# Synthesis of a New Series of 1*H*-Imidazol-1-yl Substituted 8-Phenylxanthines as Adenosine Receptor Ligands

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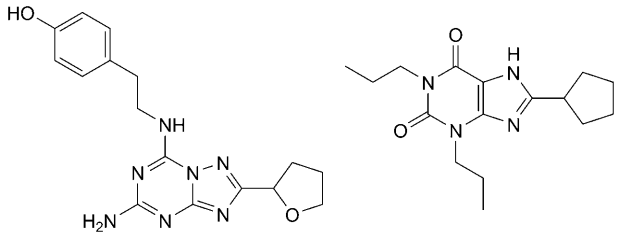
A new series of 1*H*-imidazol-1-yl substituted 8-phenylxanthine analogs has been synthesized to study the effects of the imidazole group on the binding affinity of compounds for adenosine receptors. Competition binding studies of these compounds were carried out *in vitro* with human cloned receptors using [$^3$H]DPCPX and [$^3$H]ZM 241385 as radioligands at $A_1$ and $A_{2A}$ adenosine receptors, respectively. The effect of the substitution pattern of the (imidazolyl)alkoxy group on various positions of the phenyl ring at C(8) was also studied. The xanthine derivatives displayed varying degrees of affinity and selectivity towards $A_1$ and $A_{2A}$ receptor subtypes despite a common but variedly substituted Ar–C(8).

**1. Introduction.** – Adenosine receptors represent important pharmacological targets in the treatment of a variety of diseases such as anti-inflammatory conditions, sepsis, heart attack, asthma, diabetes, obesity, and *Parkinson*'s disease [1][2]. Over the past years, the search for ligands that show selectivity and potency towards individual receptor subtypes has intensified, as the role of these receptors in many therapeutic areas is continuously expanding [3–5]. ZM 241385 and DPCPX (*Fig.*) have been reported as potent selective adenosine $A_{2A}$ and $A_1$ receptor ligands, respectively [4]. Substituted xanthines (= 3,7-dihydro-1*H*-purine-2,6-diones) represent the most potent class of adenosine receptor antagonists reported to date. 8-Phenyltheophylline is the parent member of a variety of potent adenosine receptor antagonists. It has been established that appropriate substituents on the phenyl ring at C(8) affects the potency




ZM 241385 DPCPX

Figure. *Structures of adenosine receptor ligands ZM 241385* (for $A_{2A}$ receptors) *and DPCPX* (for $A_1$ receptors)

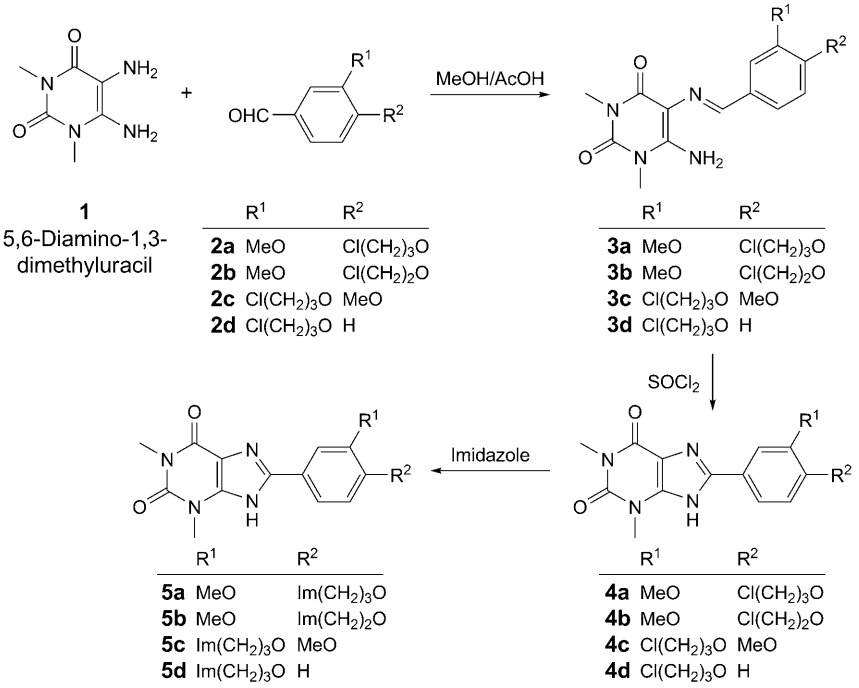
and selectivity towards adenosine receptors and thus their pharmacological effects [4][6].

As a part of our ongoing research program directed towards the search for new 8-phenyl-substituted xanthine-based highly effective ligands for the adenosine receptors [6][7], here we report a new series of 8-{[(imidazolyl)alkoxy]phenyl}xanthines along with variable substitutions at 1-, 3-, and 7-positions of the 8-phenylxanthine scaffold. The substitution pattern of the 8-phenyl substituent was also changed to study its effects on the affinity for adenosine $A_1$ and $A_{2A}$ receptors. 1*H*-Imidazole, a pharmacologically active heteroaromatic ring has been selected for substitution at C(8) of the phenyl ring, as such a moiety has been shown to induce selectivity for adenosine receptors and may also result in synergistic effects [8–10]. The substituents at 1-, 3- and 7-positions of the skeleton in some selected xanthines were also modified to study the structure–activity relationship, as alterations in substitutions at these positions lead to noticeable changes on the adenosine receptor affinity [11–13]. The newly synthesized compounds were evaluated by radioligand-binding studies using [$^3$H]DPCPX and [$^3$H]ZM 241385 as radioligands at $A_1$ and$A_{2A}$ adenosine receptors, respectively [14][15].

**2. Results and Discussion.** – 2.1. *Synthesis.* A variety of synthetic pathways have been followed by various research groups involved in the development of new therapeutically useful xanthine derivatives [16–18]. The synthesis of 8-substituted xanthine derivatives reported in this study has been carried out according to a previously described procedure from uracil and corresponding aryl aldehydes [16] as shown in *Schemes 1–3*. Oxidative cyclization of the resulting imine intermediate using $SOCl_2$ afforded the xanthines in good yields. Synthesis of 5,6-diamino-1,3-dimethyluracil (**1**), a key intermediate to the synthesis of all the 8-substituted xanthine derivatives, was performed according to the general method as reported earlier [19][20].

