Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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To cite this Article Itahara, Toshio(1999) 'NMR Study of Stacking Interactions between Thymine and 1,3-Dimethylxanthine Rings', Supramolecular Chemistry, 10: 3, 193 — 199
To link to this Article: DOI: 10.1080/10610279908559285
URL: http://dx.doi.org/10.1080/10610279908559285

SUPRAMOLECULAR CHEMISTRY, Vol. 10, pp. 193–199
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NMR Study of Stacking Interactions between Thymine and 1,3-Dimethylxanthine Rings

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(Received 11 May 1998; In final form 8 September 1998)

Stacking interactions between thymine and 1,3-dimethylxanthine rings of 7-[ω-(2,4-dioxo-1,2,3,4-tetrahydro-5-methyl-1-pyrimidinyl)alkyl]-1,3-dimethylxanthine were studied by means of ^{1}H NMR spectroscopy in aqueous solutions and organic solvents. The spectra were compared with those of 1,1′-(α,ω-alkanediyl) bis [thymine] and 7,7′-(α,ω-alkanediyl)-bis [1,3-dimethylxanthine]. On the basis of the chemical shifts of the ring protons and methyl groups of thymine and xanthine rings, a stacked conformation between thymine and 1,3-dimethylxanthine rings in aqueous solutions was estimated.

Keywords: Stacking, NMR, thymine, xanthine

INTRODUCTION

Molecular aggregation between purine and pyrimidine rings has been of interest in connection with the structure of nucleic acids [1]. The UV hypochromic effects due to purine–pyrimidine association were found in an aqueous solution containing the complementary base-pairs [2]. Leonard and co-workers [3] reported the UV hypochromism and fluorescence studies of the dinucleotide analogs linked with trimethylene group between purine and pyrimidine bases. On the other hand, the NMR studies have greatly contributed to the understanding of the molecular aggregation in solutions and have offered a significant information about the conformations. In earlier papers dealing with NMR spectroscopy of mixtures of pyrimidine nucleosides and purine, it was shown that the pyrimidine ring protons were shifted to a higher field with increasing purine concentrations [4]. Furthermore, the NMR spectroscopy of nucleotides such as purine–pyrimidine dinucleotides [5] has been investigated in detail. However, stacked conformations between purine and pyrimidine rings in solutions are still not completely elucidated.

Xanthines play an important role in vital functions and most xanthines containing caffeine and theophylline is known to inhibit both A_1- and A_2-adenosine receptors [6]. The xanthine skeleton is also of importance as synthetic medicines [7]. Therefore, a molecular aggregation caused by xanthine rings is of interest in connection with the physiological functions of xanthines. Previously we reported the intramolecular stacking interactions between two theophylline molecules of 7,7′-(α,ω-alkanediyl) bis [1,3-dimethylxanthine] (**4**)[8] by means of NMR spectroscopy. The intramolecular interactions between two thymine molecules of 1,1′-

(α,ω-alkanediyl) bis [thymine] (**3**)[9] were also examined in a similar manner. In the present investigation, NMR spectra of 7-[ω-(2,4-dioxo-1,-2, 3, 4-tetrahydro-5-methyl-1-pyrimidinyl)alkyl]-1,3-dimethylxanthine (**1**), which linked between thymine and theophylline molecules with polymethylene chains, were compared with those of **3** and **4** in order to elucidate stacking interactions between thymine and 1,3-dimethylxanthine rings (Chart 1).

