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Bioorganic & Medicinal Chemistry 14 (2006) 2697–2719
Bioorganic & Medicinal Chemistry

Synthesis and preliminary evaluation of new 1- and 3-[1-(2-hydroxy-3-phenoxypropyl)]xanthines from 2-amino-2-oxazolines as potential A_1 and A_{2A} adenosine receptor antagonists

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Received 4 October 2005; revised 22 November 2005; accepted 28 November 2005
Available online 28 December 2005

Abstract—The development of potent and selective adenosine receptor ligands as potential drugs is an active area of research. Xanthines are one of the most important classes of adenosine receptor antagonists and have been widely developed in terms of affinity and selectivity for adenosine receptors. We recently developed new original pathways for the synthesis of xanthine analogues starting from 5-substituted-2-amino-2-oxazoline **5** as a synthon. These procedures allowed us to selectively introduce a large, functionalized and β-adrenergic 2-hydroxy-3-phenoxypropyl pharmacophore at the 1- and 3-position of the xanthine moiety which allowed further structural modifications. In this study, we present a new synthetic access to racemic xanthine derivatives **1**–**4** from **5**, and their evaluation as adenosine A_1, A_{2A} and A_3 receptor ligands in radioligand binding studies. The 2-hydroxy-3-phenoxypropyl moiety was well tolerated in the 3-position of the xanthine core, while its introduction in the 1-position of the xanthine moiety led to a large decrease in adenosine receptor affinity. 1,7-Dimethyl-3-[1-(2-chloro-3-phenoxypropyl)]-8-(3,4,5-trimethoxystyryl)xanthine (**2n**) was the most potent and selective A_{2A} antagonist of the present series (K_i = 44 nM, ≫200-fold selective vs A_1). 1-Propyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-noradamantylxanthine (**3f**) was identified as a potent (K_iA_1 = 21 nM) and highly selective (≫350-fold vs A_{2A} and A_3 receptor) adenosine A_1 receptor antagonist.

1. Introduction

Adenosine regulates many physiological functions via specific cell membrane receptors. Four adenosine receptor subtypes have been identified, A_1, A_{2A}, A_{2B} and A_3, each of which exhibits a unique tissue distribution, ligand affinity and signal transduction mechanism.[1,2] Adenosine receptor subtypes belong to the family of seven transmembrane domain G protein-coupled receptors and exert their physiological role by activation or inhibition of different second messenger systems. In particular, the modulation of adenylate cyclase activity can be considered to be the prominent signal mediated by these receptor subtypes.[3,4] Selective interaction with adenosine receptor subtypes offers very broad therapeutic potentials including CNS disorders, regulation of the electrophysiological properties of heart, immune system and inflammatory diseases, cell growth, asthma, kidney failure and ischaemic injuries.[5] The development of potent and selective adenosine receptor ligands, agonists and antagonists as pharmacological tools and potential drugs has been an active area of research.[1,6–8] Adenosine receptor antagonists having selectivity for A_1 receptors have been under development as diuretic and renoprotective and cognition-enhancing drugs, while those with selectivity for A_{2A} receptors show promise as novel anti-Parkinson's and neuroprotective drugs.[9–11] A_3 selective adenosine receptor antagonists have been postulated as novel anti-inflammatory and anti-allergic agents.[11–13] Xanthines are one of the most important classes of adenosine receptor antagonists and are widely investigated in terms of affinity and selectivity for adenosine receptors (Fig. 1).[9,11] This led to structural modifications

Keywords: Xanthine; 2-Amino-2-oxazoline; Adenosine receptors antagonist; Synthesis.
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doi:10.1016/j.bmc.2005.11.050

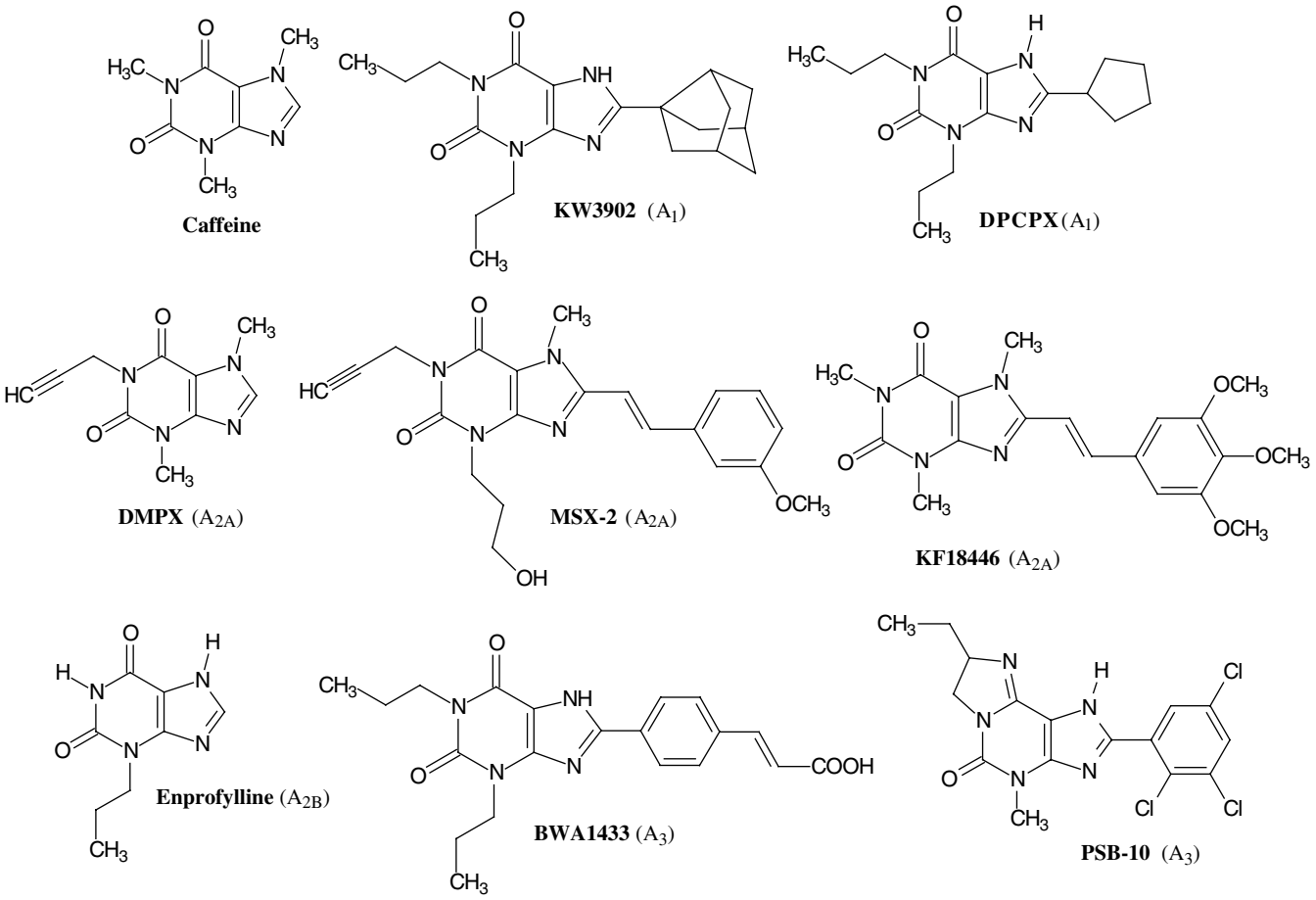


Figure 1. Structures of caffeine and examples of other xanthine derivatives that are A_1-, A_{2A}-, A_{2B}- and A_3-adenosine receptor antagonists.

at the 1-, 3-, 7- and 8-positions of the xanthine core. Substitution in the 1-position appeared to be important for activity modulation at both A_1 and A_2 receptor subtypes. Hence, 1-propyl substituent seems to be optimal for A_1 adenosine receptor affinity, whereas 1-methyl, 1-propyl or 1-propargyl is favourable for A_2 adenosine receptor affinity. Concerning the 3-position, it is difficult to establish a similar conclusion because either small or large groups appear to favour A_1 selectivity. On the other hand, phenyl and bulky cycloalkyl substituents in the 8-position appear to enhance activity of 1,3-disubstituted xanthines at A_1 adenosine receptor, and unsubstituted position 7 is also believed to be important for this target. For the A_{2A} adenosine receptor antagonists, an 8-styryl substituent in (*E*) configuration was recognized as crucial, and the introduction of a methyl substituent at the 7-position was beneficial. Finally, the incidence of either nature and position of substituents in A_3 potential adenosine receptor xanthines has not been really defined.[1–13]

We previously described a novel synthetic approach to 2-amino-2-oxazoline derivatives useful as synthons for the preparation of bioactive heterocyclic compounds.[14–19] Applied here, it permits us to prepare new adenosine receptor xanthine antagonists through a heterocyclization pathway followed by a basic hydrolysis leading to the 2-hydroxy-3-aryloxypropyl pharmacophore in either 1- or 3-position (Fig. 2). Such a substituent is commonly observed in many adrenoceptor

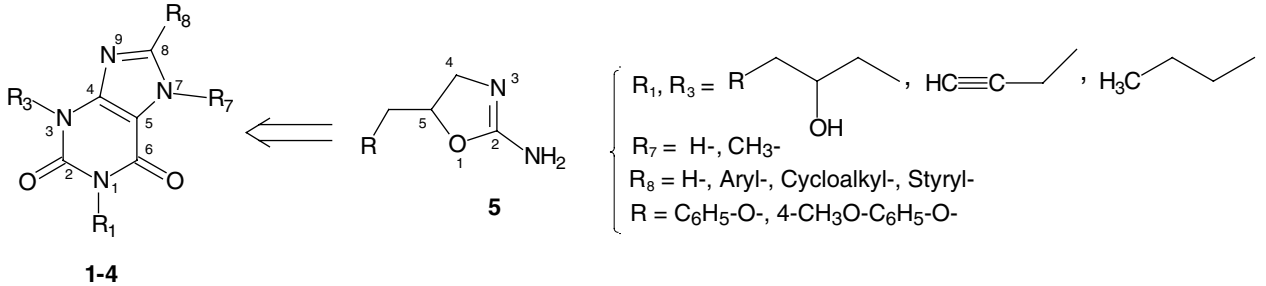


Figure 2. New 1- or 3-[1-(2-hydroxy-3-substituted)propyl]xanthines **1**–**4** and their retrosynthetic scheme from 2-amino-2-oxazolines **5**.

ligands,[20,21] but not in association on the xanthine core coupled with various substituents present in the reference adenosine receptor antagonists (Fig. 1). Because both A_{2A} and β-adrenergic receptors are coupled with the G_s signalling pathway, it could be beneficial to design xanthine compounds with the 1-(2-hydroxy-3-phenoxypropyl) β-adrenoceptor pharmacophore side chain.

Preliminary results concerning their evaluation at A_1, A_{2A} and A_3 adenosine receptor subtypes and the corresponding structure–activity relationships are reported. Introduction of 2-hydroxy-3-phenoxypropyl group in the 1- or 3-position, associated with various modifications in position 8, allows the investigation of effects of large and functionalized substituents on the xanthine moiety.

2. Chemistry

The synthesis of the isomeric 1- and 3-[1-(2-hydroxy-3-phenoxypropyl)]xanthines **1**–**4** was accomplished from racemic 5-aryloxymethyl-2-amino-2-oxazolines **5**, easily prepared from the corresponding epoxides.[14,16]

The preparation of the 7-amino-oxazolo[3,2-*a*]pyrimidine-7-ones **6**, precursors of the xanthines **1**–**3**, was achieved by reaction of **5** with methyl cyanoacetate in methanol in the presence of 1.5 equiv of sodium ethylate, according to a Pinner reaction.[22,23] 7-Amino-oxazolo[3,2-*a*]pyrimidine-7-ones **6** were then treated with sodium nitrite in acidic solution to afford the 5-amino-6-nitroso-7*H*-oxazolo[3,2-*a*]pyrimidin-7-ones **7**.[24,25] Hydrolysis of **7** in alkaline medium resulted in opening of the oxazoline ring and formation of the 6-amino-5-nitroso-uracils **8**.[26] We demonstrated that compounds **8** could also be obtained by reaction of 2-amino-2-oxazoline **5** with the sodium salt of ethyl oximinocyanoacetate giving the 6-amino-5-nitroso-1-propyluracils **8** after acidification with diluted hydrochloric acid to pH = 5–6.[27,28] The oximino group of **8** was easily reduced by sodium dithionite in aqueous solution at 90–100 °C to provide the key intermediate diaminouracils **9**.[25,29,30] Various conditions and methods for the ring closure of xanthines were attempted. In method A, the reaction of diaminouracils **9** with an excess of ethyl orthoformate in DMF as solvent gave xanthines **1a**,**b** in moderate to good yields (43–88%).[31–33] Method B consisted of condensing diaminouracils **9** with an arylaldehyde to form the imines **10**, which were oxidatively cyclized by treatment with diethyl azodicarboxylate (DEAD), in a modification of a general procedure reported by Yoneda et al., to give the xanthines **1c**–**f**,**j** and **k**.[34,35] Method C consisted of reacting **9** with a carboxylic acid chloride to give the amides **11**, which were then cyclized with aqueous sodium hydroxide to give the xanthines **1c**,**g**–**i** and **l**–**n**.[36]

The 3-substituted xanthines **1** were bismethylated using methyl iodide and potassium carbonate in dimethylformamide (DMF) at 60 °C to give the 1,7-dimethylxanthines **2a**–**k**.[36,37] The X-ray structure of **2c** confirmed the substitution of the 2-hydroxypropyl group in N-3 position of the xanthine (Fig. 3 and Table 1). Moreover, **2c** appeared as the mixture of (*R*) and (*S*) enantiomers of the 1,7-dimethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-phenylxanthine according to the determined spatial group from crystallographic data ($P2_1/c$). On the other hand, the synthesis of xanthines **2l**,**m** alkylated at the hydroxy group was performed using sodium hydride and methyl iodide in dimethylformamide. The xanthine **2g** was chlorodehydroxylated with phosphorous oxychloride to obtain the chloroxanthine **2n**. Otherwise, when the dimethylation of **1f** with methyl iodide was performed under mild conditions (room temperature), the unexpected *N*-7 monomethylated xanthine **1o** was isolated in poor yield (14%) (Scheme 2). The ^{1}H NMR spectrum of **1o** showed a singlet at 11.08 ppm, highly characteristic for a NH proton in position 1 of the xanthine moiety. In DMF in the presence of potassium carbonate, the *N*-1 alkylation of this xanthine **1o** with

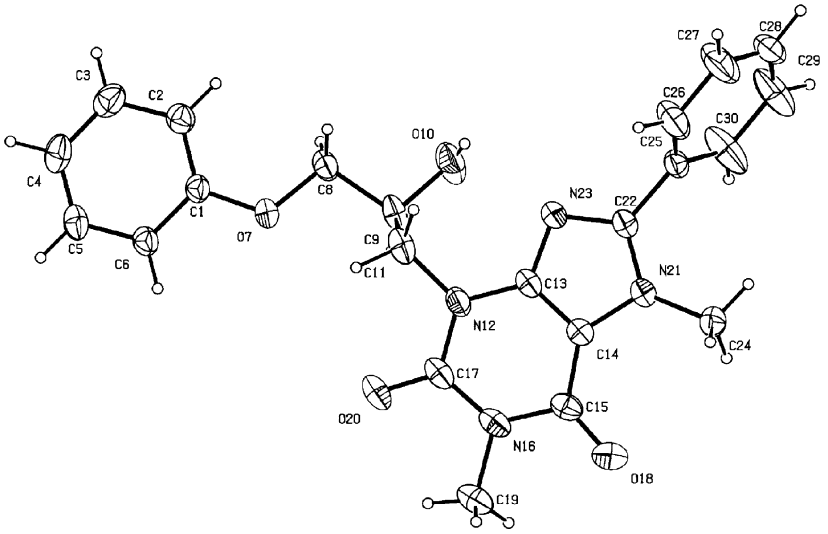


Figure 3. The ORTEP drawing of xanthine **2c** with thermal ellipsoids at 30% level.