Treatment of substituted aldehydes **2a**–**2d**, which in turn were synthesized by treating vanillin, isovanillin, and 3-hydroxybenzaldehyde with 1-bromo-3-chloropropane or 1-bromo-2-chloroethane in refluxing ethyl methyl ketone, with **1** in MeOH/AcOH 4:1 at room temperature, resulted in the formation of the corresponding (benzylidene)amino derivatives **3a**–**3d**. A *singlet* integrating for one H-atom appeared at *ca.* $\delta$(H) 9.75 for N=CH in the $^1$H-NMR spectra of **3a**–**3d**. Subsequent ring closure of these intermediates by refluxing in $SOCl_2$ for 30–40 min afforded the chloroalkoxy compounds **4a**–**4d** (*Scheme 1*). The incorporation of an imidazolyl group was achieved by fusion of **4a**–**4d** with powdered 1*H*-imidazole at 160° for 2 h to afford (imidazolyl)alkoxy derivatives **5a**–**5d**. Resonances for imidazolyl H-atoms in the $^1$H-NMR spectra appeared in the range of $\delta$(H) 6.90–8.00. The effects of varying the alkyl substituents at the 1-, 3-, and 7-positions of 8-substituted xanthines on adenosine receptor affinity are well-known [21–23]. Therefore, we also modified the substitution pattern at 1-, 3-, and 7-positions in some of the newly synthesized 8-(imidazolyl-substituted)phenylxanthines to study the structure–activity relationship. Propylation was carried out by adding PrBr to a heated mixture of **4a** and **4d**, respectively, in DMF in the presence of anhydrous $K_2CO_3$ to afford the corresponding 7-propyl derivatives **6** and **10** (*Scheme 2*), which showed NMR signals at $\delta$(H) 0.88 (*t*, *Me*$CH_2$), 1.86 (*m*, MeC*H*$_2$), and 4.29 (*t*, $CH_2$N) for H-atoms of the Pr group. Further, reaction of **6** and **10** with 1*H*-imidazole at 120° for 2 h yielded the imidazolyl-substituted counterparts **7** and

Scheme 1. *Synthetic Route to 8-Substituted Xanthines* **4a**–**4d** *and* **5a**–**5d**



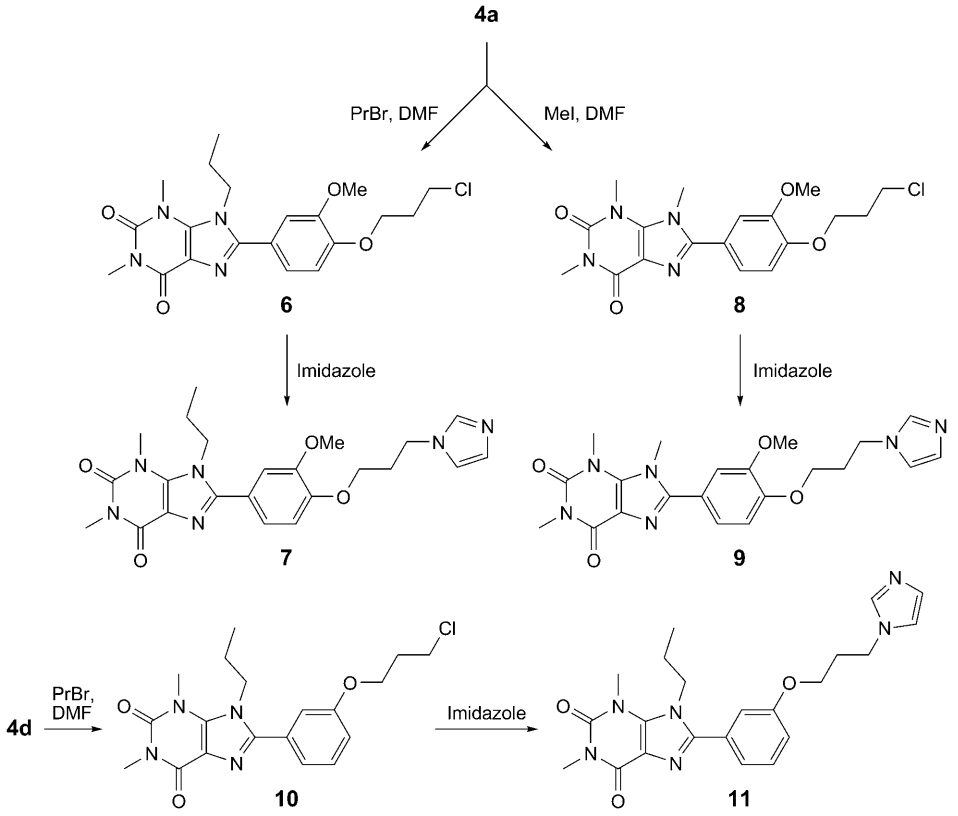

**11**, respectively (*Scheme 2*). For the synthesis of 8-(imidazolyl-substituted phenyl)-xanthines with a Me group at 7-position, **4a** and MeI were heated at 70–80° in DMF in the presence of anh. $K_2CO_3$ to give **8**, which, on treatment with imidazole, gave the desired tetra-substituted xanthine **9**. Three *singlet*s for MeN groups of the purine nucleus appeared in the NMR spectra of **8** and **9**, confirming the formation of 1,3,7-trimethylxanthine derivatives.

Condensation of 5,6-diamino-1-methyluracil [7][24] and 5,6-diamino-1-methyl-3-propyluracil [7][24] with **2a** in MeOH/AcOH 4:1 afforded the corresponding (benzylidene)amino derivatives **12a** and **12b**, which, on subsequent ring closure in refluxing $SOCl_2$, gave the corresponding chloroalkoxy derivatives **13a** and **13b** (*Scheme 3*). Further, treatment with imidazole afforded (imidazolyl)propoxy derivatives **14a** and **14b**, respectively.

2.2. *Biological Studies.* The newly synthesized compounds were evaluated using radioligand-binding studies at cloned human $A_1$ and $A_{2A}$ adenosine receptors. [$^3$H]DPCPX and [$^3$H]ZM241385 were used as radioligands for $A_1$ and $A_{2A}$ adenosine receptors, respectively [14][15].

The observed affinities of various newly synthesized 8-phenylxanthine derivatives in radioligand-binding assays at human $A_1$ and $A_{2A}$ receptors are compiled in the *Table*. The three series, *i.e.*, vanillin-, isovanillin-, and 3-hydroxybenzaldehyde-based xanthine derivatives displayed varying degrees of affinity and selectivity towards $A_1$ and $A_{2A}$ receptor subtypes despite a common substitution of chloro/(imidazolyl)alkoxy group

Scheme 2. *Synthetic Route to 7-Alkylated Xanthines* **6**–**11**




on 8-phenyl ring in accordance with our earlier report [6]. This is attributed to the varied positioning of the phenyl substituent. In general, the chloro precursors **4a**–**4d** (except **4c**), **6**, **8**, and **10** were found to be more potent and selective ligands for $A_{2A}$ over $A_1$ receptors in comparison to their imidazolyl-substituted analogues **5a**–**5d**, **7**, **9**, and **11**, respectively. The incorporation of an imidazole group in the side chain resulted in increased affinity for $A_1$ receptors and thereby decreased selectivity for $A_{2A}$ receptors in case of vanillin-derived xanthine derivatives **5a**, **7**, **9**, and **11**. However, in the case of 3-(1*H*-imidazol-1-yl)propoxy derivative **5d**, which is without an *ortho* MeO group, binding was observed only at $A_1$ receptors ($K_i$ of 3.6 μM) with little effect on $A_{2A}$ receptors at 100 μM. The isovanillin derivatives **4c** and **5c** exhibited substantial loss of binding affinity for both adenosine receptor subtypes.

