Effects of 1-Benzylxanthines on Cyclic AMP Phosphodiesterase 4 Isoenzyme

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Based on our results regarding the structure–activity relationships of alkylxanthines and imidazo[2,1-*i*]purines as phosphodiesterase 4 (PDE4) inhibitors, we designed new 1-benzylxanthines and investigated their PDE4 inhibitory activities. 3,7-Dihydro-7-acetonyl-1-(2,4-dichlorobenzyl)-3-propyl-1*H*-purine-2,4-dione (2h) exhibited both more selective and more potent PDE4 inhibitory activity than rolipram and XT-611.

Key words phosphodiesterase 4 inhibitor; 1-benzylxanthine; alkylxanthine

Theophylline has been used for over 60 years to treat bronchial asthma. However, theophylline inhibits phosphodiesterase (PDE) non-selectively and functions as an adenosine antagonist, and shows adverse effects on the cardiovascular and central nervous systems.[1—4] PDE4 is cAMP-specific, and is found in airway muscle and inflammatory cells. Selective PDE4 inhibitors are promising agents for the treatment of asthma as they have relaxation effects on bronchial smooth muscle and anti-inflammatory activities.[5—7] Although the alkylxanthine 3-isobutyl-1-methylxanthine (IBMX) is also a non-selective inhibitor of PDE,[8] denbufylline[9] and XT-44,[10] which we prepared, were the first xanthine derivatives identified as selective inhibitors of PDE4 with negligible adenosine antagonistic effects. During our investigations of the structure–activity relationships of alkylxanthines, we found that alkyl substitution at *N*1 leads to increased selectivity for PDE4.[10—12] Subsequent investigations showed that 3,4-dipropyl-4,5,7,8-tetrahydro-1*H*-imidazo-[2,1-*i*]purin-5-one (XT-611) has selective PDE4 inhibitory activity without emesis seen with rolipram at all,[13] and further, its 7- and 8-alkyl substituted derivatives inhibit PDE4 inhibitory activities more strongly than XT-611.[14]

The above results suggested that more lipophilic groups in common structural areas, such as the *N*1 position of xanthine or the 7- or 8-position of XT-611, may be important to increase selectivity for PDE4 and decrease side effects. Thus, we chose xanthines due to their ease of preparation and designed both 1-benzyl derivatives of *N*7-H xanthine (**1**) and 7-acetonylxanthine (**2**), which are models of XT-44 and denbufylline, respectively, fixing the propyl group at the 3-position (Fig. 2). Here, we report the synthesis and *in vitro* inhibitory effects of 1-benzyl compounds (**1**, **2**) against the PDE4 isoenzyme.

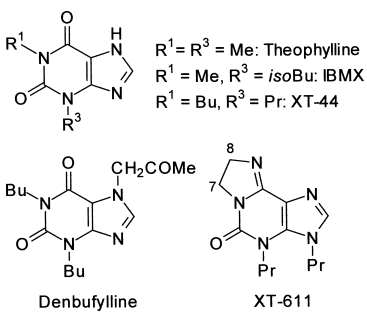

Fig. 1

Chemistry Benzylxanthines (**1**) were prepared by removal of the 4-methoxybenzyl group of 1-benzyl-7-(4-methoxybenzyl)xanthine (**4**), which was obtained by benzylation of 7-(4-methoxybenzyl)xanthine (**3**)[10] with benzyl chloride and potassium carbonate. 7-Acetonyl-1-benzylxanthines (**2**) were prepared by similar benzylation of 7-acetonylxanthines (**6**), obtained by treatment of 3-propylxanthine (**5**)[15] with acetonyl chloride in the presence of potas-