Table 1. The crystallographic data of compounds **2c** and **4f**

X-ray data	**2c**	**4f**
Cryst syst	Monoclinic	Triclinic
Space group	$P2_1/c$	P_{-1}
Cell dimension		
a	12.290(5) Å	7.365(2) Å
b	17.161(5) Å	8.573(2) Å
c	9.588(9) Å	18.338(3) Å
α	90°	89.27(2)°
β	101.65(5)°	80.28(2)°
γ	90°	73.38(2)°
V	1981(2) Å^3	1092.8(4) Å^3
Z	4	2
*D*x	1.363 Mg m^{-3}	1.326 Mg m^{-3}
F(000)	856	460
Crystal size	$0.20 \times 0.25 \times 0.37$ mm^3	$0.25 \times 0.10 \times 0.02$ mm^3
No. of unique refl. Meads	3212	2255
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.060	1.066
$R[I > 2\sigma(I)]$	0.0884	0.0521
wR^2	0.2132	0.1297

propargyl chloride gave the 1-propargylxanthine **3a** (Scheme 2).

Two alternative strategies were used for the synthesis of 1-propyl or 1-propargyl xanthines **3b–j**, as depicted in Schemes 3 and 4. The first method involved the propargylation in the position 3 of carboxamidouracil derivative **11**, followed by subsequent alkaline ring closure of compound **12** under mild conditions, to give xanthine **3b** (Scheme 3).[36,38] For the second strategy, the synthesis of the 1-substituted xanthines **3c–j** began from xanthines **1** with the protection of *N*-7 by a methyl pivalate group.[39,40] Alkylation at *N*-7 of xanthines **1** with chloromethyl pivalate (POM-Cl) generated the pivaloyloxymethyl (POM) derivatives **13a–e**. ^{1}H NMR analysis of reaction products showed that the monosubstituted products were the 7-POM derivatives **13** rather than the 1-POM derivatives. This structural assignment was based on the resonance for the proton of the unsubstituted nitrogen at 9–10 ppm, which is characteristic of the *N*-1 rather than the *N*-7 proton. The resonance of the methylene moiety of the POM group of **13** at 6.10–6.38 ppm was in accordance with those of *N*-7 methylene POM group protons, usually described at ~6.15 ppm. Successive synthesis steps included regioselective alkylation with either propyl iodide or propargyl chloride to form the 1-substituted xanthines **14a–e**, and removal of the POM group by alkaline cleavage to form the xanthines **3c–g**. Some of these new xanthines were then alkylated at the *N*-7 position with methyl iodide using potassium carbonate to give **3h–j** (Scheme 4).

The synthesis of the 1-substituted xanthines **4a–f** is depicted in Scheme 5. The 7-amino-oxazolo[3,2-*a*]pyrimidin-5-one **15** was obtained by reaction of ethyl 3-amino-3-ethoxyacrylate with the aminooxazoline **5** in refluxing ethanol.[23,25] Subsequent nitrosation gave **16**. Its hydrolysis, achieved by heating it in basic medium for 5 min, finally led to **17**. The oxazoline ring opening was followed by sodium dithionite reduction to the corresponding 5,6-diaminouracils **18**. The conversion to the xanthines **4a–d** was performed by the standard methods previously described for the synthesis of xanthines **1**, via the precursors **19** or **20**. Finally, *N*-3,*N*-7-dimethylated xanthines **4e**,**f** were obtained by alkylation with methyl iodide and K_2CO_3 in DMF. The structure of racemic **4f** was unambiguously established by X-ray crystallography (Fig. 4 and Table 1).

3. Pharmacology

The synthesized new racemic xanthines **1–4** were tested in vitro in radioligand binding assays for the affinity to adenosine A_1 and A_{2A} receptors in rat cortical membrane and rat striatal membrane, preparations,

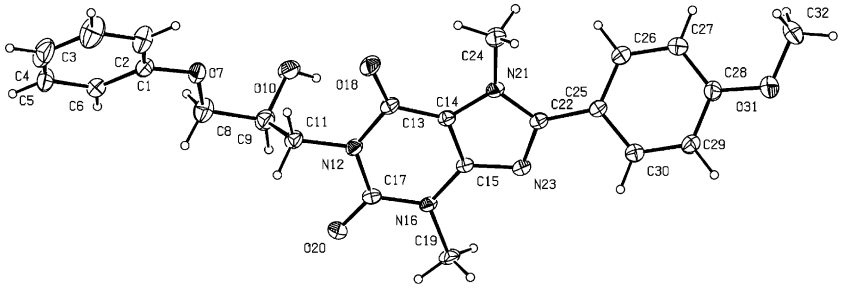


Figure 4. The ORTEP drawing of xanthine **4f** with thermal ellipsoids at 30% level.

respectively. The A_1 selective agonist [^{3}H]2-chloro-N^6-cyclopentyladenosine ([^{3}H]CCPA) and the A_{2A}-selective antagonist [^{3}H]3-(3-hydroxypropyl)-7-methyl-8-(*m*-methoxystyryl)-1-propargylxanthine ([^{3}H]MSX-2) were used as radioligands.[41,42] Selected compounds were additionally investigated in radioligand binding assays at human recombinant A_1 and/or A_{2A} receptors expressed in membranes of Chinese hamster ovary cells. Most of the compounds **1**–**4** were also tested for their affinity to human A_3 receptors recombinantly expressed in Chinese hamster ovary (CHO) cells. [^{3}H]2-Phenyl-8-ethyl-4-methyl-(8*R*)-4,5,7,8-tetrahydro-1*H*-imidazo[2,1-*i*]purine-5-one ([^{3}H]PSB-11) was used as a radioligand in the A_3 receptor binding studies.[43,44] The results, expressed as K_i values, are presented in Tables 1 and 2.

4. Results and discussion

By using the 5-amino-2-oxazolines **5** as synthons and applying a new strategy for the preparation of xanthine derivatives, 1- or 3-[1-(2-hydroxy-3-phenoxypropyl)]-xanthines were easily accessible. This permitted us to study the effects of the introduction of large and functionalized substituents in the 1- and 3-position of the xanthine skeleton, which could be useful for further structural modifications. The affinities of the new compounds for adenosine A_1, A_{2A} and A_3 receptors are given in Table 2. Affinities of standard antagonists, the non-selective caffeine, the A_1-selective 8-cyclopentyl-1,3-dipropylxanthine (DPCPX), the A_{2A}-selective KW6002 and the A_3-selective PSB-10, determined under the same conditions in our laboratory, are given for comparison.

Xanthines **1** comprise a group of derivatives bearing the 2-hydroxy-3-phenoxypropyl group in the 3-position and no substituent at N1 and N7 (Scheme 1). Most of the compounds **1a**–**n** were inactive or only moderately active at adenosine receptors with K_i values mostly greater than 10 μM. Their affinity depended on the 8-substituent. While 8-unsubstituted derivatives (**1a**,**b**) were inactive, an 8-phenyl group improved the affinity (**1c**) at all three investigated adenosine receptor subtypes. *p*-Hydroxylation at the 8-phenyl group of **1c** reduced A_{2A} affinity but slightly increased the affinity for A_1 and A_3 receptors (**1e**). Acidic substituents in the *p*-position of the phenyl ring (**1j**,**k**) were best tolerated by the A_3 receptor. An 8-styryl residue in this series was only tolerated by the A_1 receptor, but not by A_{2A} and A_3 receptors (compound **1f**). Further substitution on the styryl ring abolished affinity also at A_1 receptors (compounds **1g**–**i**). N7-Methylation of 8-styrylxanthine derivative abolished A_1 affinity resulting in the inactive derivative **1o**. Introduction of a cycloalkyl residue in the 8-position of the series 1 compounds did not lead to potent compounds (**1l**–**n**). If the phenoxy group at the N3-hydroxypropyl substituent of xanthine **1c** was methoxylated in the *p*-position, an inactive compound (**1d**) was obtained.

The second series, xanthines **2**, were 1,7-dimethylated derivatives of series 1 compounds bearing a 2-hydroxy-3-phenoxypropyl residue at N3 and various 8-substituents (Scheme 1). In one compound (**2n**) the hydroxy group in the side chain of **2g** was replaced by a chlorine atom, and in two compounds (**2l**,**m**) the hydroxy group was methylated. In series 2 all compounds were inactive at adenosine A_1 receptors. At A_{2A} receptors only those derivatives with a 3,4,5-trimethoxystyryl residue in the 8-position were active (**2g**,**n**); they were selective for the A_{2A} subtype versus A_1 and A_3 receptors. These compounds are structural analogues of the potent, selective A_{2A} antagonist KF18446. An interesting result was that the replacement of the hydroxyl group in **2g** by a chlorine atom giving **2n** caused a dramatic (>70-fold) increase in the A_{2A} affinity (3.40 μM for **2g** vs 0.044 μM for **2n**). 8-Styryl and 8-*m*-chlorostyryl as well as 8-(*p*-methylcarboxyethylidene)phenyl substitution was tolerated by the A_3 receptor leading to weakly potent, selective A_3 receptor ligands (**2e**,**f** and **k**). However, when the hydroxy group in **2f** was methylated the A_3 affinity was abolished (**2m**).

Xanthine derivatives of series **3**, substituted at the 1-position with a propyl or a propargyl group, appeared to present the best affinities of all investigated compounds at the adenosine receptors (Schemes 2–4 and Table 2). All of them bore a 2-hydroxy-3-phenoxypropyl residue at N3. Only in the 8-unsubstituted derivative **3g** the N3-residue was further substituted bearing a *p*-methoxy group on the phenyl ring. Compounds **3b**–**g** had no substituent at the N7-position. A comparison of **1b** with its N1-propyl-substituted derivative **3g** showed that the N1-substitution led to a large increase in A_1 and A_{2A} affinity thus turning a virtually inactive compound into a moderately potent A_1/A_{2A} antagonist (compare **1b/3g**). A similar effect could be observed in compound **3c**, a derivative of **1a** bearing a propargyl residue at N1. While **1a** was inactive, the 1-propargyl substitution in **3c** led to a moderately potent A_1/A_3 ligand (compare **1a/3c**). 8-Cycloalkyl- or 8-phenyl substitution in this series of compounds yielded derivatives with high affinity for adenosine A_1 receptors (compounds **3b**,**d** and **f**) with A_1 affinities in the lower nanomolar range. The most potent and selective A_1 antagonist of the present series was **3f** bearing a 1-propyl residue and a 3-noradamantyl substituent in the 8-position. The propyl group at N1 led to a more than 470-fold increase in A_1 affinity (**1n**: $K_iA_1 > 10$ μM and **3f**: $K_iA_1 = 29$ nM). Compound **3d**, an analogue of DPCPX, also showed high affinity and good selectivity for the A_1 receptor ($K_i = 55$ nM). However, the N3-modification (DPCPX: propyl, **3d**: 2-hydroxy-3-phenoxypropyl) reduced the affinity (110-fold at rat A_1, 16-fold at human A_1 receptors). It is interesting to note that the human A_1 receptor appeared to tolerate the large, amphiphilic N3-substituent much better than the rat A_1 receptor. For the most potent compounds of this series we therefore determined affinities not only at rat but also at human A_1 and A_{2A} receptors. Moderate species differences had been reported for these receptors. We found that A_1 and A_{2A} radioligand binding data at rat adenosine receptors correlated quite well with those determined at the human receptor subtypes. Determined K_i values were nearly identical for 8-cycloalkyl-substituted compounds **3d** and **f**, while the 8-phenyl-substituted **3b** was 6- to 8-fold weaker at the human as compared to the rat receptors.

Table 2. Affinities of xanthine derivatives **1-4** at adenosine A_1, A_{2A} and A_3 receptors

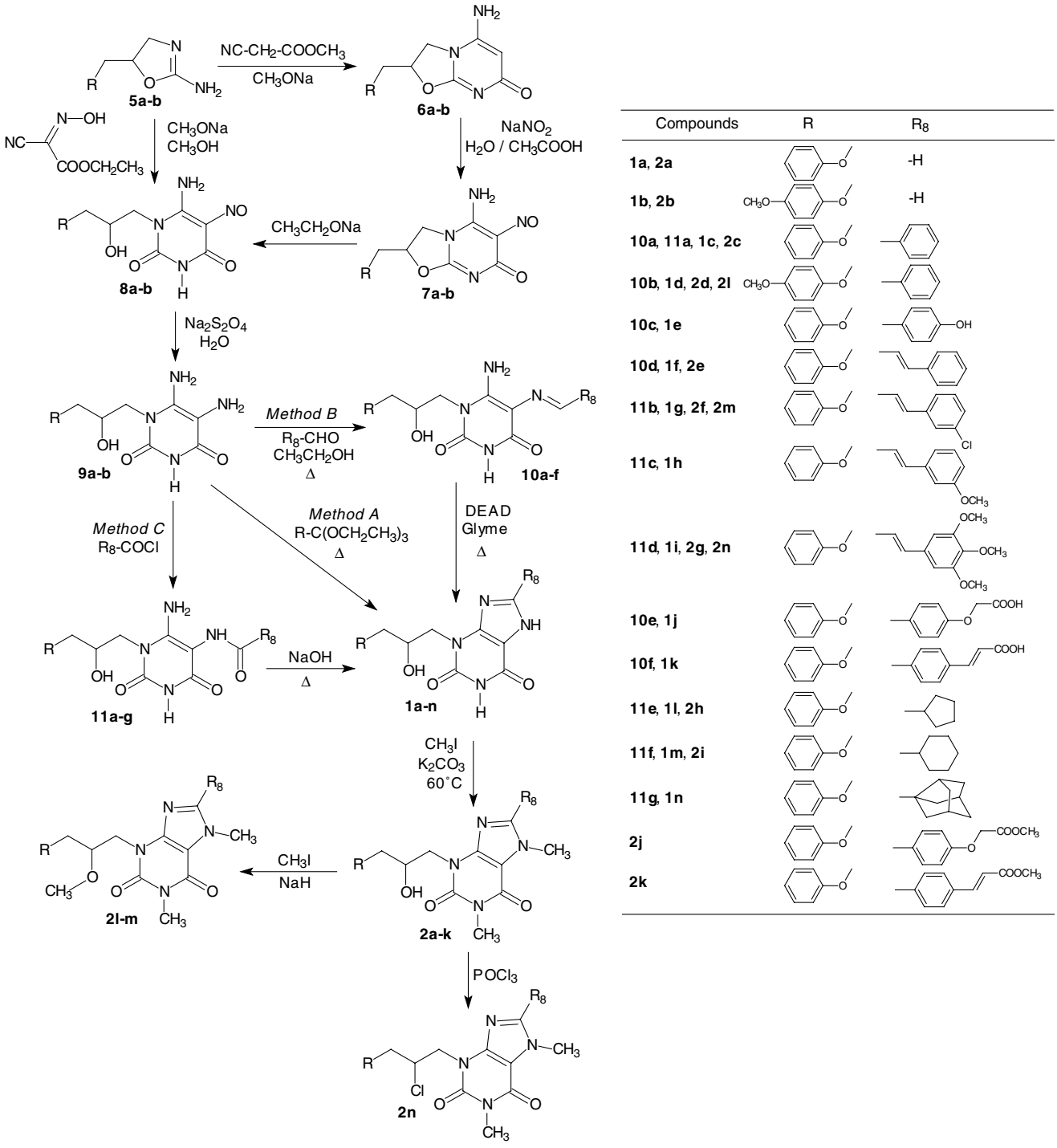
Compound	$K_i \pm$ SEM (μM)		
	Rat A_1 (human A_1)[a] versus [^{3}H]CCPA[b]	Rat A_{2A} (human A_{2A})[a] versus [^{3}H]MSX-2[b]	Human A_3 versus [^{3}H]PSB-11[b]
Caffeine	18.8 ± 5.6	32.5 ± 8.03[39]	nd[c]
DPCPX	0.0005 ± 0.0002	0.157 ± 0.006[39]	0.243 ± 0.056
KW6002	0.230 ± 0.030	0.00515 ± 0.00025	4.47 ± 4.06
PSB-10	0.805 ± 0.055[56]	6.04 ± 0.26[56]	0.997 ± 0.311[56]
1a	>10[d]	>10	>10
1b	>10	>10	nd
1c	9.63 ± 2.28	6.05 ± 1.35	4.65 ± 1.65
1d	>10	>10	nd
1e	2.20 ± 0.32	>10	2.85 ± 0.05
1f	7.16 ± 1.11	>10	>10
1g	>10	>10	>10
1h	>10	>10	nd
1i	>10	>10	nd
1j	>10	>10	183 ± 62
1k	>10	>10	26.1 ± 13.9
1l	>10	>10	>10
1m	>10	>10	>10
1n	>10	>10	nd
1o	>10	>10	nd
2a	>10	>10	>1.0
2b	>10	>10	>10
2c	>10	>10	>10
2d	>10	>10	>10
2e	>10	>10	15.6 ± 2.9
2f	>10	>10	6.95 ± 2.12
2g	>10	3.40 ± 0.87	>10
2h	>10	>10	>10
2i	>10	>10	>10
2j	>10	>10	>10
2k	>10	>10	2.05 ± 0.18
2l	>10	>10	>10
2m	>10	>10	>10
2n	>10	0.044 ± 0.02	nd
3a	0.217 ± 0.003	0.257 ± 0.007	1.27 ± 0.61
3b	0.041 ± 0.009 (0.239 ± 0.035)[a]	0.320 ± 0.040 (2.49 ± 0.55)[a]	1.59 ± 0.17
3c	3.36 ± 0.59	>10	0.505 ± 0.072
3d	0.055 ± 0.006 (0.049 ± 0.016)[a]	>10 (>10)[a]	3.55 ± 0.19
3e	2.70 ± 1.37	0.135 ± 0.025	32.1 ± 21.1
3f	0.029 ± 0.005 (0.021 ± 0.001)[a]	>10 (>10)[a]	>10
3g	1.73 ± 0.11	5.26 ± 0.36	>10
3h	>10	>10	nd
3i	>10	>10	44.5 ± 14.1
3j	5.07 ± 1.80	0.084 ± 0.031	nd
4a	>10	>10	>10
4b	>10	>10	>10
4c	0.273 ± 0.023	0.902 ± 0.142	19.0 ± 6.9
4d	0.519 ± 0.047	>10	>10
4e	>10	>10	>10
4f	>10	>10	>10

[a] Results at human adenosine A_1 receptors are given in brackets for selected compounds.
[b] All assays were performed in at least three separate experiments each performed in triplicate.
[c] nd = not determined.
[d] >10 (>1.0): less than 30% of radioligand binding at a concentration of 10 μM (1.0 μM).