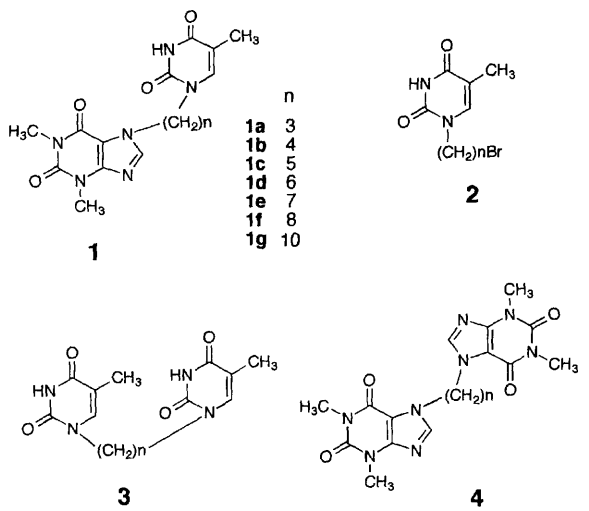


CHART 1

RESULTS AND DISCUSSION

The preparation of **1** was performed by the treatment of theophylline (1,3-dimethylxanthine) and 1-(ω-bromoalkyl)thymine (**2**)[9] in the presence of *tert*-BuOK in *N,N*-dimethylformamide (DMF). The results are shown in Table I.

The concentration dependence of chemical shifts of the ring protons and methyl groups of thymine and xanthine rings of **1a** and **1b** was investigated in D_2O and in CD_3OD at 27°C. The measurements in D_2O were made on solutions ranging in concentrations of **1a** from 0.05 mmol/dm^3 to 2.1 mmol/dm^3 and of **1b**

TABLE I Reaction of theophylline and 1-(ω-bromoalkyl)thymine (**2**) in the presence of *tert*-BuOK [a]

Substrate 2	Product/Isolated yield, % 1	2 (recovered)	theophylline (recovered)
2a	**1a**/12	**2a**/38	50
2b	**1b**/43	**2b**/20	38
2c	**1c**/46	**2c**/24	38
2d	**1d**/48	**2d**/20	34
2e	**1e**/46	**2e**/23	35
2f	**1f**/44	**2f**/25	37
2g	**1g**/48	**2g**/22	35

[a] Reaction conditions: theophylline (1 mmol), **2** (1 mmol), *tert*-BuOK (1 mmol), DMF (50 ml), stirring at room temperature for 24 h.

from 0.05 mmol/dm^3 to 3.5 mmol/dm^3, but the differences of the chemical shifts were not observed. The chemical shift differences of **1b** in CD_3OD were also not observed in concentrations from 0.25 mmol/dm^3 to 2.5 mmol/dm^3. Therefore, intermolecular association of **1** may be neglected at the concentrations of less than 2.1 mmol/dm^3.

Relationships between the chemical shifts of the protons of thymine and 1,3-dimethylxanthine rings of **1** and the carbon numbers of the polymethylene chains ($n = 3 - 10$) were investigated in several types of solvents. Table II shows the values of the chemical shifts of thymine and 1,3-dimethylxanthine rings of **1** in the buffer solution at pD 7.0[10] and organic solvents such as CD_3OD and DMSO-d_6 at 27°C. Figure 1 shows the relationships between the chemical shifts of H-6 and Me-5 of thymine ring of **1** in the buffer solution at pD 7.0, CD_3OD, DMSO-d_6, and $CDCl_3$ at 27°C. The concentrations of **1** in the buffer solutions at pD 7.0 and in CD_3OD were less than 1.0 mmol/dm^3, while the measurements in DMSO-d_6 and in $CDCl_3$ were made on solutions ranging in concentrations from 2 to 30 mmol/dm^3. It can be seen from Figure 1 that the proton resonances of the H-6 and Me-5 of thymine ring of **1** in the buffer solution at pD 7.0 were shifted to higher fields as the length of the polymethylene chains decreased but the upfield shifts were not observed in the organic solvents, although the concentration dependence of the chemical shifts in DMSO-

TABLE II Chemical shifts of the ring protons and methyl groups of **1** at 27°C[a]

