylamino)-1-propylpurin-6-one (19a) and 7-

Table 3. ^{1}H-NMR Data of Heterocycle Condensed Purines (**4**—**8**)

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR
4a[a]	3458, 1722, 1639	0.95 (3H, t, *J*=7.2 Hz), 1.77 (2H, sext., *J*=7.2 Hz), 3.82—4.36 (6H, m), 8.24 (1H, s), 12.19 (1H, br s)
4b[a]	3471, 1716, 1597	0.93 (3H, t, *J*=7.2 Hz), 1.45 (2H, sext., *J*=7.2 Hz), 1.96 (2H, quint., *J*=5.6 Hz), 3.47 (2H, t, *J*=5.6 Hz), 3.95 (2H, t, *J*=5.6 Hz), 4.18 (2H, t, *J*=7.2 Hz), 8.13 (1H, s), 12.03 (1H, br s)
4c[b]	1682, 1637	0.94 (3H, t, *J*=7.3 Hz), 0.98 (3H, t, *J*=7.3 Hz), 1.64—2.12 (4H, m), 3.86—4.25 (8H, m), 7.39 (1H, s)
4d[b]	1676, 1633	0.94 (3H, t, *J*=7.3 Hz), 0.96 (3H, t, *J*=7.3 Hz), 1.49—2.01 (6H, m), 3.53 (2H, t, *J*=5.8 Hz), 3.84—4.25 (6H, m), 7.39 (1H, s)
5a[a]	3471, 1685, 1631	0.98 (3H, t, *J*=7.5 Hz), 1.85 (2H, sext., *J*=7.5 Hz), 3.97 (2H, t, *J*=7.5 Hz), 4.08 (2H, t, *J*=5.3 Hz), 4.10 (2H, t, *J*=5.3 Hz), 7.64 (1H, s)
5b[a]	3496, 1676, 1635	0.95 (3H, t, *J*=7.3 Hz), 1.69 (2H, sext., *J*=7.3 Hz), 1.94 (2H, quint., *J*=5.7 Hz), 3.60 (2H, t, *J*=5.7 Hz), 4.01 (2H, t, *J*=5.7 Hz), 4.03 (2H, t, *J*=7.3 Hz), 7.62 (1H, s)
5c[b]	1670, 1623	0.93 (3H, t, *J*=7.5 Hz), 0.96 (3H, t, *J*=7.5 Hz), 1.71 (2H, sext., *J*=7.5 Hz), 1.71 (2H, sext., *J*=7.5 Hz), 3.75—4.26 (8H, m), 7.38 (1H, s)
5d[b]	1687, 1633	0.94 (6H, t, *J*=7.3 Hz), 1.46—1.85 (4H, m), 3.58 (2H, t, *J*=5.7 Hz), 3.93 (2H, t, *J*=5.7 Hz), 4.04 (2H, t, *J*=7.3 Hz), 4.20 (2H, t, *J*=7.3 Hz), 7.37 (1H, s)
6a[a]	3448, 1694, 1634	2.15 (2H, quint., *J*=5.7 Hz), 3.78 (2H, t, *J*=5.7 Hz), 4.01 (2H, t, *J*=5.7 Hz), 7.72 (1H, s), 10.80 (1H, br s)
6b[a]	3423, 1682	1.89—2.16 (4H, m), 4.16 (2H, t, *J*=5.3Hz), 4.30 (2H, t, *J*=5.3Hz), 7.63 (1H, s), 10.93 (1H, br s)
6c[b]	1693, 1664	0.95 (3H, t, *J*=7.3 Hz), 1.67 (2H, sext., *J*=7.3 Hz), 2.34 (2H, quint., *J*=5.9 Hz), 3.97 (2H, t, *J*=7.3 Hz), 4.01 (2H, t, *J*=5.9 Hz), 4.18 (2H, t, *J*=5.9 Hz), 7.46 (1H, s)
6d[b]	1697, 1654	0.95 (3H, t, *J*=7.3 Hz), 1.69 (2H, sext., *J*=7.3 Hz), 2.04—2.27 (4H, m), 3.99 (2H, t, *J*=7.3 Hz), 4.25 (2H, t, *J*=5.4 Hz), 4.32 (2H, t, *J*=5.4 Hz), 7.36 (1H, s), 10.93 (1H, br s)
dl-**7a**[b]	1693, 1651	0.96 (3H, t, *J*=7.2 Hz), 0.97 (3H, t, *J*=7.2 Hz), 1.34 (3H, d, *J*=6.4 Hz), 1.52—2.04 (4H, m), 3.45 (1H, dd, *J*=7.1, 9.1 Hz), 3.86—4.42 (6H, m), 7.43 (1H, s)
dl-**7b**[a]	3423, 1708, 1664	0.87 (3H, t, *J*=7.3 Hz), 1.30 (3H, d, *J*=5.9 Hz), 1.68 (2H, sext., *J*=7.3 Hz), 3.92 (2H, t, *J*=7.3 Hz), 4.05—4.34 (1H, m), 7.60 (1H, s), 12.40 (1H, br s)
dl-**7cb**[b]	1685, 1653	0.94 (3H, t, *J*=7.3 Hz), 0.97 (3H, t, *J*=7.2 Hz), 1.34 (3H, d, *J*=6.4 Hz), 1.60—2.04 (4H, m), 3.45 (1H, dd, *J*=6.8, 10.4 Hz), 3.89—4.49 (6H, m), 7.52 (1H, s)
dl-**8a**[b]	1691, 1658	0.96 (6H, t, *J*=7.4 Hz), 1.44 (3H, d, *J*=5.9 Hz), 1.64—2.05 (4H, m), 3.64 (1H, dd, *J*=4.6, 13.7 Hz), 3.88—4.48 (6H, m), 7.45 (1H, s)
dl-**8b**[a]	1710, 1654	0.87 (3H, t, *J*=7.3 Hz), 1.38 (3H, d, *J*=6.1 Hz), 1.68 (2H, sext., *J*=7.3 Hz), 4.02 (2H, t, *J*=7.3 Hz), 4.47—4.66 (1H, m), 7.69 (1H, s), 12.65 (1H, br s)
dl-**8c**[b]	1689, 1658	0.95 (3H, t, *J*=7.3 Hz), 0.97 (3H, t, *J*=7.2 Hz), 1.42 (3H, d, *J*=6.1 Hz), 1.50—2.12 (4H, m), 3.59 (1H, dd, *J*=4.4, 13.7 Hz), 3.82—4.56 (6H, m), 7.42 (1H, s)