Introduction of a *m*-methoxystyryl residue in combination with an N1-propargyl group led to the A_{2A}-selective compound **3e** (K_i = 135 nM). N7-Methylation of **3e** led to a slight reduction in A_1 affinity and an increase in A_{2A} affinity (K_iA_1 = 5 μM and K_iA_{2A} = 84 nM) yielding **3j**, a potent and quite selective A_{2A} antagonist; **3j** could be considered as a new analogue of the potent and selective A_{2A} antagonist MSX-2.[38] Similar structure–activity relationships had previously been observed for other 8-styrylxanthine derivatives.[36] N7-Methylation of the 8-unsubstituted compound **3c** yielding **3h** (an analogue of 3,7-dimethyl-1-propargylxanthine (DMPX)) or the

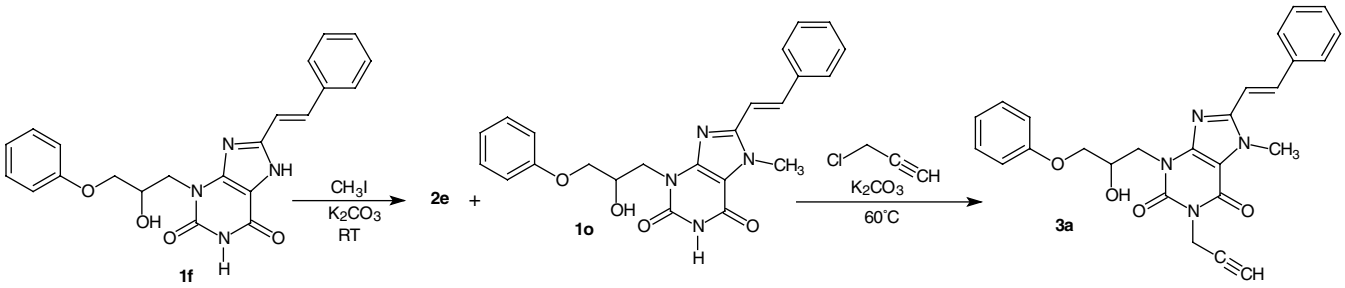
8-cyclopentyl-substituted derivative **3d** yielding **3i** virtually abolished adenosine receptor affinity. Consequently, the *N*-7-hydrogen seems to play an important role as hydrogen bond donor in A_1 receptor binding, as previously noticed.[9–11]

Series 4 compounds (Scheme 5 and Table 2) were substituted at the N1-position (instead of N3) with the 2-hydroxy-3-phenoxypropyl residue. In compounds **4e**,**f**, 3,7-dimethylation was combined with an 8-phenyl (**4e**) or an 8-*p*-methoxyphenyl group. Both compounds were inactive at all three investigated adenosine receptor subtypes. Derivatives **4a**–**d** were unsubstituted at N3 and N7. In this series, again, the 8-unsubstituted (**4a**) and the 8-phenyl-substituted derivatives (**4b**) were inactive. The 8-cyclopentyl-substituted compound **4d** exhibited some affinity for the A_1 receptor (K_i = 519 nM) and was selective for that receptor subtype. Interestingly, the *p*-hydroxyphenyl-substituted derivative **4c** showed affinity for adenosine receptors in contrast to the derivative **4e** lacking the *p*-hydroxy group (**4c**: K_iA_1 = 273 nM, K_iA_{2A} = 902 nM and K_iA_3 = 19 μM).

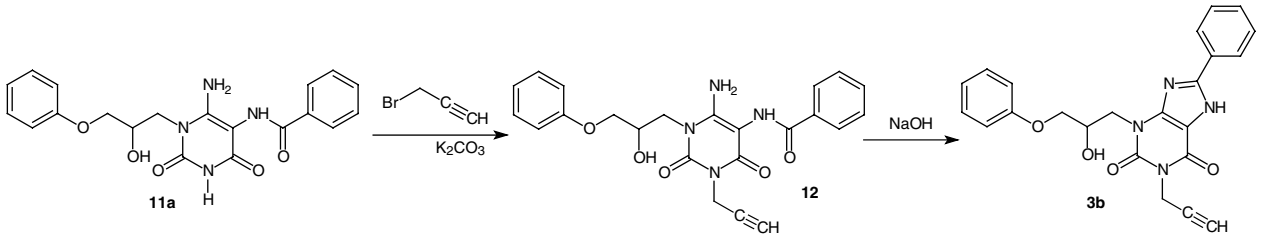


Compounds	R	R_8
1a, **2a**		-H
1b, **2b**	CH_3O	-H
10a, **11a**, **1c**, **2c**		
10b, **1d**, **2d**, **2l**	CH_3O	
10c, **1e**		OH
10d, **1f**, **2e**		
11b, **1g**, **2f**, **2m**		
11c, **1h**		Cl
		OCH_3
11d, **1i**, **2g**, **2n**		OCH_3, OCH_3, OCH_3
10e, **1j**		O, COOH
10f, **1k**		COOH
11e, **1l**, **2h**		
11f, **1m**, **2i**		
11g, **1n**		
2j		O, $COOCH_3$
2k		$COOCH_3$

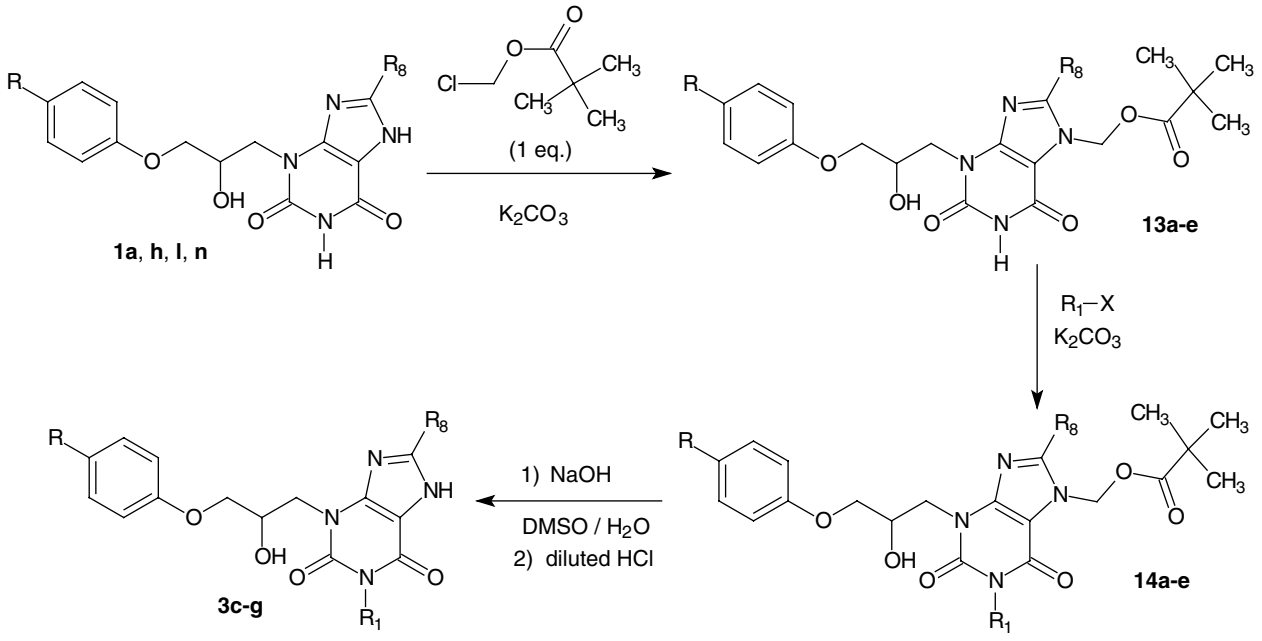
Scheme 1. Synthesis of xanthines **1a**–**n** and **2a**–**n**.

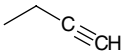
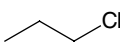
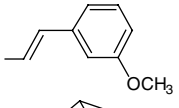
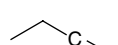
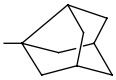
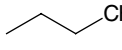
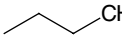


Scheme 2. Synthesis of xanthine **3a**.

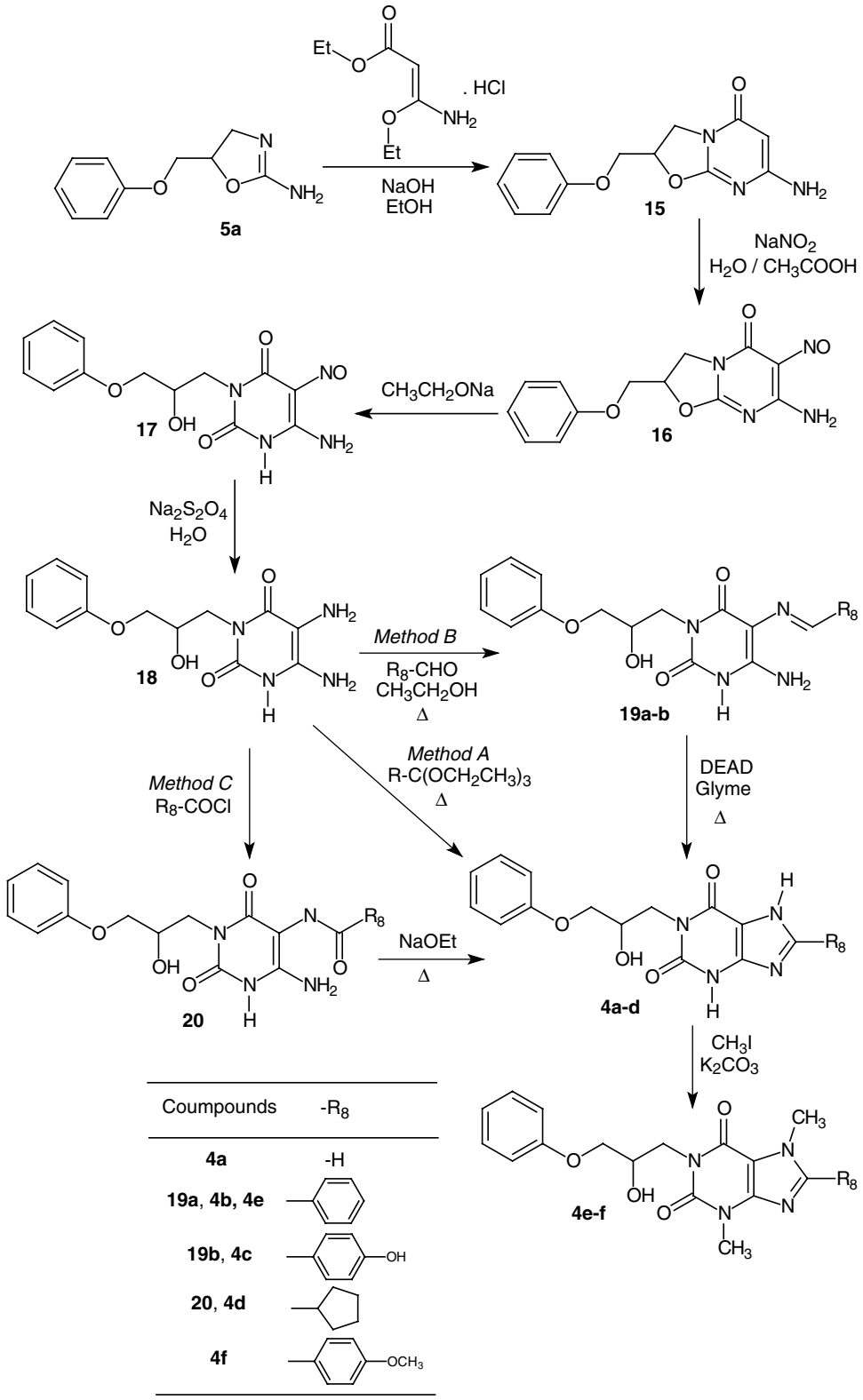


Scheme 3. Synthesis of xanthines **3b**.



Compounds	R	R_8	R_1
13a, **14a** / **3c** / **3h**	H-	-H	-H, 
13b, **14b** / **3d** / **3i**	H-		-H, 
13c, **14c** / **3e** / **3j**	H-		-H, 
13d, **14d** / **3f**	H-		-H, 
13e, **14e** / **3g**	CH_3O-	-H	-H, 

Scheme 4. Synthesis of xanthines **3c**–**j**.



Scheme 5. Synthesis of xanthines **4a**–**f**.

Some general remarks on the structure–affinity relationships may be drawn on the basis of these affinity data, in relation to the nature and position of substituents on the xanthine moiety. First, the 2-hydroxy-3-phenoxypropyl moiety bearing polar and lipophilic groups was well tolerated in the 3-position of the xanthine core by A_1 and A_{2A} receptors. On the other hand, its introduction in the 1-position of the xanthine moiety led to a large decrease in affinity at A_1 and A_{2A} receptors. Moreover, cycloalkyl moieties, such as a cyclopentyl or a 3-noradamantyl group, attached in the xanthine 8-position, associated with a propyl chain in the 1-position seem

to be optimal for affinity to A_1 adenosine receptors. As previously described,[45] an unsubstituted nitrogen atom in position 7, shown to be an important hydrogen bond donor in adenosine A_1 receptor binding, was required for high affinity and A_1 selectivity. Finally, a methoxy-substituted styryl group in position 8, associated with a propargyl chain in position 1 of the xanthine moiety, resulted in compounds with high affinity for adenosine A_{2A} receptors. Their N7-methylation led to an increase in adenosine A_{2A} receptor affinity and selectivity. This illustrates that both receptor subtypes accept large and functionalized substituents at N3 of the xanthine moiety, while retaining the well-established structure–activity relationships. 1,7-Dimethyl-3-[1-(2-chloro-3-phenoxypropyl)]-8-(3,4,5-trimethoxystyryl)xanthine (**2n**) was the most potent and selective A_{2A} antagonist of the present series (K_i = 44 nM, ≫200-fold selective vs A_1). 1-Propyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-noradamantylxanthine (**3f**) was identified as a potent (K_iA_1 = 21 nM) and highly selective (≫350-fold vs A_{2A} and A_3 receptor) adenosine A_1 receptor antagonist. In conclusion, we have developed an original new synthetic access to different series of racemic xanthines **1**–**4** from 2-amino-2-oxazolines used as precursors. It leads to the selective introduction of a large, functionalized and β-adrenergic 2-hydroxy-3-phenoxypropyl pharmacophore in the 1- or 3-position of the xanthine moiety permitting further structural modifications.