	Buffer solution of pD 7.0 (Concentration:0.5–1.0 mmol · dm^{-3})					CD_3OD (0.5–1.0 mmol · dm^{-3})					DMSO – d_6 (25–30 mmol · dm^{-3})				
	H-8[b]	H-6[c]	NMe[d]	NMe[d]	Me-5[e]	H-8[b]	H-6[c]	NMe[d]	NMe[d]	Me-5[e]	H-8[b]	H-6[c]	NMe[d]	NMe[d]	Me-5[e]
1a	8.01	7.29	3.51	3.36	1.73	7.98	7.38	3.52	3.34	1.82	8.05	7.42	3.42	3.23	1.72
1b	7.99	7.32	3.54	3.34	1.78	7.93	7.39	3.53	3.34	1.84	8.08	7.49	3.42	3.23	1.72
1c	7.97	7.39	3.55	3.36	1.82	7.94	7.42	3.55	3.36	1.86	8.07	7.49	3.42	3.23	1.74
1d	7.98	7.44	3.55	3.36	1.84	7.94	7.41	3.55	3.36	1.86	8.07	7.50	3.42	3.23	1.74
1e	7.98	7.46	3.55	3.36	1.85	7.94	7.41	3.55	3.36	1.86	8.07	7.50	3.42	3.23	1.74
1f	7.98	7.47	3.55	3.36	1.86	7.94	7.42	3.55	3.36	1.86	8.07	7.51	3.42	3.23	1.74
1g	7.98	7.48	3.55	3.36	1.87	7.94	7.42	3.55	3.36	1.87	8.07	7.51	3.42	3.23	1.74

[a] The values of the chemical shifts of **1** in D_2O (concentrations of **1a**–**f**: 1.0 mmol · dm^{-3} and of **1g**: 0.5 mmol · dm^{-3}) were shown in Figures 2–5. The values of the chemical shifts of **1** in $CDCl_3$ (concentrations of **1a**: 2 mmol · dm^{-3}, of **1b**: 14 mmol · dm^{-3}, and of **1c**–**g**: 25–30 mmol · dm^{-3}) were shown in experimental section.
[b] The protons of xanthine ring at 8-position.
[c] The protons of thymine ring at 6-position.
[d] The methyl groups of xanthine ring at 1- and 3-positions.
[e] The methyl groups of thymine ring at 5-position.

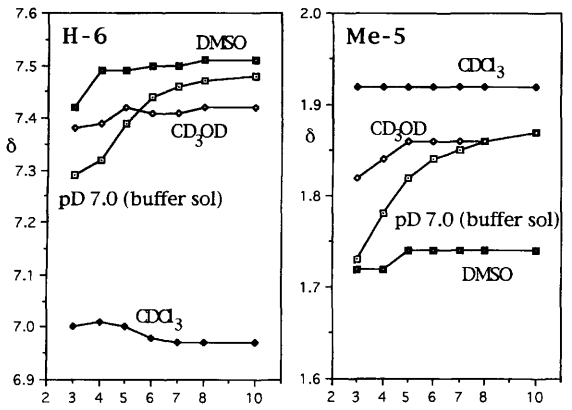


FIGURE 1 Relationship between the chemical shifts of H-6 and Me-5 of thymine ring of **1** and the carbon numbers of the polymethylene chains in the buffer solution at pD 7.0, CD_3OD, DMSO-d_6, and $CDCl_3$ at 27°C.

d_6 and in $CDCl_3$ was not studied. Since the molcular aggregation between thymine and 1,3-dimethylxanthine rings in aqueous solutions is not anticipated to result from interactions other than stacking interactions, the upfield shifts in the buffer solution at pD 7.0 are explained in terms of the effects of the ring current of xanthine ring due to the stacking interactions between thymine and 1,3-dimethylxanthine rings.

Relationships between the chemical shifts of the protons of thymine and xanthine rings of **1** and the carbon numbers of the polymethylene chains in D_2O at 27°C were in excellent agreement with those in the buffer solution at pD 7.0 shown in Figure 1 and Table II. This suggests that the ^1H NMR spectra of **1** were little affected by the pH values around neutrality. The measurements of **1** were made on solutions of concentrations of 1.0 mmol/dm^3 except for **1g** (0.5 mmol/dm^3). The ^1H NMR spectra of **1** in D_2O at 27°C were measured at least twice and the chemical shifts were reproduced within ±0.002 ppm. Since we previously investigated the NMR spectroscopy of 1,1′-(α,ω-alkanediyl)-bis[thymine] (**3**)[9] in D_2O, the chemical shifts of H-6 and Me-5 of thymine ring of **1** were compared with those of **3** in D_2O at 27°C. Figures 2 and 3 show the relationships of the chemical shifts of H-6 and Me-5 of thymine ring of **1**, respectively, in D_2O at 27°C. As can be seen from Figures 2 and 3, the proton resonances of **1** were unambiguously shifted to higher fields with the decrease of the length of the polymethylene, but the shifts of **3** were small. In view of the reported papers concerning the ring currents of nucleic acid bases [11], the difference between **1** and **3** may be attributable to the extent of the ring current effects of 1,3-dimethylxanthine ring of **1** and of thymine ring of **3**.