^{1}H-NMR spectra were recorded in *a*) DMSO-d_6 or *b*) $CDCl_3$.

Benzyl-2-(hydroxyproylamino)-1-propylpurin-6-one (19b) A mixture of **18** (0.44 g, 1.5 mmol), aminoalcohol (1 ml) and CH_3CN (20 ml) were refluxed overnight. The reaction mixture was concentrated *in vacuo* and the residue was purified by recrystallization from AcOEt–MeOH to give **19**.

19a: Yield: 52%. mp 214—215 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.87 (3H, t, *J*=7.3 Hz), 1.55 (2H, sext., *J*=7.3 Hz), 3.48 (2H, t, *J*=5.1 Hz), 3.90 (2H, t, *J*=7.3 Hz), 4.74 (2H, t, *J*=5.1 Hz), 5.44 (2H, s), 6.78 (1H, br s), 7.30 (5H, s), 8.10 (1H, s). IR (KBr) ν_{max}: 3340, 1692 cm^{-1}. *Anal.* Calcd for $C_{17}H_{21}N_5O_2$: C, 62.37; H, 6.47; N, 21.39. Found: C, 62.27; H, 6.65; N, 21.53.

19b: Yield: 57%. Oil. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, *J*=7.3 Hz), 1.48—2.04 (4H, m), 3.57—4.01 (6H, m), 5.48 (2H, s), 6.00 (1H, br s), 7.30 (5H, s), 7.62 (1H, s). IR (KBr) ν_{max}: 3356, 1681 cm^{-1}. HR-MS *m*/*z*: 341.1854 (Calcd for $C_{18}H_{23}N_5O_2$: 341.1852).

3-Benzyl-5-propyl-5,6,7,8-tetrahydro-3*H*-imidazo[2,1-*b*]purine-4-one (20a) and 3-Benzyl-5-propyl-5,6,7,8-tetrahydro-3*H*-pyrimido[2,1-*b*]-purine-4-one (20b) To a solution of **19** (0.47 mmol) in CH_2Cl_2 (5 ml) was added $SOCl_2$ (0.17 g, 1.4 mmol) at 0 °C and stirred for 12 h at rt. The reaction mixture was adjusted to pH 7—8 with 4 M NaOH. The CH_2Cl_2 layer was washed with brine, dried and concentrated. The residue was chromatographed on silica gel using $CHCl_3$–MeOH (10 : 1) as an eluent to give **20**, which was recrystallized from iso-propylether.