5. Experimental

5.1. Chemistry

Melting points were determined with an SM-LUX-POL Leitz hot-stage microscope and are uncorrected. IR spectra were recorded on a BRUKER IFS-25 spectrophotometer. NMR spectra (^{1}H, ^{13}C, ^{1}H COSY) were recorded at 300 or 75 MHz with tetramethylsilane as an internal standard using a BRUKER AVANCE 300 spectrometer. Splitting patterns have been designated as follows: s = singlet; br s = broad singlet; d = doublet; t = triplet; q = quartet; dd = double doublet; m = mutiplet. Analytical TLC was carried out on 0.25 precoated silica gel plates (POLYGRAM SIL G/UV$_{254}$) with visualisation by irradiation with a UV lamp. Silica gel 60 (70–230 mesh) was used for column chromatography. Analyses indicated by the symbols of the elements were within ±0.3% of the theoretical values.

5.1.1. General procedure for 5-amino-2-phenoxymethyl-7*H*-oxazolo[3,2-*a*]pyrimidin-7-ones (6a,b). To a solution of sodium (36 mmol) in dry methanol (50 ml) 2-amino-2-oxazoline **5** (21 mmol) and ethyl cyanoacetate (27 mmol) were added and the resulting solution was refluxed for 5 h. After cooling at 0 °C for 16 h, the resulting precipitate was collected, washed with cold methanol, dried and crystallized from appropriate solvent to give oxazolopyrimidinones **6a**,**b**.

5.1.1.1. 5-Amino-2-phenoxymethyl-7*H*-oxazolo[3,2-*a*]pyrimidin-7-one (6a). Beige crystals (43%); mp 263 °C. IR (KBr) *v*: 3480–3220 (NH_2), 1690 (CO), 1660 (C=N). ^{1}H NMR (DMSO-d_6) δ: 7.30 (t, 2H, J = 7.70 Hz, H-3′ et H-5′), 6.96 (d, 2H, J = 7.70 Hz, H-2′ et H-6′), 6.94 (t, 1H, J = 7.70 Hz, H-4′), 6.63 (s, 2H, NH_2), 5.24 (m, 1H, H-2), 4.74 (s, 1H, H-6), 4.28 (m, 3H, OCH_2 et H-3), 3.97 (m, 1H, H-3). ^{13}C NMR (DMSO-d_6) δ: 172.0 (C-7), 158.5 (C-1′), 157.9 (C-8a), 151.8 (C-5), 129.6 (C-3′ et C-5′), 121.2 (C-4′), 114.6 (C-2′ et C-6′), 80.3 (C-6), 75.2 (OCH_2), 67.8 (C-2), 44.8 (C-3). Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.33; H, 4.93; N, 16.03.

5.1.1.2. 5-Amino-2-(4-methoxy)phenoxymethyl-7*H*-oxazolo[3,2-*a*]pyrimidin-7-one (6b). White crystals (58%); mp 277 °C. IR (KBr) *v*: 3500–3240 (NH_2), 1685 (CO), 1655 (C=N). ^{1}H NMR (DMSO-d_6) δ: 6.87 (m, 4H, H-arom.), 6.70 (s, 2H NH_2), 5.23 (m, 1H, CH), 4.76 (s, 1H, H-6), 4.24 (m, 3H, OCH_2 et H-3), 3.97 (m, 1H, H-3), 3.69 (s, 3H, CH_3O). Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.12; H, 5.23; N, 14.53. Found: C, 58.42; H, 5.16; N, 14.26.

5.1.2. General procedure for 5-amino-6-nitroso-2-phenoxymethyl-7*H*-oxazolo[3,2-*a*]pyrimidin-7-ones (7a,b). Sodium nitrite (65 mmol) in acetic acid (10 ml) was added with stirring to compounds **6a**,**b** (22 mmol) in water (100 ml). The reaction mixture was stirred 1 h at room temperature, and then heated at 60 °C for 30 min. The precipitate was separated by filtration, washed with water and dried in air to give 5-amino-6-nitroso-oxazolopyrimidinones **7a**,**b**.

5.1.2.1. 5-Amino-6-nitroso-2-phenoxymethyl-7*H*-oxazolo[3,2-*a*]pyrimidin-7-one (7a). Blue crystals (83%); mp 179 °C. IR (KBr) *v*: 3460 (NH_2), 1660 (CO). ^{1}H NMR (DMSO-d_6) δ: 12.04 (sl, 1H, NH_2), 9.38 (sl, 1H, NH_2), 7.30 (t, 2H, J = 8.00 Hz, H-3′ and H-5′), 6.98 (t, 1H, J = 8.00 Hz, H-4′), 6.95 (d, 2H, J = 8.00 Hz, H-2′ and H-6′), 5.39 (m, 1H, H-2), 4.28 (m, 3H, OCH_2 and H-3), 3.95 (m, 1H, H-3). ^{13}C NMR (DMSO-d_6) δ: 167.9 (C-7), 159.2 (C-1′), 157.8 (C-8a), 142.6 (C-5), 140.5 (C-6), 129.6 (C-3′ et C-5′), 121.3 (C-4′), 114.6 (C-2′ et C-6′), 77.3 (OCH_2), 67.6 (C-2), 44.2 (C-3). Anal. Calcd for $C_{13}H_{12}N_4O_4$: C, 54.16; H, 4.19; N, 19.44. Found: C, 54.28; H, 4.10; N, 19.59.

5.1.2.2. 5-Amino-6-nitroso-2-(4-methoxy)phenoxymethyl-7*H*-oxazolo[3,2-*a*]pyrimidin-7-one (7b). Violet crystals (82%); mp 135 °C. IR (KBr) *v*: 3440 (NH_2), 1660 (CO). ^{1}H NMR (DMSO-d_6) δ: 12.06 (sl, 1H, NH_2), 9.21 (sl, 1H, NH_2), 6.89 (m, 4H, H-arom.), 5.37 (m, 1H, H-2), 4.27 (m, 3H, OCH_2 and H-3), 4.08 (m, 1H, H-3), 3.80 (s, 3H, CH_3O). Anal. Calcd. for $C_{14}H_{14}N_4O_5$: C, 52.83; H, 4.43; N, 17.60. Found: C, 53.02; H, 4.32; N, 17.51.

5.1.3. General procedure for 6-amino-5-nitroso-1-propyluracils (8a,b). *Method A:* To a solution of sodium (78 mmol) in dry ethanol (100 ml) was added **7** (19.3 mmol). The resulting solution was refluxed for 8 h. The solvent was then removed in vacuo. The solid residue was solubilized in water and the obtained solution was acidified until pH = 5–6 with a diluted aqueous solution of HCl. The precipitate was collected by

filtration, washed with ethanol then petroleum ether, and then dried.

Method B: Ethyl oximinocyanoacetate (29 mmol) and the appropriate 2-amino-2-oxazoline **5a**,**b** (26 mmol) were added to a stirred solution of sodium ethoxide (from sodium, 78 mmol) in anhydrous ethanol (80 ml) at 5–10 °C. The mixture was refluxed for 4 h and after cooling, the obtained solution salt was filtered; the solid was taken up in water and the resulting solution was acidified to pH = 5–6 with diluted hydrochloric acid. The isonitroso derivative which had separated was collected by filtration, washed with water and dried to give 6-amino-5-nitroso-1-propyluracils **8a**,**b**.

5.1.3.1. 6-Amino-5-nitroso-1-(2-hydroxy-3-phenoxypropyl)uracil (8a). Violet crystals (method A: 83%, method B: 25%); mp 242 °C. IR (KBr) *v*: 3370 (NH), 3320 (OH), 3190 (NH_2), 1730 et 1695 (CO). ^{1}H NMR (DMSO-d_6) δ: 13.31 (sl, 1H, NH_2), 11.32 (s, 1H, NH), 7.45 (sl, 1H, NH_2), 7.28 (t, 2H, J = 7.60 Hz, H-3′ and H-5′), 6.93 (d, 2H, J = 7.60 Hz, H-2′ and H-6′), 6.90 (t, 1H, J = 7.60 Hz, H-4′), 5.40 (m, 1H, OH), 4.11 (m, 1H, CH), 3.97 (m, 4H, OCH_2 and NCH_2). ^{13}C NMR (DMSO-d_6) δ: 160.5 (C-4), 158.4 (C-1′), 149.1 (C-2), 147.8 (C-6), 138.9 (C-5), 129.5 (C-3′ et C-5′), 120.6 (C-4′), 114.4 (C-2′ et C-6′), 69.7 (OCH_2), 66.0 (C-2), 43.9 (C-3). Anal. Calcd for $C_{13}H_{14}N_4O_5$: C, 50.98; H, 4.61; N, 18.29. Found: C, 51.12; H, 4.70; N, 18.25.

5.1.3.2. 6-Amino-5-nitroso-1-[2-hydroxy-3-(4-methoxy)phenoxypropyl]uracil (8b). Violet crystals (method A: 75%, method B: 31%); mp 213 °C. IR (KBr) *v*: 3400 (NH), 3340 (OH), 3200 (NH_2), 1725 et 1690 (CO). ^{1}H NMR (DMSO-d_6) δ: 13.35 (sl, 1H, NH_2), 11.40 (s, 1H, NH), 7.35 (sl, 1H, NH_2), 6.85 (m, 4H, H-arom.), 5.36 (m, 1H, OH), 4.08 (m, 1H, CH), 3.95 (m, 4H, OCH_2 and NCH_2), 3.68 (s, 3H, CH_3O). Anal. Calcd for $C_{14}H_{16}N_4O_6$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.12; H, 4.69; N, 16.74.

5.1.4. General procedure for 5,6-diamino-1-propyluracils (9a,b). To a suspension of the nitroso compounds **8a**,**b** (40 mmol) in 150 ml of boiling water was added sodium dithionite (120 mmol) in small portions until the blue colour disappeared. After refluxing for 30 min, the precipitate was filtered, washed with water then ethanol and dried to give diaminouracil **9**.

5.1.4.1. 5,6-Diamino-1-(2-hydroxy-3-phenoxypropyl)uracil (9a). White crystals (68%); mp 230 °C. IR (KBr) *v*: 1690 et 1635 (CO). ^{1}H NMR (DMSO-d_6) δ: 10.62 (s, 1H, NH), 7.28 (t, 2H, J = 7.50 Hz, H-3′ and H-5′), 6.93 (t, 2H, J = 7.50 Hz, H-4′), 6.91 (d, 1H, J = 7.50 Hz, H-2′ and H-6′), 5.93, (s, 2H, NH_2), 5.76 (d, 1H, J = 4.80 Hz, OH), 4.07 (m, 1H, CH), 3.92 (m, 4H, OCH_2 and NCH_2), 3.12 (sl, 2H, NH_2). ^{13}C NMR (DMSO-d_6) δ: 159.8 (C-4), 158.5 (C-1′), 149.7 (C-2), 146.3 (C-6), 129.5 (C-3′ et C-5′), 120.7 (C-4′), 114.5 (C-2′ et C-6′), 97.2 (C-5), 70.2 (OCH_2), 67.3 (CH), 45.5 (NCH_2). Anal. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.36; H, 5.63; N, 19.28.

5.1.4.2. 5,6-Diamino-1-[2-hydroxy-3-(4-methoxy)phenoxypropyl]uracil (9b). Yellow crystals (58%); mp 134 °C. IR (KBr) *v*: 1690 et 1640 (CO). ^{1}H NMR (DMSO-d_6) δ: 11.55 (s, 1H, NH), 6.76 (m, 4H, H-arom.), 5.86, (s, 2H, NH_2), 5.67 (d, 1H, J = 4.80 Hz, OH), 3.99 (m, 1H, CH), 3.76 (m, 4H, OCH_2 and NCH_2), 3.62 (s, 3H, CH_3O), 3.22 (sl, 2H, NH_2). Anal. Calcd for $C_{14}H_{18}N_4O_5$: C, 52.17; H, 5.63; N, 17.38. Found: C, 52.32; H, 5.69; N, 17.26.

5.1.5. General procedure for 6-amino-5-arylidenamino-1-propyluracils (10a–f). A mixture of arylaldehyde (3.12 mmol), 5,6-diaminouracils **9a**,**b** (2.7 mmol) and 0.15 ml of acetic acid was refluxed for 4 h in 15 ml of ethanol. Upon cooling of the mixture, the precipitate was filtered and washed with ethanol then diethyl ether to give the imine **10a**–**f** as a pale yellow solid, which was used directly in the next step.

5.1.5.1. 6-Amino-5-benzylidenamino-1-(2-hydroxy-3-phenoxypropyl)uracil (10a). Yellow crystals (78%); mp 225 °C. IR (KBr) *v*: 3355 (NH_2), 1695 et 1635 (CO). ^{1}H NMR (DMSO-d_6) δ: 10.78 (s, 1H, NH), 9.69 (s, 1H, N=CH), 7.88 (d, 2H, J = 6.50 Hz, H-2″ and H-6″), 7.33 (m, 5H, H-3′, H-5′, H-3″, H-4″ and H-5″), 6.92 (t, 1H, J = 7.20 Hz, H-4′), 6.90 (d, 2H, J = 7.20 Hz, H-2′ and H-6′), 5.79 (d, 1H, J = 4.90 Hz, OH), 4.16 (m, 1H, CH), 4.10 (m, 2H, NCH_2), 4.07 (m, 2H, OCH_2), 4.01 (sl, 2H, NH_2). ^{13}C NMR (DMSO-d_6) δ: 158.5 (C-4), 158.2 (C-1′), 155.3 (C-6), 149.7 (C-2), 149.5 (N=CH), 138.6 (C-1″), 129.5 (C-3′ et C-5′), 129.1 (C-4″), 128.5 (C-3″ et C-5″), 127.2 (C-2″ et C-6″), 120.7 (C-4′), 114.5 (C-2′ et C-6′), 99.5 (C-5), 70.0 (OCH_2), 66.9 (CH), 45.6 (NCH_2). Anal. Calcd for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.98; H, 5.37; N, 14.65.

5.1.5.2. 6-Amino-5-benzylidenamino-1-[2-hydroxy-3-(4-methoxyphenoxy)]propyluracil (10b). Yellow crystals (83%); mp 243 °C. IR (KBr) *v*: 3345 (NH_2), 1690 et 1635 (CO). ^{1}H NMR (DMSO-d_6) δ: 10.78 (s, 1H, NH), 9.68 (s, 1H, N=CH), 7.86 (d, 2H, J = 6.35 Hz, H-2″ and H-6″), 7.37 (m, 3H, H-3″, H-4″ and H-5″), 7.19 (s, 2H, NH_2), 6.86 (s, 4H, H-2′, H-3′, H-5′ and H-6′), 5.76 (d, 1H, J = 4.80 Hz, OH), 4.14 (m, 1H, CH), 4.06 (m, 2H, NCH_2), 3.95 (m, 2H, OCH_2), 3.68 (s, 3H, CH_3O–). Anal. Calcd for $C_{21}H_{22}N_4O_5$: C, 61.45; H, 5.40; N, 13.65. Found: C, 61.36; H, 5.48; N, 13.70.

5.1.5.3. 6-Amino-5-(4-hydroxybenzylidenamino)-1-(2-hydroxy-3-phenoxypropyl)uracil (10c). Orange crystals (42%); mp 239 °C. IR (KBr) *v*: 1685 et 1635 (CO). ^{1}H NMR (DMSO-d_6) δ: 10.64 (s, 1H, NH), 9.60 (s, 1H, N=CH), 7.68 (d, 2H, J = 8.10 Hz, H-2″ and H-6″), 7.28 (t, 2H, J = 7.40 Hz, H-3′ and H-5′), 6.92 (m, 5H, H-3″, H-5″, H-2′, H-4′ and H-6′), 5.75 (m, 1H, OH), 4.32 (m, 1H, CH), 4.15 (m, 2H, NCH_2), 4.01 (m, 2H, OCH_2), 3.98 (sl, 2H, NH_2). Anal. Calcd for $C_{20}H_{20}N_4O_5$: C, 60.60; H, 5.08; N, 14.13. Found: C, 60.73; H, 5.15; N, 14.00.