Relationships between the chemical shifts of H-8 and two methyl groups of xanthine ring of **1** and the carbon numbers of the polymethylene

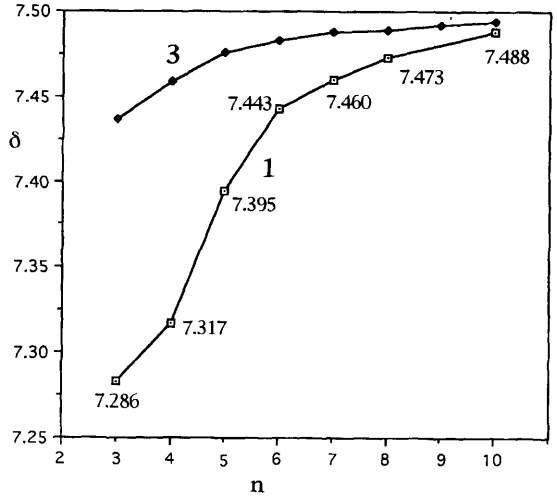


FIGURE 2 Relationship between the chemical shifts of H-6 of thymine ring of **1** and **3** and the carbon numbers of the polymethylene chains in D_2O at 27°C. The ^1H NMR spectra of **1** in D_2O at 27°C were measured at least twice and the chemical shifts were reproduced within ±0.002 ppm. The chemical shifts of **3** were reported in reference 9.

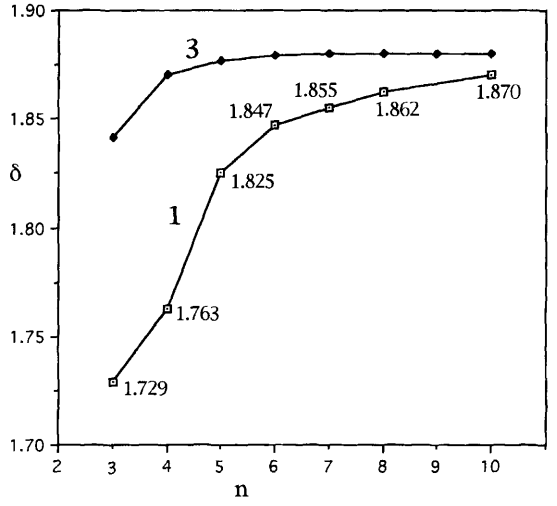


FIGURE 3 Relationship between the chemical shifts of 5-methyl groups of thymine ring of **1** and **3** and the carbon numbers of the polymethylene chains in D_2O at 27°C. The ^1H NMR spectra of **1** in D_2O at 27°C were measured at least twice and the chemical shifts were reproduced within ±0.002 ppm. The chemical shifts of **3** were reported in reference 9.

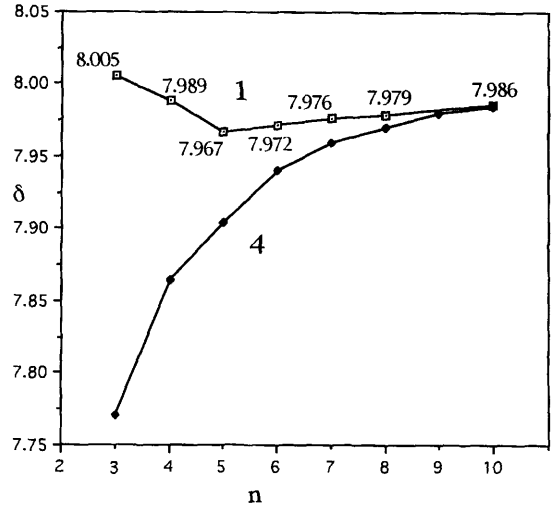


FIGURE 4 Relationship between the chemical shifts of H-8 of xanthine ring of **1** and **4** and the carbon numbers of the polymethylene chains in D_2O at 27°C. The ^1H NMR spectra of **1** in D_2O at 27°C were measured at least twice and the chemical shifts were reproduced within ±0.002 ppm. The chemical shifts of **4** were reported in reference 8.