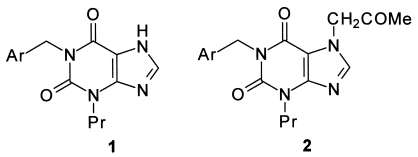

Fig. 2

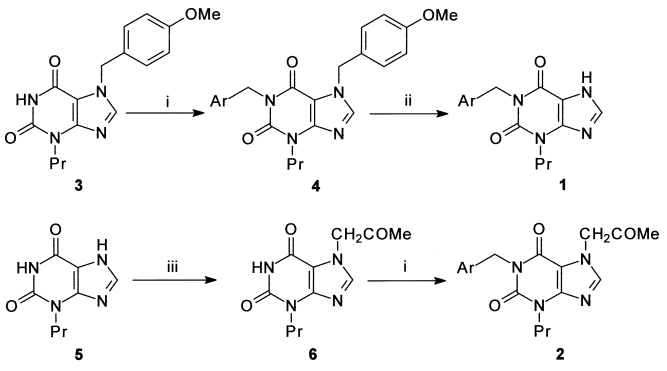

Chart 1

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sium carbonate.

BIOLOGICAL RESULTS AND DISCUSSION

The inhibitory activities of the 1-benzylxanthines (**1**, **2**) against PDE1 and 4 isoenzymes from guinea pig brain and PDE3 from guinea pig heart were determined according to published methods.[16] The results are shown in Table 1 together with the PDE inhibitory activities of the non-selective PDE inhibitor, IBMX, the PDE3 inhibitor, amrinone, and the PDE4 inhibitors, rolipram and XT-611. The results regarding PDE1, 3, and 4 isoenzymes were as follows.

1) The PDE1 inhibitory activities of methylbenzyl- (**1d**—**f**, **2d**—**f**), and chlorobenzyl-xanthines (**1a**—**c**, **2a**—**c**) as a whole were weak, as compared with PDE4. All xanthines (**1a**—**f**, **2a**—**f**) showed no or very weak inhibitory activity against the PDE3 isoenzyme.
2) The characteristics of the inhibitory activities of the chlorobenzyl- (**a**—**c**) or methylbenzyl-derivatives (**d**—**f**) of both *N*7-H xanthine (**1**) and 7-acetonylxanthine (**2**) against the PDE1, 3 and 4 isoenzymes were similar.
3) Despite having methyl- or chloro-groups, the 2-substituted benzylxanthines (**1a**, **d**, **2a**, **d**) showed more selective inhibitory effects against the PDE4 isoenzyme than the 3-substituted- (**1b**, **e**, **2b**, **e**) or the 4-substituted benzylxanthines (**1c**, **f**, **2c**, **f**). The 2-chlorobenzylxanthines (**1a**, **2a**) in paticular inhibited PDE4 activity more selectively than 2-methylbenzylxanthines (**1d**, **2d**).
4) The 4-substituted benzylxanthines (**1c**, **f**, **2c**, **f**) inhibited PDE4 activity more strongly than the 2-substituted- (**1a**, **d**, **2a**, **d**) or the 3-substituted-benzylxanthines (**1b**, **e**, **2b**, **e**). Although the position of the chloro-group of the benzylxanthines (**1a**—**c**, **2a**—**c**) for PDE4 inhibitory activity was in the order 4>3>2, the position of the methyl-group of the benzylxanthines (**1d**—**f**, **2d**—**f**) was in the order 4>2>3.

The above results (3 and 4) showed that substituents of benzylxanthines influenced both the selectivity and activity against PDE4 isoenzyme, that is, the substituent group at 2-position may be correlated to selectivity for PDE4 isoenzyme and those at 4-position may be strongly correlated to PDE4 inhibitory activity. Thus, in calling attention to the chloro-group of 1-benzylxanthine, 2,4-dichlorobenzylxanthine (**2h**) was designed to obtain a PDE4 inhibitor with high selectivity and activity. **2h**, prepared using a similar method, exhibited more selective and potent PDE4 inhibitory activities than the known PDE inhibitors, rolipram and XT-611.