7-Alkylation (propylation and methylation) of vanillin-based products **4a** and **5a** resulted in marginal loss of affinity and selectivity for adenosine receptors in both chloropropoxy (*i.e.*, **6** and **8**) and (imidazolyl)propoxy (*i.e.*, **7** and **9**) derivatives; however, the binding pattern remains the same. The effect of propylation of monosubstituted 8-phenylxanthines **4d** and **5d** was also tested. Although the effects were insignificant for chloroalkoxy derivative **10**, more than 100-fold increase in

Scheme 3. *Synthesis of 1-Unsubstituted/Substituted 8-Substituted Xanthines* **13a**, **13b**, **14a**, *and* **14b**

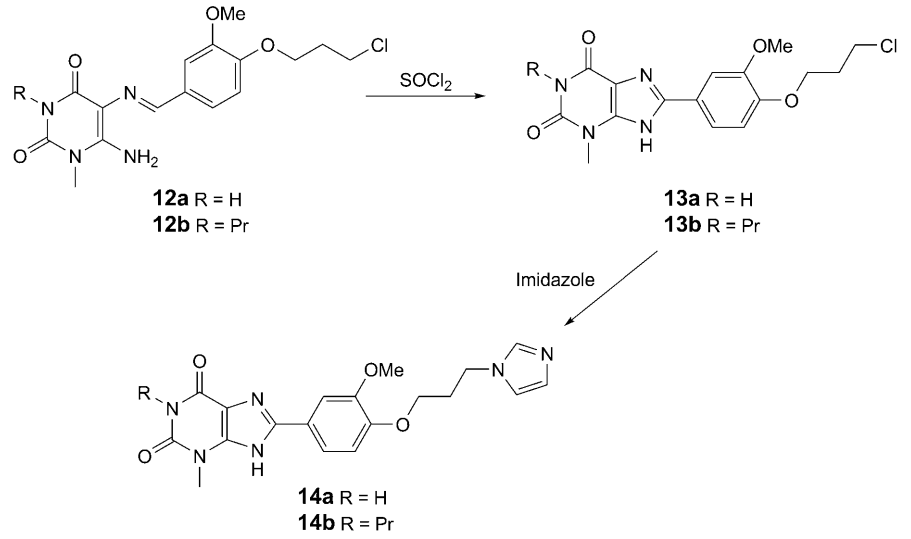



Table. *Adenosine $A_1$ and $A_{2A}$ Binding Affinities of Various Compounds*

| Compound | Code | $K_i$ [μM][a]) | | |
|---|---|---|---|---|
| | | $A_1$ | $A_{2A}$ | $A_1/A_{2A}$ |
| **4a** | RG- DPJ-28 | >100 | 0.32 (0.2–0.6) | >312 |
| **4b** | RG-DPJ-104 | >100 | 0.18 (0.08–0.37) | >555 |
| **4c** | RG-DPJ-69 | >100 | >100 | – |
| **4d** | RG-DPJ-95 | >100 | 0.1 (0.06–0.18) | >1000 |
| **5a** | RG-DPJ-29 | 3.1 (0.3–28) | 0.5 (0.25–0.98) | 6.2 |
| **5b** | RG-DPJ-105 | >100 | 0.7 (0.6–0.9) | >142 |
| **5c** | RG-DPJ-70 | >100 | >100 | – |
| **5d** | RG-DPJ-96 | 3.6 (0.8–16) | >100 | 0.036 |
| **6** | RG-DPJ-239 | >100 | 1 (0.6–1.5) | >100 |
| **7** | RG-DPJ-241 | 17.7 (0.7–43) | 0.84 (0.7–1.1) | 21 |
| **8** | RG-DPJ-237 | >100 | 0.7 (0.4–1.2) | >138 |
| **9** | RG-DPJ-295 | 18.9 (4.2–86) | 1.4 (0.8–2.5) | 13.5 |
| **10** | RG-DPJ-252 | >100 | 2.9 | >34 |
| **11** | RG-DPJ-251 | 10.8 (2.2–52) | 2.0 (1.2–3.4) | 5 |
| **13a** | RG-DPJ-256 | >100 | >100 | – |
| **13b** | RG-DPJ-264 | >100 | >100 | – |
| **14a** | RG-DPJ-257 | >100 | >100 | – |
| **14b** | RG-DPJ-296 | 1.1 (0.6–2.2) | 0.44 (0.3–0.7) | 2.5 |
| | DPCPX | 0.095 (0.06–0.15) | 0.13[b]) | 0.73 |
| | ZM241385 | 0.54[b]) | 0.064 (0.03–0.14) | 8.43 |

[a]) $K_i$ Values are given with 95% confidence limits. [b]) From [25].

binding affinity was observed for $A_{2A}$ receptors in case of (imidazolyl)propoxy derivative **11** in comparison to **5d**. 1-Unsubstituted analogs **13a** and **14a** showed little variation of binding at $A_1$ and $A_{2A}$ receptors at concentrations up to 100 μM. In contrast, introduction of 1-Pr group instead of Me led to loss of affinity for $A_{2A}$ receptors in case of chloropropoxy **13b** but almost no change in pattern of activity for (imidazolyl)propoxy derivative **14b** in comparison to their corresponding methylated derivatives **4a** and **5a**, respectively.

The newly synthesized xanthine derivatives displayed slightly to markedly weaker binding affinity for adenosine receptors in comparison to the reference adenosine receptor ligands DPCPX and ZM241385 as shown in the *Table*. However, compound **5d** displayed 28 times more selectivity for $A_1$ *vs.* $A_{2A}$ in comparison to DPCPX, which is only 1.5 times more selective, and compound **4d** exhibited 1000 times more selectivity on $A_{2A}$ *vs.* $A_1$ as compared to ZM241385 with $A_{2A}$ *vs.* $A_1$ selectivity of 8.43.

**3. Conclusion.** – A new series of 8-{[(imidazolyl)alkoxy]phenyl}xanthines has been synthesized and evaluated for adenosine-binding affinity. Varied substitutions at 1-, 3-, and 7-positions and the substitution pattern of an 8-phenyl substituent cause marked changes in the binding affinity of xanthines for adenosine $A_1$ and $A_{2A}$ receptors. Suitable selection and positioning of substituents in xanthine skeleton may lead to development of potent and selective adenosine receptor ligands of therapeutic value.

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## Experimental Part

*Chemistry. General.* All solvents were freshly distilled and dried prior to use according to standard procedures. Anh. $Na_2SO_4$ was used as drying agent. TLC: silica gel *G* according to the method of *Stahl* (*E. Merck*) with AcOEt as solvent and activated at 110° for 30 min; $I_2$ was used to develop the TLC plates. M.p.: *Veego* melting-point apparatus; uncorrected. IR Spectra: *Perkin-Elmer 882* and *RX1 FT-IR* spectrophotometer models in KBr ($\tilde{\nu}_{max}$ in $cm^{-1}$). $^1$H-NMR: *Bruker AC-300F*, 300 MHz and *Varian EM-360*, 60 MHz spectrometers in $CDCl_3$/($D_6$)DMSO; $\delta$ in ppm (TMS = 0 ppm). Elemental analyses: *Perkin-Elmer-2400* CHN elemental analyzer.