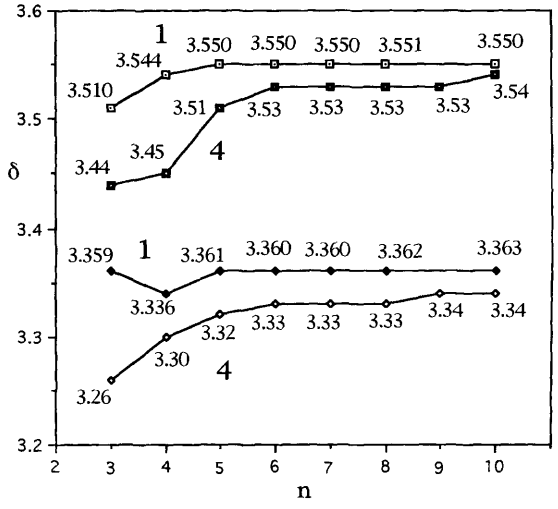


FIGURE 5 Relationship between the chemical shifts of methyl groups at 1- and 3- positions of xanthine ring of **1** and **4** and the carbon numbers of the polymethylene chains in D_2O at 27°C. The ^1H NMR spectra of **1** in D_2O at 27°C were measured at least twice and the chemical shifts were reproduced within ±0.002 ppm.

chains were compared with those of 7,7′-(α,ω-alkanediyl)bis[1,3-dimethylxanthine] (**4**) [8]. Figures 4 and 5 show the relationships of H-8 and of NMe of xanthine ring of **1**, respectively. The relationships of **1** were different form those of **4**. Contrary to the upfield shifts of H-6 and Me-5 of

thymine ring of **1** shown in Figures 2 and 3, the proton resonances of H-8 of xanthine ring of **1** were shifted to lower fields when the carbon numbers were 3 and 4, though the shifts were small. On the other hand, the chemical shifts of the signals of NMe of xanthine ring of **1a, b** ($n = 3, 4$) were slightly shifted to higher fields compared with those of **1c – g** ($n \geq 5$).

Table III shows temperature dependence of the chemical shifts of **1a** ($n = 3$) and **1b** ($n = 4$). The effect of temperature was not remarkable. However the H-8 of xanthine ring were shifted to higher fields with an increase in temperature while Me-5 of thymine ring was shifted to lower fields with an increase of temperature.

The upfield shifts of the thymine ring signals of **1** with shorter polymethylene chains are explained in terms of the influence of the local ring current fields of xanthine ring due to the stacking. Similarly, the slight upfield shifts of two NMe groups of xanthine ring of **1a, b** may be caused by the ring current fields of thymine ring. On the contrary, from a consideration of the downfield shifts of H-8 signals of the xanthine ring of **1a, b**, the protons of xanthine ring at 8-position can be assumed to be located outside the stacking. On the basis of these data, it seems to conclude that there is a stacked conformation of **1** between thymine ring and the pyrimidine part of xanthine ring. A stacked conformation between thymine and 1,3-dimethylxanthine rings of **1** may be tentatively presumed as shown in Chart 2.

EXPERIMENTAL SECTION

The melting points were determined on a Yanagimoto micro melting-point apparatus and are uncorrected. The elemental analyses were performed by the Analytical Center of Kyoto University. The preparation of 1-(ω-bromoalkyl) thymine (**2**) was previously reported [9].