In conclusion, introduction of a benzyl group at the *N*1 position of the *N*7-H xanthine (**1**) and 7-acetonylxanthine (**2**) resulted in a potent and selective PDE4 inhibitor, 3,7-dihydro-7-acetonyl-1-(2,4-dichlorobenzyl)-3-propyl-1*H*-purine-2,4-dione (**2h**), which showed the most potent PDE4 inhibitory activity among xanthine derivatives known to be PDE4 inhibitor. In the report of the crystal structure of PDE4D2 in complex with IBMX by Qing *et al.*, IBMX binds to a subpocket, which is a common site for binding non-selective inhibitors of PDEs.[17] Although IBMX has a methyl group at the 1-position of the xanthine skeleton, both denbufylline and XT-44, which are known the selective PDE4 inhibitors, have a butyl group at the same position. It may therefore be assumed that selective xanthines including **2h** against PDE4 have a bulky substituent at the *N*1 position and cannot bind to the subpocket reported by Qing *et al.*

Table 1. Inhibitory Activities of 1-Benzylxanthine Derivatives (**1**, **2**)

Compd.	Ar	IC_{50} (μM)		
		PDE1	PDE3	PDE4
1a	3-ClC_6H_4	>100	>100	16
1b	3-ClC_6H_4	9.7	>100	1.2
1c	4-ClC_6H_4	2.3	21	0.2
1d	2-$CH_3C_6H_4$	52	>100	1.1
1e	3-$CH_3C_6H_4$	16	76	3.4
1f	4-$CH_3C_6H_4$	1.4	26	0.9
2a	2-ClC_6H_4	>100	>100	5.1
2b	3-ClC_6H_4	9.5	>100	2.4
2c	4-ClC_6H_4	0.7	>100	0.6
2d	2-$CH_3C_6H_4$	53	>100	0.9
2e	3-$CH_3C_6H_4$	8.3	>100	4.8
2f	4-CH-C_6H_4	1.5	>100	0.2
2g	C_6H_5	28	>100	1.2
2h	2,4-$Cl_2C_6H_3$	>100	>100	0.01
IBMX	—	4.3	6.6	20
Amrinone	—	>100	84.3	>100
Rolipram	—	>100	>100	0.1
XT-611	—	26.4	38	5

Data are mean of three experiments.

MATERIALS AND METHODS

Melting points were measured on a Yanagimoto micro melting point hot-stage apparatus and were uncorrected. Infrared spectra (IR) were determined with a Horiba FT-720 or Hitachi 270-30 spectrometer. Mass spectra (MS) were measured with a JEOL-DX300. Nuclear magnetic resonance spectrometry (^{1}H-NMR) was performed with a JEOL EX 90A. 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 our institute.

3,7-Dihydro-1-benzyl-7-(4-methoxybenzyl)-3-propyl-1*H*-purine-2,4-dione (4) General Procedure: A mixture of 7-(4-methoxybenzyl)-3-propylxanthine (**3**, 1.0 g, 3.2 mmol), benzyl chloride (3.2 mmol), and anhydrous K_2CO_3 (0.47 g, 3.4 mmol) in DMF (5.0 ml) was heated at 60 °C for 2 h. The reaction mixture was poured into ice-water and neutralized with 2 N HCl. The mixture was extracted with CH_2Cl_2. The extract was dried and evaporated. The residue was purified by alumina column chromatography using benzene–CH_2Cl_2 (1 : 1) as the eluent and recrystallized from CH_2Cl_2–isopropyl ether to give **4**.

3,7-Dihydro-1-(2-chlorobenzyl)-7-(4-methoxybenzyl)-3-propyl-1*H*-purine-2,4-dione (**4a**): Yield 95%. mp 133—134 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 3H, J=7.5 Hz), 1.80 (2H, sext., J=7.5 Hz), 3.72 (3H, s), 4.05 (2H, t, J=7.5 Hz), 5.30 (2H, s), 5.37 (2H, s), 6.83 (2H, d, J=8.5 Hz), 6.90—7.45 (6H, m), 7.50 (1H, s). IR (KBr) ν: 1709, 1666 cm^{-1}. *Anal.* Calcd for $C_{23}H_{23}N_4O_3Cl$: C, 62.94; H, 5.28; N, 12.76. Found: C, 62.75; H, 5.30; N, 12.84.