*General Procedure for the Synthesis of the Substituted Aldehydes* **2a**–**2d**. 1-Bromo-3-chloropropane (1.5 ml, 14.15 mmol) was added to a stirred and refluxing suspension of vanillin, isovanillin, and 3-hydroxybenzaldehyde (1.0 g, 6.57 mmol) in the presence of anh. $K_2CO_3$ (2.0 g, 14.47 mmol) and ethyl methyl ketone (40 ml). In an analogous manner, vanillin was treated with 1-bromo-2-chloroethane. The mixture was further refluxed for 6 h with continuous stirring, and the reaction was monitored by TLC. The mixture was cooled, filtered, and the excess of solvent was removed under reduced pressure to afford *4-(3-chloropropoxy)-3-methoxybenzaldehyde* (**2a**), *4-(2-chloroethoxy)-3-methoxybenzaldehyde* (**2b**), *3-(3-chloropropoxy)-4-methoxybenzaldehyde* (**2c**), and *3-(3-chloropropoxy)benzaldehyde* (**2d**) [26][27], resp., as oily residues which were used as such for further reaction.

*General Procedure for the Synthesis of the (Benzylidene)amino Derivatives* **3a**–**3d** *and* **12a**–**12b**. To a stirred soln. of *5,6-diamino-1,3-dimethyluracil* (**1**; 1.0 g, 5.87 mmol) in MeOH/AcOH 4:1 (40 ml) was slowly added the soln. of the oily **2a**–**2d** in MeOH (24 ml). A precipitate formed after some time, and the mixture was further stirred overnight at r.t. The precipitate thus obtained was filtered off, washed with MeOH, and dried to afford the corresponding benzylidene derivatives **3a**–**3d**, resp., which were used as such for further cyclization. For the synthesis of **12a** and **12b**, **2a** was reacted with 5,6-diamino-1-methyluracil and 5,6-diamino-1-methyl-3-propyluracil, resp.

*6-Amino-5-{[4-(3-chloropropoxy)-3-methoxybenzylidene]amino}-1,3-dimethylpyrimidine-2,4(1*H,*3*H)-*dione* (**3a**). $^1$H-NMR (300 MHz, $CDCl_3$/($D_6$)DMSO): 2.24 (*quint.*, $CH_2$); 3.25 (*s*, MeN); 3.46 (*s*, MeN); 3.77 (*t*, $J$ = 4.40, $ClCH_2$); 3.89 (*s*, MeO); 4.15 (*t*, $J$ = 4.02, $CH_2O$); 6.93 (br. *s*, $NH_2$; disappeared on $D_2O$ exchange); 7.25 (*d*, $J_o$ = 8.19, 1 arom. H); 7.46 (*s*, 1 arom. H); 9.66 (*s*, H–C=N).

*6-Amino-5-{[4-(2-chloroethoxy)-3-methoxybenzylidene]amino}-1,3-dimethylpyrimidine-2,4(1*H,*3*H)-*dione* (**3b**). $^1$H-NMR (300 MHz, $CDCl_3$/($D_6$)DMSO): 3.38 (*s*, MeN); 3.48 (*s*, MeN); 3.83–3.87 (*m*, $ClCH_2$); 3.91 (*s*, MeO); 4.33 (*t*, $J$ = 5.79, $CH_2O$); 5.66 (br. *s*, $NH_2$; disappeared on $D_2O$ exchange); 6.92 (*d*, $J_o$ = 8.50, 1 arom. H); 7.28 (*dd*, $J_o$ = 8.26, $J_m$ = 2.00, 1 arom. H); 7.37 (*d*, $J_m$ = 1.99, 1 arom. H); 9.73 (*s*, H–C=N).

*6-Amino-5-{[3-(3-chloropropoxy)-4-methoxybenzylidene]amino}-1,3-dimethylpyrimidine-2,4(1*H,*3*H)-*dione* (**3c**). $^1$H-NMR (60 MHz, $CDCl_3$/($D_6$)DMSO): 2.10–2.60 (*m*, $CH_2$); 3.40 (*s*, MeN); 3.50 (*s*, MeN); 3.7–4.0 (*m*, $ClCH_2$); 3.95 (*s*, MeO); 4.28 (*t*, $J$ = 5.40, $CH_2O$); 5.81 (br. *s*, $NH_2$; disappeared on $D_2O$ exchange); 6.85–7.15 (*m*, 1 arom. H); 7.3–7.7 (*m*, 2 arom. H); 9.85 (*s*, H–C=N).

*6-Amino-5-{[3-(3-chloropropoxy)benzylidene]amino}-1,3-dimethylpyrimidine-2,4(1*H,*3*H)-*dione* (**3d**). $^1$H-NMR (60 MHz, $CDCl_3$/($D_6$)DMSO): 1.90–2.50 (*m*, $CH_2$); 3.35 (*s*, MeN); 3.45 (*m*, MeN, $ClCH_2$); 4.12 (*t*, $J$ = 4.50, $CH_2O$); 5.97 (br. *s*, $NH_2$; disappeared on $D_2O$ exchange); 6.90 (*m*, 1 arom. H); 7.32 (*m*, 3 arom. H); 9.70 (*s*, H–C=N).

*6-Amino-5-{[4-(3-chloropropoxy)-3-methoxybenzylidene]amino}-1-methylpyrimidine-2,4(1*H,*3*H)-*dione* (**12a**). $^1$H-NMR (300 MHz, $CDCl_3$/($D_6$)DMSO): 2.22–2.25 (*m*, $CH_2$); 3.51 (*s*, MeN); 3.77 (*t*, $ClCH_2$); 3.89 (*s*, MeO); 4.23 (*t*, $J$ = 6.0, $CH_2O$); 5.60 (br. *s*, $NH_2$; disappeared on $D_2O$ exchange); 6.92 (*d*, $J_o$ = 8.18, 1 arom. H); 7.30–7.33 (*m*, 2 arom. H); 9.72 (*s*, H–C=N).

*6-Amino-5-{[4-(3-chloropropoxy)-3-methoxybenzylidene]amino}-1-methyl-3-propylpyrimidine-2,4(1*H,*3*H)-*dione* (**12b**). $^1$H-NMR (300 MHz, $CDCl_3$): 0.96 (*t*, $J$ = 7.42, *Me*$CH_2$); 1.65–1.70 (*m*, Me$CH_2$); 2.28–2.34 (*m*, $ClCH_2CH_2$); 3.51 (*s*, MeN); 3.77 (*t*, $J$ = 6.28, $ClCH_2$); 3.90 (*s*, MeO); 3.92–3.97 (*m*, $CH_2N$); 4.21 (*t*, $J$ = 6.0, $CH_2O$); 5.62 (br. *s*, $NH_2$; disappeared on $D_2O$ exchange); 6.92 (*d*, $J_o$ = 8.18, 1 arom. H); 7.29–7.36 (*m*, 2 arom. H); 9.74 (*s*, H–C=N).