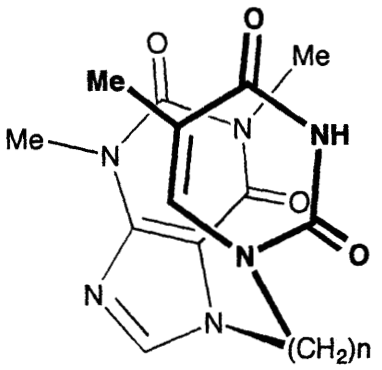
NMR Spectroscopy

The ^{1}H NMR spectra (400 MHZ) and ^{13}C NMR spectra (100 MHZ) were obtained with a JEOL GSX400 spectrometer. The chemical shifts (δ-values) were measured in parts per million (ppm) downfield from sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 in the aqueous solutions and from tetramethylsilane in organic solvents as internal references. The concentrations of 3-(trimethylsilyl)propionate-2,2,3,3-d_4 were 0.6 mmol dm^{-3} in D_2O and in the sodium phosphate buffer solution at pD 7.0 [10]. The ^{1}H NMR spectra were obtained from accumulation of 40 – 2200 free induction decays after each 45° pulse (5.7 μs) repeated every 5.73 s and were

TABLE III Effect of temperature on the chemical shifts of **1a** and **1b** in D_2O

	1a ($n = 3$) (Concentration: 2.1 mmol · dm^{-3})					**1b** ($n = 4$) (3.5 mmol · dm^{-3})				
	H-8[a]	H-6[b]	NMe[c]	NMe[c]	Me[d]	H-8[a]	H-6[a]	NMe[c]	NMe[c]	Me[d]
25°C	8.006	7.287	3.510	3.360	1.730	7.989	7.318	3.544	3.335	1.764
30°C	8.004	7.286	3.512	3.360	1.734	7.985	7.317	3.543	3.334	1.769
40°C	7.998	7.283	3.514	3.362	1.739	7.977	7.316	3.543	3.334	1.777
50°C	7.991	7.277	3.516	3.359	1.743	7.969	7.313	3.543	3.335	1.785
60°C	7.986	7.274	3.516	3.360	1.749	7.962	7.310	3.545	3.336	1.792
70°C	7.981	7.271	3.518	3.358	1.753	7.956	7.308	3.543	3.338	1.797
80°C	7.974	7.268	3.519	3.360	1.759	7.950	7.306	3.545	3.338	1.803
$\Delta(\delta)$[e]	−0.032	−0.019	+0.009	0.000	+0.029	−0.039	−0.012	+0.001	+0.003	+0.039

[a] The protons of xanthine ring at 8-position.
[b] The protons of thymine ring at 6-position.
[c] The methyl groups of xanthine ring at 1- and 3-positions.
[d] The methyl groups of thymine ring at 5-position.
[e] $\Delta(\delta) = \delta(80°C) - \delta(25°C)$.



A tentative stacked conformation

CHART 2

observed over a spectral width of 6002.4 Hz, corresponding to 32768 data points for acquisition time of 2.73 s.

7-[ω-(2, 4-Dioxo-1,2,3,4-tetrahydro-5-methyl-1-pyrimidinyl)alkyl]-1,3-dimethylxanthine (1)

Into a solution of theophylline (1,3-dimethylxanthine) (1 mmol) and *tert*-BuOK (1 mmol) in DMF (50 ml), 1-(ω-bromoalkyl)thymine (**2**) [9] (1 mmol) was added. The mixture was stirred at room temperature for 24 h. The resulting mixture was evaporated to give a residue which was submitted to chromatography over silica gel. Elution of a mixture of chloroform and methanol or a mixture of ethyl acetate and methanol gave **1**. The spectral data are given below.

7-[3-(2,4-Dioxo-1,2,3,4-tetrahydro-5-methyl-1-pyrimidinyl)propyl]-1,3-dimethylxanthine (1a)