5.1.5.4. 6-Amino-5-styrylidenamino-1-(2-hydroxy-3-phenoxypropyl)uracil (10d). Yellow crystals (72%); mp 249 °C. IR (KBr) *v*: 3340 (NH_2), 1690 et 1640 (CO).

^{1}H NMR (DMSO-d_6) δ: 10.77 (s, 1H, NH), 9.47 (t, 1H, J = 4.05 Hz, N=CH), 7.54 (d, 2H, J = 7.20 Hz, H-2″ and H-6″), 7.38 (m, 6H, =CH styryl, H-3′, H-5′, H-3″, H-4″ and H-5″), 6.95 (m, 4H, =CH styryl, H-2′, H-4′ and H-6′), 5.70 (d, 1H, J = 4.90 Hz, OH), 4.18 (m, 1H, CH), 4.10 (sl, 2H, NH_2), 4.03 (m, 2H, NCH_2), 4.00 (m, 2H, OCH_2). ^{13}C NMR (DMSO-d_6) δ: 158.5 (C-4), 157.9 (C-1′), 155.1 (C-6), 151.6 (C-2), 149.5 (N=CH), 136.6 (C=C styryl), 136.4 (C-1″), 131.5 (C=C styryl), 129.5 (C-3′ et C-5′), 128.8 (C-3″ et C-5″), 128.2 (C-4″), 126.7 (C-2″ et C-6″), 120.7 (C-4′), 114.5 (C-2′ et C-6′), 100.2 (C-5), 70.0 (OCH_2), 66.7 (CH), 47.7 (NCH_2). Anal. Calcd for $C_{22}H_{24}N_4O_4$: C, 65.01; H, 5.45; N, 13.78. Found: C, 64.86; H, 5.55; N, 13.89.

5.1.5.5. 6-Amino-5-(4-carboxymethyloxybenzylidenamino)-1-(2-hydroxy-3-phenoxypropyl)uracil (10e). Yellow crystals (57%); mp 203 °C. IR (KBr) v: 1715, 1690 et 1635 (CO). ^{1}H NMR (DMSO-d_6) δ: 10.72 (s, 1H, NH), 9.62 (s, 1H, N=CH), 7.81 (d, 2H, J = 8.50 Hz, H-2″ and H-6″), 7.29 (t, 2H, J = 7.80 Hz, H-3′ and H-5′), 6.94 (m, 5H, H-3″, H-5″, H-2′, H-4′ and H-6′), 5.77 (m, 1H, OH), 4.70 (s, 2H, CH_2O), 4.21 (m, 1H, CH), 4.10 (m, 2H, NCH_2), 4.01 (m, 2H, OCH_2). Anal. Calcd for $C_{22}H_{22}N_4O_7$: C, 58.14; H, 4.88; N, 12.33. Found: C, 58.30; H, 4.81; N, 12.45.

5.1.5.6. 6-Amino-5-(4-cinnamylidenamino)-1-(2-hydroxy-3-phenoxypropyl)uracil (10f). Yellow crystals (43%); mp > 350 °C. IR (KBr) v: 1705, 1685 et 1635 (CO). ^{1}H NMR (DMSO-d_6) δ: 12.34 (sl, 1H, CO_2H), 10.79 (s, 1H, NH), 9.69 (s, 1H, N=CH), 7.91 (d, 2H, J = 8.10 Hz, H-2″ and H-6″), 7.69 (d, 2H, J = 8.10 Hz, H-3″ and H-5″), 7.61 (d, 1H, J = 16.00 Hz, =CH styryl), 7.29 (t, 2H, J = 7.50 Hz, H-3′, H-5′), 6.93 (m, 3H, H-2′, H-4′ and H-6′), 6.56 (d, 1H, J = 16.00 Hz, =CH styryl), 5.77 (d, 1H, J = 5.55 Hz, OH), 4.32 (m, 1H, CH), 4.12 (m, 2H, NCH_2), 4.02 (m, 2H, OCH_2). Anal. Calcd for $C_{23}H_{22}N_4O_6$: C, 61.33; H, 4.92; N, 12.44. Found: C, 61.24; H, 4.86; N, 12.59.

5.1.6. General procedure for 6-amino-5-alkyl- or -aryl-carboxamido-1-propyluracils (11a–g). A suspension of 2.5 mmol of **9a**,**b** in 12 ml of dry pyridine was cooled to 0 °C, and acid chloride (2.88 mmol) was added dropwise with stirring. The mixture was stirred overnight and then evaporated to dryness. The residue was treated with water, collected by filtration and dried to yield **11a**–**g**.

5.1.6.1. 6-Amino-5-phenylcarboxamido-1-(2-hydroxy-3-phenoxypropyl)uracil (11a). Beige crystals (89%); mp 248 °C. IR (KBr) v: 1685, 1670 and 1635 (CO). ^{1}H NMR (DMSO-d_6) δ: 10.70 (s, 1H, N_1-H), 8.91 (s, 1H, NH), 7.98 (d, 2H, J = 6.65 Hz, H-2″ and H-6″), 7.50 (m, 3H, H-3″, H-4″ and H-5″), 7.29 (t, 2H, J = 7.80 Hz, H-3′ and H-5′), 6.96 (m, 3H, H-2′, H-4′ and H-6′), 6.53 (s, 2H, NH_2), 5.78 (sl, 1H, OH), 4.12 (m, 1H, CH), 4.06 (m, 2H, NCH_2), 3.97 (m, 2H, OCH_2). ^{13}C NMR (DMSO-d_6) δ: 170.5 (CO amide), 163.2 (C-1″), 162.1 (C-1′), 159.3 (C-6), 156.2 (C-2), 152.1 (C-4), 134.4 (C-5), 133.5 (C-4″), 131.1 (C-3″ and C-5″), 129.9 (C-3′ and C-5′), 129.0 (C-2″ and C-6″), 122.6 (C-4′), 115.9 (C-2′ and C-6′), 70.0 (OCH_2), 66.7 (CH), 47.7 (NCH_2). Anal. Calcd for $C_{20}H_{20}N_4O_5$: C, 60.60; H, 5.08; N, 14.13. Found: C, 60.46; H, 5.13; N, 14.22.

5.1.6.2. 6-Amino-5-(3-chlorostyryl)-carboxamido-1-(2-hydroxy-3-phenoxypropyl)uracil (11b). Beige crystals (71%); mp 274 °C. IR (KBr) v: 1685, 1670 and 1640 (CO). ^{1}H NMR (DMSO-d_6) δ: 10.70 (s, 1H, N_3-H), 8.66 (s, 1H, CONH), 7.64 (s 1H, H-2″), 7.60-7.40 (m, 4H, H-4″, H-5″, H-6″ and =CH), 7.28 (t, 2H, J = 7.70 Hz, H-3′ and H-5′), 6.93 (m, 3H, H-2′, H-4′ and H-6′),6.87 (d, 1H, J = 16.10 Hz, =CH), 6.52 (sl, 2H, NH_2), 5.78 (sl, 1H, OH), 4.29 (m, 1H, CH), 4.10 (m, 2H, NCH_2), 3.97 (m, 2H, OCH_2). Anal. Calcd for $C_{22}H_{21}N_4O_5$: C, 57.83; H, 4.63; N, 12.26. Found: C, 57.98; H, 4.52; N, 12.20.

5.1.6.3. 6-Amino-5-(3-methoxystyryl)-carboxamido-1-(2-hydroxy-3-phenoxypropyl)uracil (11c). Beige crystals (92%); mp 141 °C. IR (KBr) v: 1685, 1670 and 1640 (CO). ^{1}H NMR (DMSO-d_6) δ: 10.68 (s, 1H, N_3-H), 8.61 (s, 1H, CONH), 7.82 (t, 1H, J = 7.30 Hz, H-5″), 7.44 (d, 1H, J = 15.80 Hz, =CH), 7.42 (m, 1H, H-6″), 7.32 (t, 2H, J = 8.65 Hz, H-3′ and H-5′), 7.16 (m, 1H, H-4″),6.95 (m, 4H, H-2′, H-4′, H-6′ and H-2″), 6.85 (d, 1H, J = 15.80 Hz, =CH), 6.49 (sl, 2H, NH_2), 5.80 (m, 1H, OH), 4.12 (m, 1H, CH), 4.07 (m, 2H, NCH_2), 3.98 (m, 2H, OCH_2), 3.74 (s, 3H, OCH_3). Anal. Calcd for $C_{23}H_{24}N_4O_6$: C, 61.05; H, 5.34; N, 12.38. Found: C, 60.97; H, 5.46; N, 12.31.

5.1.6.4. 6-Amino-5-(3,4,5-trimethoxystyryl)-carboxamido-1-(2-hydroxy-3-phenoxypropyl)uracil (11d). Beige crystals (79%); mp 261 °C. IR (KBr) v: 1680, 1670 and 1645 (CO). ^{1}H NMR (DMSO-d_6) δ: 10.70 (s, 1H, N_3-H), 8.56 (s, 1H, CONH), 7.40 (d, 1H, J = 15.80 Hz, =CH), 7.29 (m, 2H, H-3′ and H-5′), 6.92 (m, 5H, H-2′, H-4′, H-6′, H-2″ and H-6″), 6.79 (d, 1H, J = 15.80 Hz, =CH), 6.50 (sl, 2H, NH_2), 5.83 (sl, 1H, OH), 4.25 (m, 1H, CH), 4.11 (m, 2H, NCH_2), 3.97 (m, 2H, OCH_2), 3.81 (s, 6H, 2 CH_3O–), 3.69 (s, 3H, CH_3O–). Anal. Calcd for $C_{25}H_{28}N_4O_8$: C, 58.59; H, 5.51; N, 10.93. Found: C, 58.46; H, 5.62; N, 11.10.

5.1.6.5. 6-Amino-5-cyclopentylcarboxamido-1-(2-hydroxy-3-phenoxypropyl)uracil (11e). Beige crystals (86%); mp 124 °C. IR (KBr) v: 1685, 1670 and 1640 (CO). ^{1}H NMR (DMSO-d_6) δ: 10.64 (s, 1H, N_3-H), 8.24 (s, 1H, CONH), 7.27 (m, 2H, H-3′ and H-5′), 6.86 (m, 3H, H-2′, H-4′ and H-6′), 6.25 (sl, 2H, NH_2), 5.85 (sl, 1H, OH), 4.26 (m, 1H, CH), 4.10 (m, 2H, NCH_2), 3.97 (m, 2H, OCH_2), 2.73 (m, 1H, CH cycl.), 1.76 (m, 2H, CH_2 cycl.), 1.55 (m, 6H, CH_2 cycl.). Anal. Calcd for $C_{19}H_{24}N_4O_5$: C, 58.75; H, 6.23; N, 14.43. Found: C, 58.87; H, 6.18; N, 14.23.

5.1.6.6. 6-Amino-5-cyclohexylcarboxamido-1-(2-hydroxy-3-phenoxypropyl)uracil (11f). Beige crystals (81%); mp 235 °C. IR (KBr) v: 1685, 1670 and 1640 (CO). ^{1}H NMR (DMSO-d_6) δ: 10.63 (s, 1H, N_3-H), 8.19 (s, 1H, CONH), 7.29 (t, 2H, J = 7.70 Hz, H-3′ and H-5′), 6.93 (m, 3H, H-2′, H-4′ and H-6′), 6.22 (sl,

2H, NH_2), 5.84 (d, 1H, $J = 4.70$ Hz, OH), 4.09 (m, 1H, CH), 3.96 (m, 4H, OCH_2 and NCH_2), 2.27 (m, 1H, CH cycl.), 1.76 (m, 5H, CH_2 cycl.), 1.29 (m, 5H, CH_2 cycl.). Anal. Calcd for $C_{20}H_{26}N_4O_5$: C, 59.69; H, 6.51; N, 13.92. Found: C, 59.81; H, 6.48; N, 13.83.

5.1.6.7. 6-Amino-5-noradamantylcarboxamido-1-(2-hydroxy-3-phenoxypropyl)uracil (11g). Beige crystals (95%); mp 239 °C. IR (KBr) *v*: 1685, 1675 and 1640 (CO). ^{1}H NMR (DMSO-d_6) δ: 10.67 (s, 1H, N_3-H), 7.80 (s, 1H, CONH), 7.29 (m, 2H, H-3′ and H-5′), 6.94 (m, 3H, H-2′, H-4′ and H-6′), 6.18 (sl, 2H, NH_2), 5.88 (sl, 1H, OH), 4.07 (m, 2H, CH et CH_2), 3.93 (m, 3H, CH_2), 2.71 (t, 1H, $J = 6.45$ Hz, CH nor.), 2.24 (m, 2H, CH nor.), 2.05 (m, 2H, CH_2 nor.), 1.81 (m, 4H, CH_2 nor.), 1.54 (m, 4H, CH_2 nor.). Anal. Calcd for $C_{23}H_{28}N_4O_5$: C, 62.71; H, 6.41; N, 12.72. Found: C, 62.45; H, 6.54; N, 12.61.

5.1.7. General procedure for 3-[1-(2-hydroxy-3-substituted-propyl)]-8-alkyl- or -arylxanthines (1a–n)

Method A: A solution of **9a**,**b** (13 mmol) in $HC(OEt)_3$ (20 ml) and DMF (10 ml) was refluxed for 4 h. The solvent was then removed under reduced pressure. The solid residue was triturated in Et_2O, collected by filtration, washed with Et_2O and dried to give **1a**,**b**.

Method B: The imines **10a**–**f** (2 mmol) were heated in 20 ml of glyme. As the mixture began to reflux, the imine dissolved. Diethylazodicarboxylate (DEAD) (4 mmol) was added through the condenser. Within 10 min a white solid was formed. After an additional 45 min, the reaction mixture was filtered and the precipitate was washed with ethanol and diethyl ether to give **1c**–**f**,**j** and **k**.

Method C: Compounds **11a**–**g** (2 mmol) were refluxed in 8 ml of 2 N NaOH aqueous solution and 3 ml of ethanol for 1.5 h. The hot solution was allowed to cool to 4 °C, diluted with water and acidified with acetic acid then with diluted hydrochloric acid until pH = 3 to form a white precipitate, which was collected by filtration to give **1g**–**i** and **1l**–**n**.

5.1.7.1. 3-[1-(2-Hydroxy-3-phenoxypropyl)]xanthine (1a). Beige crystals (59%); mp 247 °C. IR (KBr) *v*: 3390 (OH), 3180 and 3035 (NH), 1690 and 1660 (CO). ^{1}H NMR (DMSO-d_6) δ: 13.46 (s, 1H, N_7-H), 11.10 (s, 1H, N_1-H), 7.99 (s, 1H, H-8), 7.25 (t, 2H, $J = 7.90$ Hz, H-3′ and H-5′), 6.90 (t, 1H, $J = 7.90$ Hz, H-4′), 6.84 (d, 2H, $J = 7.90$ Hz, H-2′ and H-6′), 5.31 (d, 1H, $J = 5.50$ Hz, OH), 4.12 (m, 1H, CH), 4.06 (m, 2H, NCH_2), 3.93 (m, 2H, OCH_2). ^{13}C NMR (DMSO-d_6) δ: 158.9 (C-1′), 155.2 (C-6), 151.7 (C-2), 150.1 (C-4), 140.8 (C-8), 129.9 (C-3′ and C-5′), 121.0 (C-4′), 114.8 (C-2′ and C-6′), 107.4 (C-5), 70.9 (OCH_2), 66.3 (CH), 46.0 (NCH_2). Anal. Calcd for $C_{14}H_{14}N_4O_4$: C, 55.62; H, 4.67; N, 18.53. Found: C, 55.45; H, 4.73; N, 18.48.