20a: Yield: 67%. mp 133—134 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, *J*=7.5 Hz), 1.72 (2H, sext., *J*=7.5 Hz), 3.75—4.16 (6H, m), 5.44 (2H, s), 7.34 (5H, s), 7.40 (1H, s). IR (KBr) ν_{max}: 1686, 1642 cm^{-1}. *Anal.* Calcd for $C_{17}H_{19}N_5O$: C, 66.00; H, 6.19; N, 22.64. Found: C, 65.95; H, 6.27; N, 22.58.

20b: Yield: 72%. mp 160—161 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, *J*=7.3 Hz), 1.74 (2H, sext., *J*=7.3 Hz), 1.91 (2H, quint., *J*=5.7 Hz), 3.56 (2H, t, *J*=5.7 Hz), 3.95 (2H, t, *J*=7.3 Hz), 3.97 (2H, t, *J*=5.7 Hz), 5.46 (2H, s), 7.33 (5H, s), 7.39 (1H, s). IR (KBr) ν_{max}: 1684, 1634 cm^{-1}. *Anal.* Calcd for $C_{18}H_{21}N_5O$: C, 66.85; H, 6.55; N, 21.66. Found: C, 66.70; H, 6.64; N, 21.48.

Propyl-5,6,7,8-tetrahydro-3*H*-imidazo[2,1-*b*]purine-4-one (5a) and 5-Propyl-5,6,7,8-tetrahydro-3*H*-pyrimido[2,1-*b*]purine-4-one (5b) A mixture of **20** (0.81 mmol) and 20% palladium hydroxide on carbon (0.25 g) in MeOH (30 ml) was shaken under hydrogen (3 atom) for 24 h. The catalyst was removed and the filtrate was concentrated *in vacuo*, and the residue was recrystallized from AcOEt–MeOH to yield **5**.

3,5-Dipropyl-5,6,7,8-tetrahydro-3*H*-imidazo[2,1-*b*]purine-4-one (5c) and 3,5-Dipropyl-5,6,7,8-tetrahydro-3*H*-pyrimido[2,1-*b*]purine-4-one (5d) To a mixture of **5a** or **5b** (1.7 mmol) and anhydrous K_2CO_3 (0.35 g, 2.5 mmol) in DMF (10 ml) was added propyl bromide (0.31 g, 2.5 mmol) and the mixture was stirred at rt for 10 h, then concentrated *in vacuo*. The residue was chromatographed on silica gel using $CHCl_3$–MeOH (20 : 1) as an eluent to give **5c** or **5d**, which was recrystallized from petrolum ether.

4,5-Dihydro-9*H*-pyrimido[1,2,3-*c*,*d*]purine-8,10-dione (6a) and 4,5-Dihydro-10*H*-diazepino[1,2,3-*c*,*d*]purine-9,11-dione (6b) A suspension of **21** (4.6 mmol) in H_2O (100 ml) was hydrogenated over 10% palladium on carbon (0.15 g) at 3 atom for 15 h. The catalyst was removed and the filtrate was concentrated *in vacuo*. A mixture of the residue, DMF (20 ml), triethyl orthoformate (1.1 g, 7.5 mmol) and *p*-toluenesulfonic acid (0.050 g) was stirred overnight at 100 °C. The reaction mixture was then concentrated *in vacuo* and the residue was chromatographed on silica gel using $CHCl_3$–MeOH (3 : 1) as an eluent to give **6**, which was recrystallized from EtOH.

9-Propyl-4,5-dihydro-9*H*-pyrimido[1,2,3-*c*,*d*]purine-8,10-dione (6c) and 10-Propyl-4,5-dihydro-10*H*-diazepino[1,2,3-*c*,*d*]purine-9,11-dione (6d) A mixture of **6a** or **6b** (6.0 mmol) and anhydrous K_2CO_3 (1.5 g, 12 mmol) and propyl bromide (1.6 g, 12 mmol) in DMF (20 ml) was stirred overnight at 60 °C. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel using $CHCl_3$–MeOH (10 : 1) as an eluent to give **6c** or **6d**, which was recrystallized from AcOEt–MeOH.

***dl*-6-[(2-Hydroxy-1-methyl)ethylamino]-3,7-dipropylpurin-2-one (*dl*-24)** To **23** (0.51 g, 2.0 mmol) in pyridine (10 ml) was added *dl*-2-amino-1-propanol (4 ml) and the mixture was refluxed overnight. The reaction mixture was evaporated *in vacuo* and the residue was chromatographed on silica gel using $CHCl_3$–MeOH (3 : 1) as an eluent to give *dl*-**24** (0.39 g, 83%). ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, *J*=7.3 Hz), 0.98 (3H, t, *J*=7.3 Hz), 1.27 (3H, d, *J*=6.6 Hz), 1.64—2.03 (4H, m), 2.45 (1H, br s), 3.50—4.28 (7H, m), 4.49

(1H, br s), 7.47 (1H, s). IR (KBr) ν_{max}: 3390, 1633 cm^{-1}. HR-MS *m*/*z*: 293.1857 (Calcd for $C_{14}H_{23}N_5O_2$: 293.1852).