Mp 306–310°C; ^{1}H NMR ($CDCl_3$) δ 8.09 (s, 1H, NH), 7.70 (s, 1H), 7.00 (q, 1H, J=1 Hz), 4.35 (t, 2H, J=6.6 Hz), 3.78 (t, 2H, J=6.6 Hz), 3.60 (s, 3H), 3.42 (s, 3H), 2.32 (quintet, 2H, J=6.6 Hz), 1.92 (d, 3H, J=1 Hz); ^{1}H NMR (DMSO-d_6) δ 11.20 (s, 1H, NH), 8.05 (s, 1H), 7.42 (s, 1H), 4.28 (t, 2H, J=6.6 Hz), 3.65 (t, 2H, J=6.6 Hz), 3.42 (s, 3H), 3.23 (s, 3H), 2.14 (quintet, 2H, J=6.6 Hz), 1.72 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 164.4, 154.5, 151.2, 151.1, 148.6, 142.6, 141.2, 108.8, 106.2, 44.6, 44.0, 29.6, 29.5, 27.7, 12.0. Found: C, 51.75; H, 5.28; N, 24.37%. calcd for $C_{15}H_{18}N_6O_4$: C, 52.02; H, 5.24; N, 24.27%.

7-[4-(2,4-Dioxo-1,2,3,4-tetrahydro-5-methyl-1-pyrimidinyl)butyl]-1,3-dimethylxanthine (1b)

Mp 236–238°C; ^{1}H NMR ($CDCl_3$) δ=7.96 (s, 1H, NH), 7.57 (s, 1H), 7.01 (q, 1H, J=1 Hz), 4.34 (t, 2H, J=7.0 Hz), 3.75 (*t*, 2H, J=7.0 Hz), 3.60 (s, 3H), 3.42 (s, 3H), 1.93 (quintet, 2H, J=7.0 Hz), 1.92 (d, 3H, J=1 Hz), 1.73 (quintet, 2H, J=7.0 Hz); ^{13}C NMR ($CDCl_3$) δ=163.7, 155.2, 151.6, 150.7, 149.1, 141.1, 140.2, 111.0, 106.9, 47.6, 46.3, 29.8, 28.0, 27.9, 25.7, 12.3. Found: C, 53.26; H, 5.59; N, 23.05%. Calcd for $C_{16}H_{20}N_6O_4$: C, 53.32; H, 5.59; N, 23.32%.

7-[5-(2,4-Dioxo-1,2,3,4-tetrahydro-5-methyl-1-pyrimidinyl)pentyl]-1,3-dimethylxanthine (1c)

Mp 204–206°C; ^{1}H NMR ($CDCl_3$) δ=8.92 (s, 1H, NH), 7.57 (s, 1H), 7.00 (q, 1H, J=1 Hz), 4.29 (t, 2H, J=7.2 H), 3.70 (t, 2H, J=7.2 Hz), 3.60 (s, 3H), 3.42 (s, 3H), 1.96 (broad quintet, 2H, J=7.2 Hz), 1.92 (d, 3H, J=1 Hz), 1.75 (broad quintet, 2H, J=7.2 Hz), 1.39 (broad quintet, 2H, J=7.2 Hz); 13C NMR ($CDCl_3$) δ=164.1, 155.2, 151.7, 150.9, 149.1, 140.9, 140.3, 110.9, 107.0, 48.0, 46.9, 30.4, 29.8, 28.3, 28.0, 23.1, 12.3. Found: C, 52.22; H, 6.00; N, 21.77%. Calcd for $C_{17}H_{22}N_6O_4 \cdot H_2O$: C, 52.03; H, 6.16; N, 21.42%.

7-[6-(2,4-Dioxo-1,2,3,4-tetrahydro-5-methyl-1-pyrimidinyl)hexyl]-1,3-dimethylxanthine (1d)

Mp 207–208.5°C; ^{1}H NMR ($CDCl_3$) δ=8.83 (s, 1H, NH), 7.57 (s, 1H), 6.98 (q, 1H, J=1 Hz), 4.28 (t, 2H, J=7.2 Hz), 3.68 (t, 2H, J=7.2 Hz), 3.60

(s, 3H), 3.42 (s, 3H), 1.92 (d, 3H, J=1Hz), 1.90 (broad quintet, 2H, =7.2 Hz), 1.68 (broad quintet, 2H, J=7.2 Hz),1.44–1.37 (broad m, 4H); ^{13}C NMR ($CDCl_3$) δ=164.1, 155.2, 151.7, 150.8, 149.0, 140.9, 140.2, 110.8, 107.0, 48.2, 47.1, 30.7, 29.8, 28.8, 28.0, 25.9, 25.8, 12.3. Found: C, 53.00; H, 5.96; N, 20.87%. Calcd for $C_{18}H_{24}N_6O_4 \cdot H_2O$: C, 53.19; H, 6.45; N, 20.68%.