5.1.7.2. 3-{1-[2-Hydroxy-3-(4-methoxyphenoxy)-propyl]}xanthine (1b). Beige crystals (88%); mp 251 °C. IR (KBr) *v*: 3380 (OH), 3170 et 3035 (NH), 1685 and 1665 (CO). ^{1}H NMR (DMSO-d_6) δ: 13.47 (s, 1H, N_7-H), 11.19 (s, 1H, N_1-H), 7.98 (s, 1H, H-8), 6.85 (d, 2H, $J = 9.40$ Hz, H-3′ and H-5′), 6.80 (d, 2H, $J = 9.40$ Hz, H-2′ and H-6′), 5.28 (sl, 1H, OH), 4.28 (m, 1H, CH), 4.06 (m, 2H, NCH_2), 3.87 (m, 2H, OCH_2), 3.68 (s, 3H, CH_3O). Anal. Calcd for $C_{15}H_{16}N_4O_5$: C, 54.21; H, 4.85; N, 16.86. Found: C, 54.35; H, 4.76; N, 16.78.

5.1.7.3. 3-[1-(2-Hydroxy-3-phenoxypropyl)]-8-phenylxanthine (1c). White crystals (51%); mp 353 °C. IR (KBr) *v*: 3390 (OH), 3185 and 3035 (NH), 1680 and 1650 (CO). ^{1}H NMR (DMSO-d_6) δ: 13.76 (s, 1H, N_7-H), 11.14 (s, 1H, N_1-H), 8.02 (m, 2H, H-2″ and H-6″), 7.46 (m, 3H, H-3″, H-4″ and H-5″), 7.23 (t, 2H, $J = 7.50$ Hz, H-3′ and H-5′), 6.89 (t, 1H, $J = 7.50$ Hz, H-4′), 6.86 (d, 2H, $J = 7.50$ Hz, H-2′ et H-6′), 5.34 (d, 1H, $J = 4.70$ Hz, OH), 4.39 (m, 1H, CH), 4.14 (m, 2H, NCH_2), 4.01 (m, 2H, OCH_2). ^{13}C NMR (DMSO-d_6) δ: 158.4 (C-1′), 154.6 (C-6), 151.2 (C-2), 150.2 (C-8), 149.5 (C-4), 130.1 (C-1″), 129.4 (C-3′ and C-5′), 128.9 (C-3″ and C-5″), 128.8 (C-2″ and C-6″), 126.3 (C-4″), 120.5 (C-4′), 114.4 (C-2′ and C-6′), 108.3 (C-5), 70.3 (OCH_2), 65.9 (CH), 45.5 (NCH_2). Anal. Calcd for $C_{20}H_{18}N_4O_4$: C, 63.48; H, 4.79; N, 14.81. Found: C, 63.59; H, 4.72; N, 14.93.

5.1.7.4. 3-{1-[2-Hydroxy-3-(4-methoxyphenoxy) propyl]}-8-phenylxanthine (1d). White crystals (81%); mp 353 °C. IR (KBr) *v*: 3375 (OH), 3190 and 3040 (NH), 1680 and 1655 (CO). ^{1}H NMR (DMSO-d_6) δ: 13.76 (s, 1H, N_7-H), 11.13 (s, 1H, N_1-H), 8.02 (m, 2H, H-2″ and H-6″), 7.46 (m, 3H, H-3″, H-4″ and H-5″), 6.80 (s, 4H, H-2′, H-3′, H-5′ and H-6′), 5.30 (d, 1H, $J = 3.85$ Hz, OH), 4.35 (m, 1H, CH), 4.12 (m, 2H, NCH_2), 3.93 (m, 2H, OCH_2). Anal. Calcd for $C_{21}H_{20}N_4O_5$: C, 61.76; H, 4.93; N, 13.70. Found: C, 61.67; H, 4.78; N, 13.86.

5.1.7.5. 3-[1-(2-Hydroxy-3-phenoxypropyl)]-8-(4-hydroxyphenyl)xanthine (1e). Orange crystals (75%); mp 321 °C. IR (KBr) *v*: 3400 (OH), 3190 and 3030 (NH), 1685 and 1645 (CO). ^{1}H NMR (DMSO-d_6) δ: 13.38 (sl, 1H, N_7-H), 10.97 (s, 1H, N_1-H), 9.93 (s, 1H, OH ar), 7.87 (d, 2H, $J = 8.60$ Hz, H-2″ and H-6″), 7.24 (t, 2H, $J = 7.80$ Hz, H-3′ and H-5′), 6.85 (m, 5H, H-3″, H-5″, H-2′, H-4′ and H-6′), 5.27 (d, 1H, $J = 5.50$ Hz, OH), 4.38 (m, 1H, CH), 4.09 (m, 2H, NCH_2), 3.99 (m, 2H, OCH_2). ^{13}C NMR (DMSO-d_6) δ: 159.9 (C-4″), 158.9 (C-1′), 155.2 (C-6), 152.2 (C-2), 151.6 (C-8), 149.8 (C-4), 130.3 (C-3′ and C-5′), 129.2 (C-2″ et C-6″), 121.6 (C-1″), 120.4 (C-4′), 116.5 (C-3″ and C-5″), 115.2 (C-2′ and C-6′), 108.3 (C-5), 70.6 (OCH_2), 66.8 (CH), 46.1 (NCH_2). Anal. Calcd for $C_{20}H_{18}N_4O_5$: C, 60.91; H, 4.60; N, 14.21. Found: C, 61.03; H, 4.66; N, 14.17.

5.1.7.6. 3-[1-(2-Hydroxy-3-phenoxypropyl)]-8-styrylxanthine (1f). White crystals (70%); mp 304 °C. IR (KBr) *v*: 3420 (OH), 3145 and 3025 (NH), 1695 and 1670 (CO). ^{1}H NMR (DMSO-d_6) δ: 13.52 (sl, 1H, N_7-H), 11.16 (s, 1H, N_1-H), 7.59 (d, 2H, $J = 6.80$ Hz, H-2″ and H-6″), 7.56 (d, 1H, $J = 16.55$ Hz, =CH styryl), 7.41 (m, 3H, H-3″, H-4″ and H-5″), 7.24 (t, 2H,

J = 7.85 Hz, H-3′ and H-5′), 6.97 (d, 1H, J = 16.55 Hz, =CH styryl), 6.89 (t, 1H, J = 7.85 Hz, H-4′), 6.87 (d, 2H, J = 7.85 Hz, H-2′ and H-6′), 5.34 (sl, 1H, , OH), 4.36 (m, 1H, CH), 4.22 (m, 2H, NCH_2), 3.98 (m, 2H, OCH_2). ^{13}C NMR (DMSO-d_6) δ: 158.5 (C-1′), 154.4 (C-6), 151.2 (C-2), 150.3 (C-8), 149.1 (C-4), 135.4 (C=C styryl), 134.8 (C=C styryl), 129.4 (C-3′ and C-5′), 129.1 (C-1″), 129.0 (C-3″ and C-5″), 127.1 (C-2″ and C-6″), 120.5 (C-4′), 115.8 (C-4″), 114.4 (C-2′ and C-6′), 107.7 (C-5), 70.4 (OCH_2), 65.8 (CH), 45.5 (NCH_2). Anal. Calcd for $C_{22}H_{20}N_4O_4$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.45; H, 4.86; N, 13.98.

5.1.7.7. 3-[1-(2-Hydroxy-3-phenoxypropyl)]-8-(3-chlorostyryl)xanthine (1g). Beige crystals (60%); mp 274 °C. IR (KBr) v: 3430 (OH), 3150 and 3025 (NH), 1690 and 1665 (CO). ^1H NMR (DMSO-d_6) δ: 13.54 (sl, 1H, N_7-H), 11.13 (s, 1H, N_1-H), 7.66 (m, 1H, H-2″), 7.55–7.39 (m, 4H, H-4″, H-5″, H-6″ and =CH), 7.24 (t, 2H, J = 7.30 Hz, H-3′ and H-5′), 7.04 (d, 1H, J = 16.65 Hz, =CH styryl), 6.87 (m, 3H, H-2′, H-4′ and H-6′), 5.36 (sl, 1H, OH), 4.36 (m, 1H, CH), 4.14 (m, 2H, NCH_2), 3.97 (m, 2H, OCH_2). Anal. Calcd for $C_{22}H_{19}ClN_4O_4$: C, 61.73; H, 4.96; N, 12.00. Found: C, 60.88; H, 5.02; N, 12.11.

5.1.7.8. 3-[1-(2-Hydroxy-3-phenoxypropyl)]-8-(3-methoxystyryl)xanthine (1h). Beige crystals (84%); mp 286 °C. IR (KBr) v: 3450 (OH), 3150 and 3025 (NH), 1680 and 1655 (CO). ^1H NMR (DMSO-d_6) δ: 13.46 (sl, 1H, N_7-H), 11.07 (s, 1H, N_1-H), 7.54 (d, 1H, J = 16.90 Hz, =CH), 7.33–7.15 (m, 5H, H-4″, H-5″, H-6″, H-3′ and H-5′), 7.00 (d, 1H, J = 16.90 Hz, =CH), 6.88 (m, 4H, H-2″, H-2′, H-4′ and H-6′), 5.32 (sl, 1H, OH), 4.37 (m, 1H, CH), 4.18 (m, 1H, NCH_2), 4.11 (m, 1H, NCH_2), 3.98 (m, 2H, OCH_2), 3.81 (s, 3H, OCH_3). Anal. Calcd for $C_{23}H_{22}N_4O_5$: C, 63.58; H, 5.10; N, 12.90. Found: C, 63.71; H, 5.02; N, 13.05.

5.1.7.9. 3-[1-(2-Hydroxy-3-phenoxypropyl)]-8-(3,4,5-trimethoxystyryl)xanthine (1i). Pale-yellow crystals (76%); mp 189 °C. IR (KBr) v: 3415 (OH), 3140 and 3030 (NH), 1690 and 1670 (CO). ^1H NMR (DMSO-d_6) δ: 13.44 (sl, 1H, N_7-H), 11.10 (s, 1H, N_1-H), 7.52 (d, 1H, J = 16.15 Hz, =CH), 7.25 (m, 2H, H-3′ and H-5′), 7.03 (d, 1H, J = 16.15 Hz, =CH), 6.90 (m, 5H, H-2′, H-4′, H-6′, H-2″ and H-6″), 5.34 (sl, 1H, OH), 4.36 (m, 1H, CH), 4.06 (m, 2H, NCH_2), 3.96 (m, 2H, OCH_2), 3.83 (s, 6H, 2 CH_3O–), 3.68 (s, 3H, CH_3O–). Anal. Calcd for $C_{25}H_{26}N_4O_7$: C, 60.72; H, 5.30; N, 11.33. Found: C, 60.86; H, 5.23; N, 11.06.

5.1.7.10. 3-[1-(2-Hydroxy-3-phenoxypropyl)]-8-(4-carboxymethyloxyphenyl)xanthine (1j). Beige crystals (60%); mp 243 °C. IR (KBr) v: 3500–2830 (OH), 1715, 1690 and 1655 (CO). ^1H NMR (DMSO-d_6) δ: 13.52 (sl, 1H, N_7-H), 12.10 (sl, 1H, CO_2H), 11.07 (s, 1H, N_1-H), 7.96 (d, 2H, J = 8.10 Hz, H-2″ and H-6″), 7.24 (m, 2H, H-3′ and H-5′), 6.94 (m, 5H, H-3″, H-5″, H-2′, H-4′ and H-6′), 5.32 (m, 1H, OH), 4.74 (s, 2H, CH_2O), 4.38 (m, 1H, CH), 4.13 (m, 2H, NCH_2), 3.99 (m, 2H, OCH_2). ^{13}C NMR (DMSO-d_6) δ: 170.0 (CO_2H), 159.3 (C-4″), 158.5 (C-1′), 154.5 (C-6), 151.2 (C-2), 150.2 (C-8), 149.7 (C-4), 129.4 (C-3′ and C-5′), 127.9 (C-2″ and C-6″), 120.5 (C-4′), 114.8 (C-3″ and C-5″), 114.5 (C-1″), 114.4 (C-2′ and C-6′), 107.8 (C-5), 70.3 (OCH_2), 65.9 (CH), 64.6 (OCH_2-Ar), 45.4 (NCH_2). Anal. Calcd for $C_{22}H_{20}N_4O_7$: C, 58.40; H, 4.45; N, 12.38. Found: C, 58.22; H, 4.53; N, 12.49.

5.1.7.11. 3-[1-(2-Hydroxy-3-phenoxypropyl)]-8-(4-cinnamyl)xanthine (1k). Orange crystals (65%); mp > 400 °C. IR (KBr) v: 3420-2805 (OH), 1700, 1685 and 1665 (CO). ^1H NMR (DMSO-d_6) δ: 13.85 (sl, 1H, N_7-H), 12.42 (sl, 1H, CO_2H), 11.15 (s, 1H, N_1-H), 8.05 (d, 2H, J = 7.30 Hz, H-2″ and H-6″), 7.78 (d, 2H, J = 7.30 Hz, H-3″ and H-5″), 7.61 (d, 1H, J = 16.10 Hz, =CH styryl), 7.24 (m, 2H, H-3′, H-5′), 6.87 (m, 3H, H-2′, H-4′ and H-6′), 6.61 (d, 1H, J = 16.10 Hz, =CH styryl), 5.33 (m, 1H, OH), 4.39 (m, 1H, CH), 4.23 (m, 2H, NCH_2), 4.00 (m, 2H, OCH_2). ^{13}C NMR (DMSO-d_6) δ: 167.5 (CO_2H), 158.5 (C-1′), 154.6 (C-6), 151.2 (C-2), 150.2 (C-8), 148.6 (C-4), 143.0 (C=C styryl), 135.7 (C=C styryl), 130.0 (C-1″), 129.4 (C-3′ and C-5′), 128.7 (C-2″ and C-6″), 126.6 (C-3″ and C-5″), 120.4 (C-4′), 114.4 (C-2′ and C-6′), 108.6 (C-5), 70.3 (OCH_2), 65.9 (CH), 45.5 (NCH_2). Anal. Calcd for $C_{23}H_{20}N_4O_6$: C, 61.60; H, 4.49; N, 12.49. Found: C, 61.86; H, 4.32; N, 12.60.

5.1.7.12. 3-[1-(2-Hydroxy-3-phenoxypropyl)]-8-cyclopentylxanthine (1l). Beige crystals (55%); mp 213 °C. IR (KBr) v: 3430 (OH), 3150 and 3025 (NH), 1690 and 1665 (CO). ^1H NMR (DMSO-d_6) δ: 13.00 (sl, 1H, N_7-H), 10.96 (s, 1H, N_1-H), 7.22 (t, 2H, J = 7.45 Hz, H-3′ and H-5′), 6.88 (t, 1H, J = 7.45 Hz, H-4′), 6.78 (d, 2H, J = 7.45 Hz, H-2′ and H-6′), 5.33 (sl, 1H, OH), 4.27 (m, 1H, CH), 4.04 (m, 2H, NCH_2), 3.92 (m, 2H, OCH_2), 3.04 (m, 1H, CH cycl.), 1.90 (m, 2H, CH_2 cycl.), 1.66 (m, 6H, CH_2 cycl.). ^{13}C NMR (DMSO-d_6) δ: 158.4 (C-8), 157.5 (C-1′), 154.4 (C-6), 151.2 (C-2), 149.6 (C-4), 129.3 (C-3′ and C-5′), 120.5 (C-4′), 114.2 (C-2′ and C-6′), 106.5 (C-5), 70.4 (OCH_2), 65.8 (OCH), 45.4 (NCH_2), 38.7 (CH cycl.), 31.8 (CH_2 cycl.), 25.0 (CH_2 cycl.). Anal. Calcd for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99; N, 15.13. Found: C, 61.53; H, 6.08; N, 15.25.

5.1.7.13. 3-[1-(2-Hydroxy-3-phenoxypropyl)]-8-cyclohexylxanthine (1m). Beige crystals (75%); mp 115 °C. IR (KBr) v: 3430 (OH), 3150 and 3025 (NH), 1690 and 1665 (CO). ^1H NMR (DMSO-d_6) δ: 12.95 (sl, 1H, N_7-H), 10.98 (s, 1H, N_1-H), 7.21 (t, 2H, J = 7.0 Hz, H-3′ and H-5′), 6.89 (t, 1H, J = 7.0 Hz, H-4′), 6.86 (d, 2H, J = 7.0 Hz, H-2′ and H-6′), 5.33 (sl, 1H, OH), 4.27 (m, 1H, CH), 4.05 (m, 2H, NCH_2), 3.92 (m, 2H, OCH_2), 2.62 (m, 1H, CH cycl.), 1.72 (m, 5H, CH_2 cycl.), 1.42 (m, 5H, CH_2 cycl.). ^{13}C NMR (DMSO-d_6) δ: 158.4 (C-8), 157.8 (C-1′), 154.5 (C-6), 151.2 (C-2), 149.5 (C-4), 129.4 (C-3′ and C-5′), 120.5 (C-4′), 114.3 (C-2′ and C-6′), 106.4 (C-5), 70.4 (OCH_2), 65.9 (OCH), 45.4 (NCH_2), 37.5 (CH cycl.), 30.9 (CH_2 cycl.), 30.8 (CH_2 cycl.). Anal. Calcd for $C_{20}H_{24}N_4O_4$: C, 62.48; H, 6.29; N, 14.57. Found: C, 62.59; H, 6.20; N, 14.46.