3,7-Dihydro-1-(3-chlorobenzyl)-7-(4-methoxybenzyl)-3-propyl-1*H*-purine-2,4-dione (**4b**): Yield 77%. mp 109—110 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, t, 3H, J=7.5 Hz), 1.80 (2H, sext., J=7.5 Hz), 3.71 (3H, s), 4.05 (2H, t,

J=7.5 Hz), 5.15 (2H, s), 5.40 (2H, s), 6.87 (2H, d, J=8.5 Hz), 6.90—7.47 (6H, m), 7.50 (1H, s). IR (KBr) ν: 1703, 1660 cm^{-1}. *Anal.* Calcd for $C_{23}H_{23}N_4O_3Cl$: C, 62.94; H, 5.28; N, 12.76. Found: C, 62.67; H, 5.24; N, 12.97.

3,7-Dihydro-1-(4-chlorobenzyl)-7-(4-methoxybenzyl)-3-propyl-1*H*-purine-2,4-dione (**4c**): Yield 70%. mp 133—134 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 3H, J=7.5 Hz), 1.80 (2H, sext., J=7.5 Hz), 3.71 (3H, s), 4.06 (2H, t, J=7.5 Hz), 5.17 (2H, s), 5.35 (2H, s), 6.82 (2H, d, J=8.5 Hz), 7.08—7.40 (4H, m), 7.45 (1H, s). IR (KBr) ν: 1707, 1666 cm^{-1}. *Anal.* Calcd for $C_{23}H_{23}N_4O_3Cl$: C, 62.94; H, 5.28; N, 12.76. Found: C, 62.61; H, 5.19; N, 12.82.

3,7-Dihydro-1-(2-methylbenzyl)-7-(4-methoxybenzyl)-3-propyl-1*H*-purine-2,4-dione (**4d**): Yield 69%. mp 127—128 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 3H, J=7.5 Hz), 1.70 (2H, sext., J=7.5 Hz), 2.42 (3H, s), 3.75 (3H, s), 4.07 (2H, t, J=7.5 Hz), 5.20 (2H, s), 5.40 (2H, s), 6.86 (2H, d, J=8.6 Hz), 6.80—7.50 (7H, m). IR (KBr) ν: 1707, 1666 cm^{-1}. *Anal*. Calcd for $C_{24}H_{26}N_4O_3$: C, 68.88; H, 6.26; N, 13.39. Found: C, 68.62; H, 6.35; N, 13.54.

3,7-Dihydro-1-(3-methylbenzyl)-7-(4-methoxybenzyl)-3-propyl-1*H*-purine-2,4-dione (**4e**): Yield 74%. Oil. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 3H, J=7.5 Hz), 1.80 (2H, sext., J=7.5 Hz), 2.27 (3H, s), 3.70 (3H, s), 4.05 (2H, t, J=7.5 Hz), 5.10 (2H, s), 5.33 (2H, s), 6.80 (2H, d, J=8.5 Hz), 6.90—7.40 (7H, m), 7.47 (1H, s). IR (KBr) ν: 1705, 1666 cm^{-1}. HR-MS *m/z*: 418.2010 (Calcd for 418.2005).

3,7-Dihydro-1-(2-methylbenzyl)-7-(4-methoxybenzyl)-3-propyl-1*H*-purine-2,4-dione (**4f**): Yield 72%. mp 105—110 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, 3H, J=7.5 Hz), 1.69 (2H, sext., J=7.5 Hz), 2.31 (3H, s), 3.80 (3H, s), 4.03 (2H, t, J=7.5 Hz), 5.16 (2H, s), 5.45 (2H, s), 6.89 (2H, d, J=8.6 Hz), 6.96—7.40 (6H, m), 7.55 (1H, s). IR (KBr) ν: 1707, 1666 cm^{-1}. *Anal.* Calcd for $C_{24}H_{26}N_4O_3$: C, 68.88; H, 6.26; N, 13.39. Found: C, 68.66; H, 6.34; N, 13.20.