Compounds *dl*-**25**, *dl*-**027** and *dl*-**28** were prepared by a similar procedure to that described above from **23** or **26**.[9)]

dl-6-[(2-Hydroxy-2-methyl)ethylamino]-3,7-dipropylpurin-2-one (*dl*-**25**): Yield: 72%. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (6H, t, J=7.1 Hz), 1.18 (3H, d, J=6.2 Hz), 1.64—2.03 (4H, m), 2.70 (1H, br s), 3.20—3.48 (2H, m), 3.73—4.31 (5H, m), 6.07 (1H, br s), 7.48 (1H, s). IR (KBr) ν_{max}: 3323, 1628, 1610 cm^{-1}. HR-MS *m*/*z*: 293.1856 (Calcd for $C_{14}H_{23}N_5O_2$: 293.1852).

dl-6-[(2-Hydroxy-1-methyl)ethylamino]-3-propylpurin-2-one (*dl*-**27**): Yield: 85%. mp 296—297 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.94 (3H, t, J=7.3 Hz), 1.17 (3H, d, J=6.8 Hz), 1.62 (2H, sext., J=7.3 Hz), 3.88 (2H, t, J=7.3 Hz), 4.23 (1H, br s), 4.95 (1H, br s), 7.23 (1H, br s) 7.88 (1H, s). IR (KBr) ν_{max}: 3325, 1635, 1612 cm^{-1}. *Anal.* Calcd for $C_{11}H_{17}N_5O_2$: C, 52.58; H, 6.82; N, 27.87. Found: C, 57.92; H, 6.34; N, 22.56.

dl-6-[(2-Hydroxy-2-methyl)ethylamino]-3-propylpurin-2-one (*dl*-**28**): Yield: 81%. mp 288—289 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.85 (3H, t, J=7.3 Hz), 1.10 (3H, d, J=6.2 Hz), 1.62 (2H, sext., J=7.3 Hz), 3.87 (2H, t, J=7.3 Hz), 5.10 (1H, br s), 7.60 (1H, br s) 7.88 (1H, s). IR (KBr) ν_{max}: 3448, 3309, 3238, 1643, 1614 cm^{-1}. *Anal.* Calcd for $C_{11}H_{17}N_5O_2$: C, 52.58; H, 6.82; N, 27.87. Found: C, 57.92; H, 6.34; N, 22.56.

***dl*-1,4-Dipropyl-8-methyl-4,5,7,8-tetrahydro-3*H*-imidazo[2,1-*i*]purin-5-one (*dl*-7a), *dl*-1,4-Dipropyl-7-methyl-4,5,7,8-tetrahydro-3*H*-imidazo-[2,1-*i*]purin-5-one (*dl*-8a), *dl*-4-Propyl-8-methyl-4,5,7,8-tetrahydro-3*H*-imidazo[2,1-*i*]purin-5-one (*dl*-7b), and *dl*-4-Propyl-7-methyl-4,5,7,8-tetrahydro-3*H*-imidazo[2,1-*i*]purin-5-one (*dl*-8b)** To a mixture of *dl*-**24**, *dl*-**25**, *dl*-**27** or *dl*-**28** (1.3 mmol) and triethylamine (0.16 g, 1.6 mmol) was added methanesulfonyl chloride (0.18 g, 1.6 mmol) at 0 °C. The reaction mixture was stirred for 6 h at rt, and then concentrated *in vacuo*. The residue was chromatographed on silica gel using $CHCl_3$–MeOH (6 : 1) as an eluent to give *dl*-**7a**, *dl*-**8a**, *dl*-**7b** or *dl*-**8b**, which was recrystallized from AcOEt or petroleum ether.

***dl*-3,4-Dipropyl-8-methyl-4,5,7,8-tetrahydro-3*H*-imidazo[2,1-*i*]purin-5-one (*dl*-7c) and *dl*-3,4-Dipropyl-7-methyl-4,5,7,8-tetrahydro-3*H*-imidazo[2,1-*i*]purin-5-one (*dl*-8c)** Compounds *dl*-**7c** and *dl*-**8c** were prepared from *dl*-**7b** and *dl*-**8b**, respectively as described above for **4c**.

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