*General Procedure for the Synthesis of 8-[(Chloroalkoxy)phenyl]xanthines* **4a**–**4d** *and* **13a**–**13b**. The *Schiff* bases **3a** – **3d** and **12a**–**12b** (1.0 g, 2.63 mmol) were heated in $SOCl_2$ (20 ml) for 30–40 min to undergo cyclization. The excess $SOCl_2$ was removed under reduced pressure to obtain a solid product. Ice-cold $H_2O$ was added to it, and the resultant suspension was neutralized with $NH_4OH$ soln. The precipitate obtained was collected by filtration, dried, and recrystallized from a mixture DMF/MeOH to obtain the desired products **4a**–**4d** and **13a**–**13b**, resp.

*8-[4-(3-Chloropropoxy)-3-methoxyphenyl]-3,7-dihydro-1,3-dimethyl-1*H-*purine-2,6-dione* (**4a**). Yield: 0.75 g (75.45%). M.p. >270°. IR (KBr): 3200, 2960, 1690, 1640, 1490. $^1$H-NMR (300 MHz, $CDCl_3$/($D_6$)DMSO): 2.22 (*quint.*, $CH_2$); 3.28 (*s*, MeN); 3.51 (*s*, MeN); 3.79 (*t*, $J$ = 6.37, $ClCH_2$); 3.87 (*s*, MeO); 4.15 (*t*, $J$ = 5.98, $CH_2O$); 7.02 (*d*, $J_o$ = 8.31, 1 arom. H); 7.68–7.73 (*m*, 2 arom. H); 13.48 (br. *s*, NH). Anal. calc. for $C_{17}H_{19}ClN_4O_4$ (378.80): C 53.89, H 5.05, N 14.79; found: C 53.76, H 4.78, N 14.24.

*8-[4-(2-Chloroethoxy)-3-methoxyphenyl]-3,7-dihydro-1,3-dimethyl-1*H-*purine-2,6-dione* (**4b**). Yield: 0.68 g (68.68%). M.p. 296–298°. FT-IR (KBr): 3176, 2950, 1690, 1640, 1490, 1235. $^1$H-NMR (300 MHz, $CDCl_3$/($D_6$)DMSO): 3.33 (*s*, MeN); 3.58 (*s*, MeN); 3.64–3.90 (*m*, $J$ = 5.80, $ClCH_2$); 3.92 (*s*, MeO); 4.29 (*t*, $J$ = 5.79, $CH_2O$); 6.96 (*d*, $J_o$ = 8.50, 1 arom. H); 7.70 (*dd*, $J_o$ = 8.26, $J_m$ = 2.00, 1 arom. H); 7.74 (*d*, $J_m$ = 1.99, 1 arom. H); 13.2 (*s*, NH). Anal. calc. for $C_{16}H_{17}ClN_4O_4$ (364.5): C 52.68, H 4.69, N 15.36; found: C 52.33, H 4.17, N 14.90.

*8-[3-(3-Chloropropoxy)-4-methoxyphenyl]-3,7-dihydro-1,3-dimethyl-1*H-*purine-2,6-dione* (**4c**). Yield: 0.96 g (96.98%). M.p. 236–238°. IR (KBr): 3300, 1680, 1650, 1480, 1200. $^1$H-NMR (300 MHz, $CDCl_3$/($D_6$)DMSO): 2.30 (*quint.*, $J$ = 6.07, $CH_2$); 3.43 (*s*, MeN); 3.66 (*s*, MeN); 3.76 (*t*, $J$ = 6.24, $ClCH_2$); 3.90 (*s*, MeO); 4.23 (*t*, $J$ = 5.89, $CH_2O$); 6.90 (*s*, 1 arom. H); 7.50 (*s*, 1 arom. H); 12.50 (*s*, NH). Anal. calc. for $C_{17}H_{19}ClN_4O_4$ (378.80): C 53.89, H 5.05, N 14.79; found: C 53.76, H 4.85, N 14.42.

*8-[3-(3-Chloropropoxy)phenyl]-1,3-dimethyl-3,7-dihydro-1*H-*purine-2,6-dione* (**4d**). Yield: 0.43 g (43.46%). M.p. 240–242°. IR (KBr): 3190, 2960, 1700, 1650, 1480, 1210. $^1$H-NMR (300 MHz, $CDCl_3$/($D_6$)DMSO): 2.23–2.39 (*m*, $CH_2$); 3.40 (*s*, MeN); 3.63 (*s*, MeN); 3.79 (*t*, $J$ = 5.79, $ClCH_2$); 4.18 (*t*, $J$ = 5.77, $CH_2O$); 6.95–7.0 (*m*, 1 arom. H); 7.35 (*t*, $J_o$ = 8.11, 1 arom. H); 7.71–7.77 (*m*, 2 arom. H); 13.50 (br. *s*, NH). Anal. calc. for $C_{16}H_{17}ClN_4O_3$ (348.78): C 55.09, H 4.91, N 16.06; found: C 54.88, H 4.44, N 15.98.

*8-[4-(3-Chloropropoxy)-3-methoxyphenyl]-3,7-dihydro-3-methyl-1*H-*purine-2,6-dione* (**13a**). Yield: 0.75 g (75.45%). M.p. >300°. FT-IR (KBr): 3161, 3016, 1679, 1592, 1493, 1250, 1031. $^1$H-NMR (300 MHz, $CDCl_3$/($D_6$)DMSO): 2.30–2.34 (*m*, $CH_2$); 3.69 (*s*, MeN); 3.78 (*t*, *J* = 6.06, $ClCH_2$); 3.96 (*s*, MeO); 4.27 (*t*, *J* = 5.87, $CH_2O$); 7.06 (*d*, $J_o$ = 8.73, 1 arom. H); 7.61 (*s*, 1 arom. H); 7.69 (*d*, $J_o$ = 8.37, 1 arom. H). Anal. calc. for $C_{16}H_{17}ClN_4O_4$ (364.78): C 52.6, H 4.70, N 15.30; found: C 52.22, H 4.38, N 15.19.

*8-[4-(3-Chloropropoxy)-3-methoxyphenyl]-3,7-dihydro-3-methyl-1-propyl-1*H-*purine-2,6-dione* (**13b**). Yield: 0.80 g (80.64%). M.p. 212–216°. FT-IR (KBr): 3148, 3003, 2819, 1687, 1593, 1493, 1427, 1254, 1229, 1023. $^1$H-NMR (300 MHz, $CDCl_3$): 0.97 (*t*, *J* = 7.35, *Me*$CH_2$); 1.69–1.77 (*m*, MeC$H_2$); 2.29–2.37 (*m*, $ClCH_2CH_2$); 3.76 (*s*, MeN); 3.79 (*t*, *J* = 6.13, $ClCH_2$); 3.99 (*s*, MeO); 4.07 (*t*, *J* = 7.48, $CH_2N$); 4.24 (*t*, *J* = 5.89, $CH_2O$); 6.99 (*d*, $J_o$ = 8.35, 1 arom. H); 7.75 (*s*, 1 arom. H); 7.79 (*d*, $J_o$ = 8.34, 1 arom. H). Anal. calc. for $C_{19}H_{23}ClN_4O_4$ (406.85): C 56.09, H 5.69, N 13.77; found: C 55.95, H 5.57, N 13.58.