5.1.7.14. 3-[1-(2-Hydroxy-3-phenoxypropyl)]-8-noradamantylxanthine (1n). Beige crystals (75%); mp 135 °C. IR (KBr) v: 3440 (OH), 3150 and 3030 (NH),

1690 and 1670 (CO). ^{1}H NMR (DMSO-d_6) δ: 12.9 (sl, 1H, N_7-H), 10.98 (s, 1H, N_1-H), 7.24 (t, 2H, J = 7.40 Hz, H-3′ and H-5′), 6.90 (t, 1H, J = 7.40 Hz, H-4′), 6.78 (d, 2H, J = 7.40 Hz, H-2′ and H-6′), 5.38 (sl, 1H, OH), 4.29 (m, 1H, CH), 4.07 (m, 2H, NCH_2), 3.92 (m, 2H, OCH_2), 2.50 (m, 1H, CH nor.), 2.25 (m, 2H, CH nor.), 2.04 (m, 2H, CH_2 nor.), 1.82 (m, 4H, CH_2 nor.), 1.58 (m, 4H, CH_2 nor.). Anal. Calcd for $C_{23}H_{26}N_4O_4$: C, 65.39; H, 6.20; N, 13.26. Found: C, 65.56; H, 6.04; N, 13.31.

5.1.8. General procedure for 1,7-dimethyl-3-[1-(2-hydroxy-3-phenoxy)propyl]-8-alkyl or -arylxanthines (2a–k). Xanthine **1** (1.2 mmol) was dissolved in 8 ml DMF, K_2CO_3 (3.7 mmol) and methyl iodide (36 mmol) were added, and the mixture was heated at 60 °C for 2 h then allowed at room temperature overnight. The product was precipitated by addition of H_2O, collected by filtration, washed with H_2O and extracted with CH_2Cl_2. The organic layer was then dried over Na_2SO_4 and evaporated to dryness to give xanthine **2a**–**k**.

5.1.8.1. 1,7-Dimethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]xanthine (2a). White crystals (32%); mp 156 °C. IR (KBr) v: 3415 (OH), 1700 and 1660 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.96 (s, 1H, H-8), 7.24 (t, 2H, J = 7.40 Hz, H-3′ and H-5′), 6.89 (t, 1H, J = 7.40 Hz, H-4′), 6.81 (d, 2H, J = 7.40 Hz, H-2′ and H-6′), 5.29 (d, 1H, J = 5.30 Hz, OH), 4.27 (m, 1H, CH), 4.15 (m, 2H, NCH_2), 3.94 (m, 2H, OCH_2), 3.85 (s, 3H, N_7-CH_3), 3.19 (s, 3H, N_1-CH_3). ^{13}C NMR (DMSO-d_6) δ: 158.8 (C-1′), 155.5 (C-6), 151.9 (C-2), 148.8 (C-8), 143.3 (C-4), 130.1 (C-3′ and C-5′), 121.4 (C-4′), 114.9 (C-2′ and C-6′), 107.5 (C-5), 70.8 (OCH_2), 66.4 (CH), 46.8 (NCH_2), 33.8 (N_7-CH_3), 28.3 (N_1-CH_3). Anal. Calcd for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 28.32; H, 5.36; N, 17.05.

5.1.8.2. 1,7-Dimethyl-3-{1-[2-hydroxy-3-(4-methoxyphenoxy)propyl]}xanthine (2b). Pale-yellow crystals (62%); mp 99 °C. IR (KBr) v: 3390 (OH), 1720 and 1660 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.97 (s, 1H, H-8), 6.81 (d, 2H, J = 9.35 Hz, H-3′ and H-5′), 6.74 (d, 1H, J = 9.35 Hz, H-2′ and H-6′), 5.26 (d, 1H, J = 5.30 Hz, OH), 4.27 (m, 1H, CH), 4.04 (m, 2H, NCH_2), 3.92 (s, 3H, N_7-CH_3), 3.86 (m, 2H, OCH_2), 3.67 (s, 3H, OCH_3), 3.19 (s, 3H, N_1-CH_3). Anal. Calcd for $C_{17}H_{20}N_4O_5$: C, 56.66; H, 5.59; N, 15.55. Found: C, 56.75; H, 5.46; N, 15.32.

5.1.8.3. 1,7-Dimethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-phenylxanthine (2c). White crystals (58%); mp 139 °C. IR (KBr) v: 3420 (OH), 1705 and 1660 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.67 (m, 2H, H-2″ and H-6″), 7.54 (m, 3H, H-3″, H-4″ and H-5″), 7.21 (t, 2H, J = 7.60 Hz, H-3′ and H-5′), 6.87 (t, 1H, J = 7.60 Hz, H-4′), 6.81 (d, 2H, J = 7.60 Hz, H-2′ and H-6′), 5.33 (d, 1H, J = 5.40 Hz, OH), 4.35 (m, 1H, CH), 4.19 (m, 2H, NCH_2), 3.97 (m, 2H, OCH_2), 3.93 (s, 3H, N_7-CH_3), 3.22 (s, 3H, N_1-CH_3). ^{13}C NMR (DMSO-d_6) δ: 158.3 (C-1′), 154.8 (C-6), 150.9 (C-2), 150.7 (C-8), 147.6 (C-4), 130.1 (C-1″), 129.3 (C-3′ and C-5′), 129.0 (C-3″ and C-5″), 128.7 (C-2″ and C-6″), 128.1 (C-4″), 120.4 (C-4′), 114.2 (C-2′ and C-6′), 107.8 (C-5), 70.4 (OCH_2), 65.6 (CH), 46.2 (NCH_2), 33.5 (N_7-CH_3), 27.6 (N_1-CH_3). Anal. Calcd for $C_{22}H_{22}N_4O_4$: C, 65.01; H, 5.45; N, 13.78. Found: C, 64.89; H, 5.52; N, 13.97.

5.1.8.4. 1,7-Dimethyl-3-{1-[2-hydroxy-3-(4-methoxyphenoxy)propyl]}-8-phenylxanthine (2d). Beige crystals (68%); mp 136 °C. IR (KBr) v: 3400 (OH), 1715 and 1665 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.70 (m, 2H, H-2″ and H-6″), 7.54 (m, 3H, H-3″, H-4″ and H-5″), 6.75 (m, 4H, H-2′, H-3′, H-5′ and H-6′), 5.29 (d, 1H, J = 5.35 Hz, OH), 4.30 (m, 1H, CH), 4.15 (m, 2H, NCH_2), 3.94 (s, 3H, N_7-CH_3), 3.89 (m, 2H, OCH_2), 3.64 (s, 3H, OCH_3), 3.23 (s, 3H, N_1-CH_3). Anal. Calcd for $C_{23}H_{24}N_4O_5$: C, 63.29; H, 5.54; N, 12.84. Found: C, 63.18; H, 5.62; N, 12.90.

5.1.8.5. 1,7-Dimethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-styrylxanthine (2e). White crystals (71%); mp 199 °C. IR (KBr) v: 3420 (OH), 1705 and 1655 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.73 (d, 2H, J = 7.80 Hz, H-2″ and H-6″), 7.57 (d, 1H, J = 15.80 Hz, =CH styryl), 7.42 (m, 3H, H-3″, H-4″ and H-5″), 7.26 (d, 1H, J = 15.80 Hz, =CH styryl), 7.23 (t, 2H, J = 7.60 Hz, H-3′ and H-5′), 6.87 (m, 3H, H-2′, H-4′ and H-6′), 5.34 (d, 1H, J = 5.35 Hz, OH), 4.36 (m, 1H, CH), 4.17 (m, 2H, NCH_2), 4.00 (m, 2H, OCH_2), 3.99 (s, 3H, N_7-CH_3), 3.19 (s, 3H, N_1-CH_3). Anal. Calcd for $C_{24}H_{24}N_4O_4$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.53; H, 5.68; N, 13.10.

5.1.8.6. 1,7-Dimethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-(3-chlorostyryl)xanthine (2f). Pale-yellow crystals (64%); mp 191 °C. IR (KBr) v: 3415 (OH), 1705 and 1660 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.88 (s, 1H, H-2″), 7.63 (m, 1H, H arom.), 7.50 (d, 1H, J = 15.90 Hz, =CH), 7.44 (m, 2H, H arom.), 7.36 (d, 1H, J = 15.90 Hz, =CH), 7.22 (t, 2H, J = 7.50 Hz, H-3′ and H-5′), 6.87 (t, 1H, J = 7.50 Hz, H-4′), 6.84 (d, 2H, J = 7.50 Hz, H-2′ and H-6′), 5.34 (d, 1H, J = 5.30 Hz, OH), 4.31 (m, 1H, CH), 4.15 (m, 2H, NCH_2), 3.98 (s, 3H, CH_3), 3.97 (m, 2H, OCH_2), 3.18 (s, 3H, CH_3). Anal. Calcd for $C_{24}H_{23}ClN_4O_4$: C, 66.02; H, 5.30; N, 13.39. Found: C, 66.18; H, 5.24; N, 13.30.

5.1.8.7. 1,7-Dimethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-(3,4,5-trimethoxystyryl)xanthine (2g). Pale-yellow crystals (74%); mp 207 °C. IR (KBr) v: 3420 (OH), 1680 and 1660 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.54 (d, 1H, J = 15.95 Hz, =CH), 7.23 (m, 2H, H-3′ and H-5′), 7.21 (m, 1H, H-4′), 7.06 (s, 2H, H-2″ and H-6″), 6.87 (d, 1H, J = 15.95 Hz, =CH), 6.86 (t, 2H, J = 7.80 Hz, H-2′ and H-6′), 5.35 (d, 1H, J = 5.15 Hz, OH), 4.37 (m, 1H, CH), 4.14 (m, 2H, NCH_2), 4.00 (s, 3H, N_7-CH_3), 3.98 (m, 2H, OCH_2), 3.84 (s, 6H, OCH_3), 3.69 (s, 3H, OCH_3), 3.19 (s, 3H, N_1-CH_3). Anal. Calcd for $C_{27}H_{30}N_4O_7$: C, 62.06; H, 5.79; N, 10.72. Found: C, 61.91; H, 5.92; N, 10.63.

5.1.8.8. 1,7-Dimethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-cyclopentylxanthine (2h). Beige crystals (47%); mp 119 °C. IR (KBr) v: 3420 (OH), 1705 and 1660 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.21 (t, 2H, J = 7.70 Hz, H-3′ and H-5′), 6.87 (t, 1H, J = 7.70 Hz, H-4′), 6.73 (d, 2H, J = 7.70 Hz, H-2′ and H-6′), 5.34 (d, 1H,

J = 5.40 Hz, OH), 4.25 (m, 1H, CH), 4.09 (m, 2H, NCH_2), 3.80 (m, 2H, OCH_2), 3.25 (m, 1H, CH cyclopentyl), 3.18 (s, 3H, CH_3), 1.87 (m, 2H, CH_2 cyclopentyl), 1.68 (m, 4H, CH_2 cyclopentyl). ^{13}C NMR (DMSO-d_6) δ: 158.3 (C-8), 157.4 (C-1′), 154.5 (C-6), 151.0 (C-2), 147.3 (C-4), 129.3 (C-3′ and C-5′), 120.4 (C-4′), 114.1 (C-2′ and C-6′), 106.4 (C-5), 70.4 (OCH_2), 65.6 (OCH), 46.0 (NCH_2), 35.5 (CH cyclopentyl), 31.1 (CH_2 cyclopentyl), 31.0 (CH_3), 27.5 (CH_3), 25.2 (CH_2 cyclopentyl). Anal. Calcd for $C_{21}H_{26}N_4O_4$: C, 63.30; H, 6.58; N, 14.06. Found: C, 63.12 ; H, 6.65; N, 14.22.

5.1.8.9. 1,7-Dimethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-cyclohexylxanthine (2i). Beige crystals (57%); mp 163 °C. IR (KBr) v: 3420 (OH), 1695 and 1655 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.22 (t, 2H, H-3′ and H-5′), 6.88 (t, 1H, J = 7.65 Hz, H-4′), 6.76 (d, 2H, J = 7.65 Hz, H-2′ and H-6′), 5.33 (d, 1H, J = 5.35 Hz, OH), 4.26 (m, 1H, CH), 4.09 (m, 2H, NCH_2), 3.92 (m, 2H, OCH_2), 3.81 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 2.78 (m, 1H, CH cyclohexyl), 1.69 (m, 5H, CH_2 cyclohexyl), 1.34 (5H, CH_2 cyclohexyl). ^{13}C NMR (DMSO-d_6) δ: 158.0 (C-8), 157.1 (C-1′), 154.2 (C-6), 150.7 (C-2), 147.1 (C-4), 129.0 (C-3′ and C-5′), 120.1 (C-4′), 113.8 (C-2′ and C-6′), 105.8 (C-5), 70.0 (OCH_2), 65.3 (OCH), 45.6 (NCH_2), 33.9 (CH cyclohexyl), 30.7 (CH_2 cyclohexyl), 30.1 (CH_2 cyclohexyl), 27.2 (CH_3), 25.0 (CH_2 cyclohexyl), 24.9 (CH_3). Anal. Calcd for $C_{22}H_{28}N_4O_4$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.25; H, 6.77; N, 13.69.

5.1.8.10. 1,7-Dimethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-(4-methylcarboxymethyloxyphenyl) xanthine (2j). Orange crystals (40%); mp 98 °C. IR (KBr) v: 3450–2850 (OH), 1725, 1690 and 1660 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.63 (d, 2H, J = 8.55 Hz, H-2″ and H-6″), 7.22 (t, 2H, J = 7.70 Hz, H-3′ and H-5′), 7.07 (d, 2H, J = 8.55 Hz, H-3″ and H-5″), 6.84 (t, 1H, J = 7.70 Hz, H-4′), 6.79 (d, 2H, J = 7.70 Hz, H-2′ and H-6′), 5.35 (d, 1H, J = 5.25 Hz, OH), 4.90 (s, 2H, CH_2O-Ar), 4.33 (m, 1H, CH), 4.17 (m, 2H, NCH_2), 3.96 (m, 2H, OCH_2), 3.94 (s, 3H, N_7-CH_3), 3.71 (s, 3H, OCH_3), 3.23 (s, 3H, N_1-CH_3). ^{13}C NMR (DMSO-d_6) δ: 169.0 (CO ester), 158.9 (C-4″), 158.3 (C-1′), 154.7 (C-6), 151.0 (C-2), 150.8 (C-8), 147.7 (C-4), 130.6 (C-3′ and C-5′), 129.4 (C-2″ and C-6″), 121.2 (C-4′), 120.5 (C-1″), 114.7 (C-3″ and C-5″), 114.2 (C-2′ and C-6′), 107.7 (C-5), 70.4 (OCH_2), 65.6 (OCH), 64.6 (OCH_2 ar), 51.9 (OCH_3), 46.2 (NCH_2), 33.6 (NCH_3), 27.6 (NCH_3). Anal. Calcd for $C_{25}H_{26}N_4O_7$: C, 60.72; H, 5.30; N, 11.33. Found: C, 60.65; H, 5.42; N, 11.45.