3,7-Dihydro-1-benzyl-3-propyl-1*H*-purine-2,4-dione (1) General Procedure: A mixture of **4** (2.0 mmol), conc. H_2SO_4 (1 drop), and anisole (324 mg, 3.0 mmol) in trifluoroacetic acid (4 ml) was refluxed for 9 h and then evaporated. The oily residue was diluted with water and adjusted to pH 6 by addition of 20% NaOH with stirring. The resultant precipitate was filtered, washed with water, and then isopropyl ether, dried, and recrystallized from benzene to afford **1**.

3,7-Dihydro-1-(2-chlorobenzyl)-3-propyl-1*H*-purine-2,4-dione (**1a**): Yield 67%. mp 230—231 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, t, 3H, J=7.4 Hz), 1.70 (2H, sext., J=7.4 Hz), 4.10 (2H, t, J=7.4 Hz), 5.30 (2H, s), 6.90—7.20 (4H, m), 7.70 (1H, s), 13.00 (1H, br s). IR (KBr) ν: 3425, 1705, 1664 cm^{-1}. *Anal.* Calcd for $C_{15}H_{15}N_4O_2Cl$: C, 56.52; H, 4.74; N, 17.58. Found: C, 56.82; H, 4.67; N, 17.84.

3,7-Dihydro-1-(3-chlorobenzyl)-3-propyl-1*H*-purine-2,4-dione (**1b**): Yield 65%. mp 179—180 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 3H, J=7.4 Hz), 1.70 (2H, sext., J=7.4 Hz), 4.12 (2H, t, J=7.4 Hz), 5.30 (2H, s), 7.15—7.57 (4H, m), 7.87 (1H, s), 12.60 (1H, br s). IR (KBr) ν: 3425, 1709, 1660 cm^{-1}. *Anal.* Calcd for $C_{15}H_{15}N_4O_2Cl$: C, 56.52; H, 4.74; N, 17.58. Found: C, 56.68; H, 4.61; N, 17.79.

3,7-Dihydro-1-(4-chlorobenzyl)-3-propyl-1*H*-purine-2,4-dione (**1c**): Yield 53%. mp 177—178 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 3H, J=7.4 Hz), 1.70 (2H, sext., J=7.4 Hz), 4.15 (2H, t, J=7.4 Hz), 5.20 (2H, s), 7.22 (2H, d, J=9.0 Hz), 7.41 (2H, d, J=9.0 Hz), 7.72 (1H, s), 12.50 (1H, br s). IR (KBr) ν: 3425, 1705, 1662 cm^{-1}. *Anal.* Calcd for $C_{15}H_{15}N_4O_2Cl$: C, 56.52; H, 4.74; N, 17.58. Found: C, 56.47; H, 4.68; N, 17.42.

3,7-Dihydro-1-(2-methylbenzyl)-3-propyl-1*H*-purine-2,4-dione (**1d**): Yield 57%. mp 198—199 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 3H, J=7.4 Hz), 1.70 (2H, sext., J=7.4 Hz), 2.50 (3H, s), 4.13 (2H, t, J=7.4 Hz), 5.28 (2H, s), 6.90—7.15 (4H, m), 7.58 (1H, s), 12.51 (1H, br s). IR (KBr) ν: 3425, 1705, 1662 cm^{-1}. *Anal.* Calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.14; H, 6.23; N, 18.84.

3,7-Dihydro-1-(3-methylbenzyl)-3-propyl-1*H*-purine-2,4-dione (**1e**): Yield 58%. mp 174—175 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 3H, J=7.4 Hz), 1.70 (2H, sext., J=7.4 Hz), 2.38 (3H, s), 4.10 (2H, t, J=7.4 Hz), 5.23 (2H, s), 6.95—7.40 (4H, m), 7.60 (1H, s), 12.60 (1H, br s). IR (KBr) ν: 3425, 1709, 1664 cm^{-1}. *Anal.* Calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.67; H, 6.22; N, 18.61.