*General Procedure for the Synthesis of 7-Alkylated Xanthine Derivatives* **6**, **8**, *and* **10**. 1-Bromopropane (1.2 ml, 13.98 mmol) was added to a stirred slurry of **4a** and **4c** (0.7 g, 1.85 mmol) in presence of anh. $K_2CO_3$ (1.5 g, 10.85 mmol) in DMF (15 ml). Further, the mixture was stirred at 70–80° for 5 h, and completion of the reaction was monitored by TLC. The resultant suspension was filtered, cooled, and $H_2O$ was added. The precipitate obtained was filtered, washed thoroughly with cold $H_2O$, dried, and recrystallized from MeOH to afford corresponding 7-propylated chloroalkoxy derivatives **6** and **10**. The 7-methylated derivative **8** was synthesized by the same procedure by adding MeI as an alkylating agent to the stirred slurry of **4a**.

*8-[4-(3-Chloropropoxy)-3-methoxyphenyl]-3,7-dihydro-1,3-dimethyl-7-propyl-1*H-*purine-2,6-dione* (**6**). Yield: 0.4 g (51.9%). M.p. 108–112°. IR (KBr): 2965, 1695, 1537, 1438, 1275, 1036. $^1$H-NMR (300 MHz, $CDCl_3$): 0.88 (*t*, *J* = 7.40, *Me*$CH_2$); 1.83–1.88 (*m*, MeC$H_2$); 2.09–2.15 (*m*, $ClCH_2CH_2$); 3.44 (*s*, MeN); 3.64 (*s*, MeN); 3.90 (*t*, *J* = 5.94, $ClCH_2$); 3.94 (*s*, MeO); 4.25–4.33 (*m*, $CH_2N$, $CH_2O$); 7.00 (*d*, $J_o$ = 8.79, 1 arom. H); 7.13–7.16 (*m*, 2 arom. H). Anal. calc. for $C_{20}H_{25}ClN_4O_4$ (420.88): C 57.07, H 5.99, N 13.31; found: C 56.91, H 5.97, N 13.05.

*8-[4-(3-Chloropropoxy)-3-methoxyphenyl]-3,7-dihydro-1,3,7-trimethyl-1*H-*purine-2,6-dione* (**8**). Yield: 0.65 g (75%). M.p. 182–184°. FT-IR (KBr): 2945, 1694, 1656, 1538, 1486, 1427, 1235, 1031. $^1$H-NMR (300 MHz, $CDCl_3$): 2.31–2.39 (*m*, $CH_2CH_2$); 3.39–3.43 (*m*, MeN, $ClCH_2$); 3.63 (*s*, MeN); 3.93 (*s*, MeN); 4.05 (*s*, MeO); 4.16 (*t*, *J* = 5.88, $CH_2O$); 6.99 (*d*, $J_o$ = 8.87, 1 arom. H); 7.19 (*dd*, $J_o$ = 8.08, $J_m$ = 2.0, 1 arom. H); 7.24 (*d*, $J_m$ = 1.95, 1 arom. H). Anal. calc. for $C_{18}H_{21}ClN_4O_4$ (392.83): C 55.03, H 5.39, N 14.26; found: C 54.98, H 4.82, N 14.06.

*8-[3-(3-Chloropropoxy)phenyl]-3,7-dihydro-1,3-dimethyl-7-propyl-1*H-*purine-2,6-dione* (**10**). Yield: 0.15 g (19.10%). M.p. 118–120°. FT-IR (KBr): 2957, 1698, 1659, 1540, 1432, 1289, 1222, 1044. $^1$H-NMR (300 MHz, $CDCl_3$): 0.87 (*t*, *J* = 7.39, *Me*$CH_2$); 1.71–1.90 (*m*, MeC$H_2$); 2.23–2.39 (*m*, $ClCH_2CH_2$); 3.44 (*s*, MeN); 3.61 (*s*, MeN); 3.77 (*t*, *J* = 6.38, $ClCH_2$); 4.18 (*t*, *J* = 5.70, $CH_2O$); 4.32 (*t*, *J* = 7.81, $CH_2N$); 7.06 (*dd*, $J_o$ = 7.79, $J_m$ = 1.66, 1 arom. H); 7.17–7.19 (*m*, 2 arom. H); 7.44 (*t*, $J_o$ = 8.20, 1 arom. H). Anal. calc. for $C_{19}H_{23}ClN_4O_3$ (390.85): C 58.39, H 5.93, N 14.33; found: C 58.12, H 5.72, N 13.95.

*General Procedure for the Synthesis of 8-[(Imidazolylalkoxy)phenyl]xanthines* **5a**–**5d**, **7**, **9**, **11**, *and* **14a** *and* **14b**. The chloroalkoxy derivatives **4a**–**4d**, **6**, **8**, **10**, and **13a** and **13b** (0.40 g, 1.06 mmol) were treated with powdered 1*H*-imidazole (0.40 g, 5.87 mmol) at 140° for 3 h. The mixture was refluxed in dist. $H_2O$ for 1 h to remove the excess imidazole and filtered. Ice-cold $H_2O$ was added to the mixture and cooled in ice for complete precipitation. The precipitate thus obtained was filtered, washed with $H_2O$, and dried to obtain corresponding (imidazolyl)alkoxy compounds **5a**–**5d**, **7**, **9**, **11**, and **14a** and **14b**. The compounds **5a**–**5d** and **14a** and **14b** were recrystallized from a mixture DMF/MeOH, whereas **7**, **9**, and **11** were recrystallized from acetone.

*3,7-Dihydro-8-{4-[3-(1*H-*imidazol-1-yl)propoxy]-3-methoxyphenyl}-1,3-dimethyl-1*H-*purine-2,6-dione* (**5a**). Yield: 0.17 g (39.26%). M.p. 254–258°. IR (KBr): 3200, 2950, 1690, 1640, 1490, 1235. $^1$H-NMR (300 MHz, $CDCl_3$/($D_6$)DMSO): 2.20 (*quint.*, $CH_2CH_2CH_2$); 3.25 (*s*, MeN); 3.48 (*s*, MeN); 3.87 (*s*, MeO); 3.95 (*t*, *J* = 6.14, $CH_2N$); 4.15 (*t*, *J* = 6.84, $CH_2O$); 6.91 (*s*, 1 imidazole H); 7.05 (*d*, $J_o$ = 8.40, 1 arom. H); 7.22 (*s*, 1 imidazole H); 7.64–7.69 (*m*, 2 arom. H); 7.73 (*s*, 1 imidazole H). Anal. calc. for $C_{20}H_{22}N_6O_4$ (410.43): C 58.52, H 5.40, N 20.47; found: C 58.47, H 5.22, N 20.29.