7-[7-(2,4-Dioxo-1,2,3,4-tetrahydro-5-methyl-1-pyrimidinyl)heptyl]-1,3-dimethylxanthine (1e)

Mp 178–179.5°C; ^{1}H NMR ($CDCl_3$) δ=8.84 (s, 1H, NH), 7.57 (s, 1H), 6.97 (q, 1H, J=1 Hz), 4.28 (t, 2H, J=7.2 Hz), 3.68 (t, 2H, J=7.2 Hz), 3.60 (s, 3H), 3.42 (s, 3H), 1.92 (d, 3H, J=1 Hz), 1.88 (quintet, 2H, J=7.2 Hz), 1.66 (quintet, 2H, J=7.2 Hz), 1.43–1.30 (broad m, 6H); ^{13}C NMR ($CDCl_3$) δ=164.1, 155.2, 151.7, 150.8, 149.0, 140.9, 140.2, 110.7, 107.0, 48.3, 47.2, 30.8, 29.8, 29.0, 28.5, 28.0, 26.2, 12.3. Found: C, 56.73; H, 6.49; N, 20.85%. Calcd for $C_{19}H_{26}N_6O_4$: C, 56.70; H, 6.51; N, 20.88%.

7-[8-(2,4-Dioxo-1,2,3,4-tetrahydro-5-methyl-1-pyrimidinyl)octyl]-1,3-dimethylxanthine (1f)

Mp 167–168°C; ^{1}H NMR ($CDCl_3$) δ=8.95 (s, 1H, NH), 7.57 (s, 1H), 6.97 (q, 1H, J=1 Hz), 4.28 (t, 2H, J=7.2 Hz), 3.68 (t, 2H, J=7.2 Hz), 3.60 (s, 3H), 3.42 (s, 3H), 1.92 (d, 3H, J=1 Hz), 1.87 (quintet, 2H, J=7.2 Hz), 1.66 (quintet, 2H, J=7.2 Hz), 1.38–1.27 (broad, 8H); ^{13}C NMR ($CDCl_3$) δ=164.2, 155.2, 151.7, 150.8, 149.0, 140.9, 140.3, 110.6, 107.0, 48.4, 47.2, 30.8, 29.8, 29.0, 28.9, 28.8, 28.0, 26.2, 12.3. Found:C, 57.58; H, 6.83; N, 20.06%. Calcd for $C_{20}H_{28}N_6O_4$: C, 57.67; H, 6.78; N, 20.18%.

7-[10-(2,4-Dioxo-1,2,3,4-tetrahydro-5-methyl-1-pyrimidinyl)decyl]-1,3-dimethylxanthine(1g)

Mp 134–135°C; ^{1}H NMR ($CDCl_3$) δ=8.59 (s, 1H, NH), 7.57 (s, 1H), 6.97 (q, 1H, J=1 Hz), 4.28 (t, 2H, J=7.2 Hz), 3.68 (t, 2H, J=7.2 Hz), 3.60 (s, 3H), 3.42 (s, 3H), 1.92 (d, 3H, J=1 Hz), 1.87 (quintet, 2H, J=7.2 Hz), 1.66 (broad quintet, 2H, J=7.2 Hz), 1.36–1.24 (broad, 12H); ^{13}C NMR ($CDCl_3$) δ=164.0, 155.2, 151.7, 150.7, 148.9, 140.9, 140.4, 110.6, 107.0, 48.5, 47.3, 30.9, 29.8, 29.2, 29.2, 29.0, 29.0, 28.9, 28.0, 26.3, 26.3, 12.3. Found: C, 59.23; H, 7.32; N, 18.73%. Calcd for $C_{22}H_{32}N_6O_4$: C, 59.44; H, 7.26; N, 18.91%.

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