3,7-Dihydro-1-(4-methylbenzyl)-3-propyl-1*H*-purine-2,4-dione (**1f**): Yield 60%. mp 175—176 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 3H, J=7.4 Hz), 1.70 (2H, sext., J=7.4 Hz), 2.30 (3H, s), 4.15 (2H, t, J=7.4 Hz), 5.22 (2H, s), 7.10 (2H, d, J=9.0 Hz), 7.40 (2H, d, J=9.0 Hz), 7.70 (1H, s), 12.70 (1H, br s). IR (KBr) ν: 3425, 1707, 1664 cm^{-1}. *Anal.* Calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.64; H, 6.29; N, 18.79.

3,7-Dihydro-7-acetonyl-3-propyl-1*H*-purine-2,4-dione (6) A mixture of 3-propylxanthine (**5**, 0.97 g, 5.0 mmol), acetonyl chloride (0.46 g, 5.0 mmol), and anhydrous K_2CO_3 (0.71 g, 5.1 mmol) in DMF (10 ml) was heated at 60 °C for 2 h. The reaction mixture was poured into ice-water and neutralized with 2 N HCl. The resultant precipitate was filtered, and recrystallized from MeOH to give **6** (0.86 g, 67%). mp 231—232 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.67 (3H, t, J=7.2 Hz), 1.70 (2H, sext., J=7.2 Hz), 2.20 (3H, s), 3.90 (2H, t, J=7.2 Hz), 5.45 (2H, s), 5.20 (2H, s), 7.90 (1H, s), 10.90 (1H, br s). IR (KBr) ν: 3453, 1725, 1691 cm^{-1}. *Anal.* Calcd for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.81; H, 5.57; N, 22.51.

3,7-Dihydro-7-acetonyl-1-benzyl-3-propyl-1*H*-purine-2,4-dione (2) General Procedure: A mixture of **6** (0.5 g, 2.0 mmol), benzyl chloride (2.2 mmol), and anhydrous K_2CO_3 (0.3 g, 2.2 mmol) in DMF (5.0 ml) was heated at 60 °C for 2 h. The reaction mixture was poured into ice-water and neutralized with 2 N HCl. The mixture was extracted with CH_2Cl_2. The extract was dried and evaporated. The resulting solid was recrystallized from CH_2Cl_2–diisopropyl ether to afford **2**.

3,7-Dihydro-7-acetonyl-1-(2-chlorobenzyl)-3-propyl-1*H*-purine-2,4-dione (**2a**): Yield 92%. mp 191—192 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 3H, J=7.2 Hz), 1.80 (2H, sext., J=7.2 Hz), 2.30 (3H, s), 4.10 (2H, t, J=7.2 Hz), 5.15 (2H, s), 5.30 (2H, s), 7.10—7.40 (4H, m), 7.55 (1H, s). IR (KBr) ν: 1731, 1689 cm^{-1}. *Anal.* Calcd for $C_{18}H_{19}N_4O_3Cl$: C, 57.68; H, 5.11; N, 14.95. Found: C, 57.75; H, 5.30; N, 14.84.

3,7-Dihydro-7-acetonyl-1-(3-chlorobenzyl)-3-propyl-1*H*-purine-2,4-dione (**2b**): Yield 90%. mp 119—120 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 3H, J=7.2 Hz), 1.80 (2H, sext., J=7.2 Hz), 2.30 (3H, s), 4.05 (2H, t, J=7.2 Hz), 5.15 (4H, s), 7.15—7.45 (4H, m), 7.50 (1H, s). IR (KBr) ν: 1730, 1701, 1668 cm^{-1}. *Anal.* Calcd for $C_{18}H_{19}N_4O_3Cl$: C, 57.68;

H, 5.11; N, 14.95. Found: C, 57.67; H, 5.24; N, 14.97.

3,7-Dihydro-7-acetonyl-1-(4-chlorobenzyl)-3-propyl-1*H*-purine-2,4-dione (**2c**): Yield 61%. mp 136—137 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 3H, J=7.2 Hz), 1.80 (2H, sext., J=7.2 Hz), 2.30 (3H, s), 4.05 (2H, t, J=7.2 Hz), 5.05 (2H, s), 5.10 (2H, s), 7.20—7.35 (4H, m), 7.45 (1H, s). IR (KBr) ν: 1734, 1701, 1660 cm^{-1}. *Anal.* Calcd for $C_{18}H_{19}N_4O_3Cl$: C, 57.68; H, 5.11; N, 14.95. Found: C, 57.61; H, 5.19; N, 14.82.