*3,7-Dihydro-8-{4-[2-(1*H-*imidazol-1-yl)ethoxy]-3-methoxyphenyl}-1,3-dimethyl-1*H-*purine-2,6-dione* (**5b**). Yield: 0.32 g (74.07%). M.p. 288–292°. FT-IR (KBr): 3184, 2944, 1684, 1643, 1555, 1488, 1446, 1276,

1223, 1038. $^1$H-NMR (300 MHz, $CDCl_3$/($D_6$)DMSO): 3.40 (*s*, MeN); 3.63 (*s*, MeN); 3.95 (*s*, MeO); 4.34 (*t*, *J* = 4.92, $CH_2N$); 4.48 (*t*, *J* = 4.77, $CH_2O$); 6.91 (*d*, $J_o$ = 9.10, 1 arom. H); 7.10 (*s*, 1 imidazole H); 7.26 (*s*, 1 imidazole H); 7.73 (*dd*, $J_o$ = 8.44, $J_m$ = 1.76, 1 arom. H); 7.77 (*d*, $J_m$ = 1.6, 1 arom. H); 7.99 (*s*, 1 imidazole H). Anal. calc. for $C_{19}H_{20}N_6O_4$ (396): C 57.57, H 5.09, N 21.20; found: C 57.74, H 4.84, N 21.09.

*3,7-Dihydro-8-{3-[3-(1*H*-imidazol-1-yl)propoxy]-4-methoxyphenyl}-1,3-dimethyl-1*H*-purine-2,6-dione* (**5c**). Yield: 0.3 g (69.23%). M.p. 236°. IR (KBr): 3320, 1680, 1620, 1480, 1200. $^1$H-NMR (300 MHz, $CDCl_3$/($D_6$)DMSO): 2.29 (*quint.*, *J* = 6.15, $CH_2$); 3.42 (*s*, MeN); 3.63 (*s*, MeN); 3.93 (*s*, MeO); 4.02 (*t*, *J* = 5.70, $CH_2$); 4.25 (*t*, *J* = 6.65, $CH_2O$); 6.97–7.03 (*m*, 2 imidazole H, 1 arom. H); 7.37 (*s*, 1 arom. H), 7.60 (*s*, 1 imidazole H); 12.85 (*s*, NH). Anal. calc. for $C_{20}H_{22}N_6O_4$ (410.43): C 58.52, H 5.40, N 20.48; found: C 58.48, H 5.12, N 19.98.

*3,7-Dihydro-8-{3-[3-(1*H*-imidazol-1-yl)propoxy]phenyl}-1,3-dimethyl-1*H*-purine-2,6-dione* (**5d**). Yield: 0.16 g (36.69%). M.p. 218–220°. FT-IR (KBr): 3190, 2950, 1700, 1650, 1450, 1210. $^1$H-NMR (300 MHz, $CDCl_3$/($D_6$)DMSO): 2.26 (*quint.*, *J* = 6.10, $CH_2CH_2CH_2$); 3.32 (*s*, MeN); 3.56 (*s*, MeN); 4.00 (*t*, *J* = 5.65, $CH_2N$); 4.22 (*t*, *J* = 6.70, $CH_2O$); 6.85 (*s*, 2 imidazole H); 7.04 (*s*, 1 arom. H); 7.32 (*t*, $J_o$ = 7.90, 1 arom. H); 7.54 (*s*, 1 imidazole H); 7.70–7.74 (*m*, 2 arom. H). Anal. calc. for $C_{19}H_{20}N_6O_3$ (380.4): C 59.99, H 5.30, N 22.09; found: C 59.94, H 5.30, N 21.87.

*3,7-Dihydro-8-{4-[3-(1*H*-imidazol-1-yl)propoxy]-3-methoxyphenyl}-1,3-dimethyl-7-propyl-1*H*-purine-2,6-dione* (**7**). Yield: 0.18 g (40.74%). M.p. 158–160°. FT-IR (KBr): 2963, 1690, 1655, 1537, 1477, 1418, 1227, 1033. $^1$H-NMR (300 MHz, $CDCl_3$): 0.89 (*t*, *J* = 7.39, *Me*$CH_2$); 1.84–1.91 (*m*, MeC$H_2$); 2.29–2.37 (*m*, $CH_2CH_2CH_2$); 3.44 (*s*, MeN); 3.63 (*s*, MeN); 3.95 (*s*, MeO); 4.01 (*t*, *J* = 5.77, $CH_2O$); 4.26–4.33 (*m*, 2 $CH_2N$); 6.92 (*d*, $J_o$ = 8.28, 1 arom. H); 7.00 (*s*, 1 imidazole H); 7.11–7.14 (*m*, 2 arom. H), 7.18 (*s*, 1 imidazole H); 7.75 (*s*, 1 imidazole H). Anal. calc. for $C_{23}H_{28}N_6O_4$ (452.5): C 61.05, H 6.24, N 18.57; found: C 60.72, H 6.18, N 18.41.

*3,7-Dihydro-8-{4-[3-(1*H*-imidazol-1-yl)propoxy]-3-methoxyphenyl}-1,3,7-trimethyl-1*H*-purine-2,6-dione* (**9**). Yield: 0.32 g (74.07%). M.p. 180–184°. FT-IR (KBr): 2959, 1694, 1649, 1538, 1488, 1426, 1259, 1034. $^1$H-NMR (300 MHz, $CDCl_3$): 2.27–2.35 (*m*, $CH_2CH_2CH_2$); 3.43 (*s*, MeN); 3.62 (*s*, MeN); 3.96 (*s*, MeN); 4.00 (*t*, *J* = 5.74, $CH_2N$); 4.05 (*s*, MeO); 4.26 (*t*, *J* = 5.84, $CH_2O$); 6.91 (*d*, $J_o$ = 8.48, 1 arom. H); 6.99–7.02 (*m*, 1 arom. H); 7.09 (*s*, 1 imidazole H); 7.17 (*dd*, $J_o$ = 8.34, $J_m$ = 1.73, 1 arom. H); 7.22 (*m*, 1 imidazole H); 7.24 (*s*, 1 imidazole H). Anal. calc. for $C_{21}H_{24}N_6O_4$ (424.45): C 59.42, H 5.70, N 19.80; found: C 59.12, H 5.41, N 19.47.

*3,7-Dihydro-8-{3-[3-(1*H*-imidazol-1-yl)propoxy]phenyl}-1,3-dimethyl-7-propyl-1*H*-purine-2,6-dione* (**11**). Yield: 0.18 g (50.92%). M.p. 128–130°. FT-IR (KBr): 3114, 2954, 1694, 1652, 1539, 1459, 1223, 1045. $^1$H-NMR (300 MHz, $CDCl_3$): 0.86 (*t*, *J* = 7.67, *Me*$CH_2$); 1.79–1.86 (*m*, MeC$H_2$); 2.25–2.33 (*m*, $CH_2CH_2CH_2$); 3.44 (*s*, MeN); 3.62 (*s*, MeN); 3.99 (*t*, *J* = 5.71, $CH_2O$); 4.19–4.34 (*m*, 2 $CH_2N$); 6.95 (*s*, 1 imidazole H); 7.02 (*dd*, $J_o$ = 8.23, $J_m$ = 2.63, 1 arom. H); 7.11 (*s*, 1 imidazole H); 7.16–7.20 (*m*, 2 arom. H); 7.43 (*t*, $J_o$ = 7.98, 1 arom. H); 7.75 (*s*, 1 imidazole H). Anal. calc. for $C_{22}H_{26}N_6O_3$ (422.48): C 62.54, H 6.20, N 19.89; found: C 62.28, H 5.95, N 19.47.

*3,7-Dihydro-8-{4-[3-(1*H*-imidazol-1-yl)propoxy]-3-methoxyphenyl}-3-methyl-1*H*-purine-2,6-dione* (**14a**). Yield: 0.32 g (73.66%). M.p. >300°. FT-IR (KBr): 3155, 3039, 2941, 1688, 1592, 1498, 1423, 1391, 1249, 1029. $^1$H-NMR (300 MHz, $CDCl_3$/($D_6$)DMSO): 2.44–2.48 (*m*, $CH_2CH_2CH_2$); 3.70 (*s*, MeN); 3.94 (*s*, MeO); 4.17 (*t*, *J* = 5.33, $CH_2N$); 4.52 (*t*, *J* = 6.37, $CH_2O$); 7.01 (*d*, $J_o$ = 8.58, 1 arom. H); 7.42 (*s*, 1 arom. H, 1 imidazole H); 7.58 (*s*, 1 imidazole H); 7.67 (*dd*, $J_o$ = 8.61, $J_m$ = 1.67, 1 arom. H); 8.74 (*s*, 1 imidazole H). Anal. calc. for $C_{19}H_{20}N_6O_4$ (396.4): C 57.57, H 5.08, N 21.20; found: C 57.85, H 4.78, N 20.98.

*3,7-Dihydro-8-{4-[3-(1*H*-imidazol-1-yl)propoxy]-3-methoxyphenyl}-3-methyl-1-propyl-1*H*-purine-2,6-dione* (**14b**). Yield: 0.33 g (77.39%). M.p. 226–230°. FT-IR (KBr): 3120, 2959, 1694, 1652, 1567, 1488, 1319, 1265, 1076. $^1$H-NMR (300 MHz, $CDCl_3$): 0.97 (*t*, *J* = 8.88, *Me*$CH_2$); 1.67–1.74 (*m*, MeC$H_2$); 2.30–2.34 (*m*, $ClCH_2CH_2$); 3.68 (*s*, MeN); 3.98 (*s*, MeO); 4.03 (*t*, *J* = 7.23, 2 $CH_2N$); 4.28 (*t*, *J* = 6.31, $CH_2O$); 6.87 (*d*, $J_o$ = 7.88, 1 arom. H); 6.97 (*s*, 1 imidazole H); 7.12 (*s*, 1 imidazole H); 7.68–7.76 (*m*, 3 arom. H, 1 imidazole H). Anal. calc. for $C_{22}H_{26}N_6O_4$ (438.48): C 60.26, H 5.98, N 19.17; found: C 60.14, H 5.73, N 18.88.

*Biological Activity.* Radioligand-binding assays of xanthine analogs were performed using cloned human adenosine $\mathbf{A_1}$ and $\mathbf{A_{2A}}$ receptors and [$^3$H]DPCPX and [$^3$H]ZM 241385 as radioligands, resp. [$^3$H]DPCPX from *Tocris Cookson* (Bristol, UK) with specific activity 3.8 TBq/mmol, concentration

37 MBq/ml, was used in assays at 20 nM. The receptor membrane preparation (human recombinant adenosine $A_1$ receptor – ES-010-M) was from *Euroscreen* (B-Brussels). The recombinant adenosine $A_1$ receptor was stably expressed in CHO–K1 cells; the membrane suspensions (received as frozen aliquots in 7.5 mM *Tris*·HCl pH 7.5; 12.5 mM $MgCl_2$, 0.3 mM EDTA, 1 mM EGTA, and 250 mM sucrose) were diluted in assay buffer on thawing. [$^3$H]ZM 241385 from *Tocris Cookson* (UK-Bristol) with specific activity 0.777 TBq/mmol, concentration 37 MBq/ml, was used in assays at 20 nM. Receptor membrane preparation (human $A_{2A}$ receptor membrane RBHA2AM) was from *Wallac* (UK-Beaconsfield). The human recombinant $A_{2A}$ receptor was expressed in HEK-293 cells. The membrane suspensions were received as frozen aliquots in 50 mM *Tris*·HCl (pH 7.4) and 10% sucrose, and were diluted in assay buffer on thawing. The assays were performed using a similar method as described in [7][14][15]. Binding assays were performed using *Milipore* (Watford, UK) *Multiscreen MHAF B3 H60* filter plates presoaked in 0.3% polyethyleneimine (PEI). Ten mg of membrane protein was used in the final assay volume of 0.2 ml *Tris*·HCl buffer (50 mM *Tris*·HCl, 0.5 mM EDTA, and 10 mM $MgCl_2$; pH 7.4) supplemented with 1 U/ml adenosine deaminase for $A_{2A}$ binding assays and *HEPES* buffer (20 mM *HEPES*, 10 mM NaCl, 10 mM $MgCl_2$, pH 7.4) for $A_1$ binding assays were used. Stock solns. of the compounds were prepared in DMSO, the final concentration of DMSO in assays was $\leq 1\%$. Nonspecific binding was determined in the presence of 100 μM known non-radioactive ligands and accounted for less than 5% of total binding. The incubation time was 1 h at 25°. Termination of the incubation was performed by rapid filtration using a *Millipore* manifold at a pressure of 700 mbr. Filters were washed three times with 200 μl of the relevant assay buffer. Scintillation fluid was added (100 μl/well), and bound radioactivity was counted in a *Wallac Microbeta* scintillation counter (UK-Beaconsfield). Testing was performed in three stages: first, all of the compounds were tested at 100 μM; second, those causing greater than 60% displacement of binding were retested at three different concentrations from 1 to 100 μM; third, those that were consistently active in a concentration-dependent manner were tested over a full concentration range to determine the $IC_{50}$ and $K_i$ values. Data were analyzed using GraphPad Prism, Version 2.0 (*GraphPad*, San Diego, CA). For nonlinear regression analysis, the *Cheng–Prusoff* equation and $K_D$ values of 1.6 nM (human $A_1$) for [$^3$H]DPCPX and 1 nM (human $A_{2A}$) for [$^3$H]ZM241385 were used to calculate $K_i$ values from $IC_{50}$ values.

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