3,7-Dihydro-7-acetonyl-1-(2-methylbenzyl)-3-propyl-1*H*-purine-2,4-dione (**2d**): Yield 90%. mp 130—131 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 3H, J=7.2 Hz), 1.80 (2H, sext., J=7.2 Hz), 2.27 (3H, s), 2.40 (3H, s), 4.10 (2H, t, J=7.2 Hz), 5.10 (2H, s), 5.13 (2H, s), 6.90—7.30 (4H, m), 7.55 (1H, s). IR (KBr) ν: 1732, 1699, 1660 cm^{-1}. *Anal.* Calcd for $C_{19}H_{22}N_4O_3$: C, 64.39; H, 6.26; N, 15.81. Found: C, 64.42; H, 6.35; N, 15.84.

3,7-Dihydro-7-acetonyl-1-(3-methylbenzyl)-3-propyl-1*H*-purine-2,4-dione (**2e**): Yield 74%. mp 104—105 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 3H, J=7.2 Hz), 1.80 (2H, sext., J=7.2 Hz), 2.27 (6H, s), 4.10 (2H, t, J=7.2 Hz), 5.07 (2H, s), 5.10 (2H, s), 6.90—7.20 (4H, m), 7.47 (1H, s). IR (KBr) ν: 1736, 1701, 1668 cm^{-1}. *Anal.* Calcd for $C_{19}H_{22}N_4O_3$: C, 64.39; H, 6.26; N, 15.81. Found: C, 64.35; H, 6.28; N, 15.78.

3,7-Dihydro-7-acetonyl-1-(4-methylbenzyl)-3-propyl-1*H*-purine-2,4-dione (**2f**): Yield 91%. mp 139—140 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 3H, J=7.2 Hz), 1.80 (2H, sext., J=7.2 Hz), 2.27 (6H, s), 4.10 (2H, t, J=7.2 Hz), 5.10 (2H, s), 5.13 (2H, s), 7.10 (1H, d, J=9.0 Hz), 7.36 (2H, d, J=9.0 Hz), 7.50 (1H, s). IR (KBr) ν: 1726, 1701, 1662 cm^{-1}. *Anal.* Calcd for $C_{19}H_{22}N_4O_3$: C, 64.39; H, 6.26; N, 15.81. Found: C, 64.36; H, 6.34; N, 15.80.

3,7-Dihydro-7-acetonyl-1-benzyl-3-propyl-1*H*-purine-2,4-dione (**2g**): Yield 94%. mp 129—130°C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 3H, J=7.2 Hz), 1.80 (2H, sext., J=7.2 Hz), 2.27 (3H, s), 4.03 (2H, t, J=7.2 Hz), 5.07 (4H, s), 7.17—7.40 (5H, m), 7.50 (1H, s). IR (KBr) ν: 1732, 1701, 1655 cm^{-1}. *Anal.* Calcd for $C_{18}H_{20}N_4O_3$: C, 63.52; H, 5.92; N, 16.46. Found: C, 63.66; H, 5.82; N, 16.32.

3,7-Dihydro-7-acetonyl-1-(2,4-dichlorobenzyl)-3-propyl-1*H*-purine-2,4-dione (**2h**): Yield 90%. mp 158—159 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, 3H, J=7.2 Hz), 1.80 (2H, sext., J=7.2 Hz), 2.30 (3H, s), 4.00 (2H, t, J=7.2 Hz), 5.05 (2H, s), 5.15 (2H, s), 6.75 (1H, d, J=8.0 Hz), 7.05 (1H, dd, J=8.0, 2.0 Hz), 7.47 (1H, s). IR (KBr) ν: 1726, 1712, 1664 cm^{-1}. *Anal.* Calcd for $C_{18}H_{18}N_4O_3Cl_2$: C, 52.83; H, 4.43; N, 13.69. Found: C, 52.66; H, 4.39; N, 13.77.

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