5.1.8.11. 1,7-Dimethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-(4-methylcarboxyethylidene)phenylxanthine (2k). Yellow crystals (86%); mp 133 °C. IR (KBr) v: 3500-2830 (OH), 1715, 1690 and 1655 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.84 (m, 2H, H-2″ and H-6″), 7.74 (m, 3H, H-3″, H-5″ and =CH styryl), 7.22 (m, 2H, H-3′ and H-5′), 6.80 (m, 4H, H-2′, H-4′, H-6′ and =CH), 5.35 (m, 1H, OH), 4.32 (m, 1H, CH), 4.16 (m, 2H, NCH_2), 4.00 (m, 2H, OCH_2), 3.97 (s, 3H, N_7-CH_3), 3.74 (s, 3H, OCH_3), 3.22 (s, 3H, N_1-CH_3). ^{13}C NMR (DMSO-d_6) δ: 166.5 (CO ester), 158.3 (C-1′), 154.8 (C-6), 150.9 (C-2), 150.0 (C-8), 147.6 (C-4), 143.4 (C=C), 135.5 (C=C), 129.6 (C-1″), 129.4 (C-3′ and C-5′), 129.3 (C-3″ and C-5″), 128.5 (C-2″ and C-6″), 120.5 (C-4″), 119.3 (C-4′), 114.2 (C-2′ and C-6′), 108.2 (C-5), 70.3 (OCH_2), 65.6 (OCH), 51.6 (OCH_3), 46.2 (NCH_2), 33.7 (NCH_3), 27.7 (NCH_3). Anal. Calcd for $C_{26}H_{26}N_4O_6$: C, 63.66; H, 5.34; N, 11.42. Found: C, 63.78; H, 5.23; N, 11.30.

5.1.9. General procedure for 1,7-dimethyl-3-[1-(2-methoxy-3-phenoxy)propyl]-8-arylxanthines (2l,m). To a solution of xanthine **2d** or **2f** (1 mmol) in 6 ml DMF was added sodium hydride (1.5 mmol). After 1 h of stirring at room temperature, methyl iodide (3 mmol) was added to the reaction mixture, which was heated at 90–100 °C for 4 h. After cooling, the product was precipitated by addition of water, collected by filtration, washed with water and extracted with methylene chloride. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was then triturated in petroleum ether, filtered, washed and dried to give **2l**,**m**.

5.1.9.1. 1,7-Dimethyl-3-{1-[2-methoxy-3-(4-methoxyphenoxy)propyl]}-8-phenylxanthine (2l). White crystals (65%); mp 111 °C. IR (KBr) v: 3410 (OH), 1715 and 1675 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.68 (m, 2H, H-2″ and H-6″), 7.51 (m, 3H, H-3″, H-4″ and H-5″), 6.78 (m, 4H, H-2′, H-3′, H-5′ and H-6′), 4.26 (m, 2H, CH and NCH_2), 4.08 (m, 3H, OCH_2 and NCH_2), 3.96 (s, 3H, N_7-CH_3), 3.65 (s, 3H, Ar-OCH_3), 3.34 (s, 3H, OCH_3), 3.23 (s, 3H, N_1-CH_3). Anal. Calcd for $C_{24}H_{26}N_4O_5$: C, 63.99; H, 5.82; N, 12.44. Found: C, 63.76; H, 6.04; N, 12.31.

5.1.9.2. 1,7-Dimethyl-3-[1-(2-methoxy-3-phenoxypropyl)]-8-(3-chlorostyryl)xanthine (2m). Pale-yellow crystals (71%); mp 157 °C. IR (KBr) v: 3420 (OH), 1705 and 1650 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.84 (s, 1H, H-2″), 7.60 (m, 1H, H arom.), 7.47 (d, 1H, J = 15.75 Hz, =CH), 7.41 (m, 2H, H arom.), 7.35 (d, 1H, J = 15.75 Hz, =CH), 7.23 (t, 2H, J = 7.80 Hz, H-3′ and H-5′), 6.88 (m, 3H, H-2′, H-4′ and H-6′), 4.32 (m, 1H, CH), 4.24 (m, 1H, NCH_2), 4.16 (m, 2H, OCH_2 and NCH_2), 4.02 (m, 1H, OCH_2), 3.98 (s, 3H, N_7-CH_3), 3.38 (s, 3H, OCH_3), 3.19 (s, 3H, N_1-CH_3). Anal. Calcd for $C_{25}H_{25}ClN_4O_4$: C, 62.43; H, 5.24; N, 11.65. Found: C, 62.34; H, 5.43; N, 11.60.

5.1.10. 1,7-Dimethyl-3-[1-(2-chloro-3-phenoxypropyl)]-8-(3,4,5-trimethoxystyryl)xanthine (2n). To a suspension of xanthine **2g** (0.8 mmol) in 7 ml of methylene chloride was added thionyl chloride (4 mmol). The reaction mixture was refluxed for 2 h and then evaporated to dryness under reduced pressure. The residue was triturated in water, and the mixture was alkalinised with K_2CO_3 until pH = 8. The precipitate was extracted with methylene chloride, and the organic layer was dried over Na_2SO_4 and evaporated to dryness to give **2n**. Yellow crystals (42%); mp 86 °C. IR (KBr) v: 1670 and 1645 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.45 (d, 1H, J = 15.65 Hz, =CH), 7.26 (m, 3H, H-3′, H-4′ and H-5′), 7.06 (s, 2H, H-2″ and H-6″), 6.91 (m, 3H, =CH, H-2′ and H-6′), 4.88 (m, 1H, CH), 4.46 (m, 1H, NCH_2), 4.31 (m, 2H,

OCH_2 and NCH_2), 4.20 (m, 1H, OCH_2), 4.03 (s, 3H, N_7-CH_3), 3.92 (s, 6H, OCH_3), 3.69 (s, 3H, OCH_3), 3.22 (s, 3H, N_1-CH_3). Anal. Calcd for $C_{27}H_{29}ClN_4O_6$: C, 59.94; H, 5.40; N, 10.36. Found: C, 60.12; H, 5.56; N, 10.27.

5.1.11. 7-Methyl-3-[1-(2-hydroxy-3-phenoxy)propyl]-8-styrylxanthine (1o). Xanthine **1f** (0.9 mmol) was dissolved in 8 ml of DMF, K_2CO_3 (2.8 mmol) and methyl iodide (27 mmol) were added and the mixture was stirred at room temperature for 24 h. The product was precipitated by addition of H_2O, collected by filtration, washed with H_2O and dried. The solid residue was triturated in methylene chloride, filtered, washed and dried to give **1o**. White crystals (63%); mp 335 °C. IR (KBr) *v*: 3440 (OH), 3025 (NH), 1690 and 1665 (CO). ^{1}H NMR (DMSO-d_6) δ: 11.08 (sl, 1H, N_1-H), 7.73 (d, 2H, J = 6.80 Hz, H-2″ and H-6″), 7.54 (d, 1H, J = 15.70 Hz, =CH styryl), 7.39 (m, 3H, H-3″, H-4″ and H-5″), 7.27 (d, 1H, J = 15.70 Hz, =CH styryl), 7.24 (t, 2H, J = 7.70 Hz, H-3′ and H-5′), 6.87 (m, 3H, H-2′, H-4′ and H-6′), 5.35 (sl, 1H, OH), 4.34 (m, 1H, CH), 4.11 (m, 2H, NCH_2), 4.01 (m, 2H, OCH_2), 3.97 (s, 3H, N_7-CH_3). Anal. Calcd for $C_{23}H_{22}N_4O_4$: C, 66.02; H, 5.30; N, 13.39. Found: C, 66.18; H, 5.24; N, 13.30.

5.1.12. 7-Methyl-1-propargyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-styrylxanthine (3a). A solution of xanthine **1o** (0.41 mmol) in dry DMF (6 ml) was treated with K_2CO_3 (0.61 mmol) and propargyl chloride (0.82 mmol). The reaction mixture was heated at 60–70 °C for 2 h, allowed at room temperature under stirring overnight, then diluted with 15 ml of water and extracted with methylene chloride. The combined extracts were dried over Na_2SO_4 and evaporated to dryness. The solid residue was triturated in diethyl ether, filtered, washed with diethyl ether and dried to yield **3a**. White crystals (56%); mp 105 °C. IR (KBr) *v*: 3435 (OH), 2125 (C≡C), 1700 and 1655 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.77 (d, 2H, J = 7.80 Hz, H-2″ and H-6″), 7.58 (d, 1H, J = 15.75 Hz, =CH styryl), 7.39 (m, 3H, H-3″, H-4″ and H-5″), 7.31 (d, 1H, J = 15.75 Hz, =CH styryl), 7.21 (t, 2H, J = 7.20 Hz, H-3′ and H-5′), 6.88 (m, 3H, H-2′, H-4′ and H-6′), 5.38 (d, 1H, J = 5.30 Hz, OH), 4.59 (d, 2H, J = 2.00 Hz, N_1-CH_2), 4.36 (m, 1H, CH), 4.18 (m, 2H, NCH_2), 4.00 (s, 3H, N_7-CH_3), 3.95 (m, 2H, OCH_2), 3.10 (t, 1H, J = 2.00 Hz, ≡CH). ^{13}C NMR (DMSO-d_6) δ: 158.4 (C-1′), 153.3 (C-6), 150.2 (C-2), 149.8 (C-8), 148.4 (C-4), 136.8 (C=C styryl), 135.5 (C=C styryl), 129.4 (C-1″, C-3′ and C-5′), 128.8 (C-3″ and C-5″), 127.6 (C-2″ and C-6″), 120.5 (C-4′), 114.3 (C-2′ and C-6′), 112.7 (C-4″), 107.2 (C-5), 79.7 (≡CH), 72.9 (C≡), 70.4 (OCH_2), 65.6 (CH), 46.2 (NCH_2), 31.4 (N_7-CH_3), 30.0 (CH_2 propargyl). Anal. Calcd for $C_{26}H_{24}N_4O_4$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.57; H, 5.16; N, 12.09.

5.1.13. 6-Amino-5-phenylcarboxamido-3-propargyl-1-(2-hydroxy-3-phenoxypropyl)uracil (12). To a solution of uracil **11a** (2.5 mmol) in DMF (10 ml) were added K_2CO_3 (3 mmol) and propargyl chloride (5 mmol). The mixture was heated at °C for 6 h, then stirred at room temperature for 16 h and the product was precipitated by the addition of water (50 ml), collected by filtration and washed with water and subsequently extracted with methylene chloride. The organic layer was dried over Na_2SO_4, filtered and evaporated to dryness. The crystalline residue was triturated in diethyl ether, filtered, washed with diethyl ether and dried to yield **12**. Beige crystals (54%); mp 189 °C. IR (KBr) *v*: 1680, 1670 and 1630 (CO). ^{1}H NMR (DMSO-d_6) δ: 9.02 (s, 1H, NH), 7.98 (m, 2H, H-2″ and H-6″), 7.68 (m, 3H, H-3″, H-4″ and H-5″), 7.28 (m, 2H, H-3′ and H-5′), 6.93 (m, 3H, H-2′, H-4′ and H-6′), 6.69 (sl, 2H, NH_2), 5.84 (m, 1H, OH), 4.49 (s, 2H, CH_2 propargyl), 4.34 (m, 1H, CH), 4.15 (m, 2H, NCH_2), 4.00 (m, 2H, OCH_2), 3.18 (s, 1H, ≡CH). Anal. Calcd for $C_{23}H_{22}N_4O_5$: C, 63.58; H, 5.10; N, 12.90. Found: C, 63.69; H, 5.24; N, 12.76.

5.1.14. Propargyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-phenylxanthine (3c). Uracil **12** (1.38 mmol) was refluxed in 8 ml of 2N NaOH aqueous solution and 3 ml of ethanol for 1.5 h. The hot solution was allowed to cool to 4 °C, diluted with water and acidified with acetic acid then with diluted hydrochloric acid until pH = 3 to form a white precipitate, which was collected by filtration to give **3b**. Beige Crystals (42%); mp 236 °C. IR (KBr) *v*: 3370 (OH), 3100 (NH), 1675 and 1640 (CO). ^{1}H NMR (DMSO-d_6) δ: 13.90 (s, 1H, N_7-H), 8.04 (m, 2H, H-2″ and H-6″), 7.48 (m, 3H, H-3″, H-4″ and H-5″), 7.23 (m, 2H, H-3′ and H-5′), 6.89 (m, 1H, H-2′, H-4′ and H-6′), 5.37 (d, 1H, J = 5.30 Hz, OH), 4.63 (s, 2H, CH_2 propargyl), 4.37 (m, 1H, CH), 4.19 (m, 2H, NCH_2), 4.02 (m, 2H, OCH_2), 3.11 (s, 1H, ≡CH). Anal. Calcd for $C_{23}H_{20}N_4O_4$: C, 66.33; H, 4.84; N, 13.45. Found: C, 66.18; H, 5.01; N, 13.31.

5.1.15. General procedure for 7-pivaloyloxymethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-alkyl- or -arylxanthines (13a–e). A mixture of xanthines **1a**,**h**,**l** and **n** (3 mmol), chloromethyl pivalate (POM-Cl, 3 mmol) and K_2CO_3 (6 mmol) in anhydrous DMF (10 ml) was heated at 60–70 °C for 6 h, then stirred overnight at room temperature, diluted with 25 ml of water and extracted with methylene chloride. The combined extracts were washed with water and brine, dried over Na_2SO_4 and evaporated to dryness.

5.1.15.1. 7-Pivaloyloxymethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]xanthine (13a). Yellow oil (51%). IR (KBr) *v*: 3430 (OH), 3210 (NH), 1730, 1685 and 1670 (CO). ^{1}H NMR (DMSO-d_6) δ: 11.28 (sl, 1H, N_1-H), 8.20 (s, 1H, H-8), 7.24 (t, 2H, J = 7.70 Hz, H-3′ and H-5′), 6.91 (d, 2H, J = 7.70 Hz, H-2′ and H-6′), 6.84 (t, 1H, J = 7.70 Hz, H-4′), 6.10 (s, 2H, CH_2 pival.), 5.34 (d, 1H, J = 5.50 Hz, OH), 4.48 (m, 1H, CH), 4.29 (m, 1H, NCH_2), 4.14 (m, 2H, OCH_2 and NCH_2), 3.94 (m, 1H, OCH_2), 1.09 (s, 9H, $C(CH_3)_3$). Anal. Calcd for $C_{20}H_{24}N_4O_6$: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.55; H, 5.99; N, 13.53.

5.1.15.2. 7-Pivaloyloxymethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-cyclopentylxanthine (13b). Orange oil (61%). IR (KBr) *v*: 3420 (OH), 3150 (NH), 1725, 1685

and 1660 (CO). ^{1}H NMR (DMSO-d_6) δ: 11.08 (s, 1H, N_1-H), 7.22 (t, 2H, J = 7.65 Hz, H-3′ and H-5′), 6.89 (t, 1H, J = 7.65 Hz, H-4′), 6.78 (d, 2H, J = 7.65 Hz, H-2′ and H-6′), 6.15 (s, 2H, CH_2 pival.), 5.40 (sl, 1H, OH), 4.26 (m, 1H, CH), 4.12 (m, 2H, NCH_2), 3.92 (m, 2H, OCH_2), 3.35 (m, 1H, CH cycl.), 1.88 (m, 2H, CH_2 cycl.), 1.68 (m, 6H, CH_2 cycl.), 1.11 (s, 9H, $C(CH_3)_3$). Anal. Calcd for $C_{25}H_{32}N_4O_6$: C, 61.97; H, 6.65; N, 11.56. Found: C, 62.13; H, 6.51; N, 11.67.

5.1.15.3. 7-Pivaloyloxymethyl-3-[1-(2-Hydroxy-3-phenoxypropyl)]-8-(3-methoxystyryl)xanthine (13c). Yellow crystals (64%); mp 150 °C. IR (KBr) v: 3415 (OH), 3240 (NH), 1720, 1660 and 1635 (CO). ^{1}H NMR (DMSO-d_6) δ: 11.21 (sl, 1H, N_1-H), 7.63 (d, 1H, J = 16.15 Hz, =CH), 7.49-7.22 (m, 6H, H-2″, H-4″, H-5″, H-6″, H-3′ and H-5′), 6.98–6.86 (m, 4H, =CH, H-2′, H-4′ and H-6′), 6.39 (s, 2H, CH_2 pival.), 5.34 (d, 1H, J = 4.90 Hz, OH), 4.37 (m, 1H, CH), 4.16 (m, 1H, NCH_2), 4.08 (m, 1H, NCH_2), 4.01 (m, 2H, OCH_2), 3.82 (s, 3H, OCH_3), 1.10 (s, 9H, $C(CH_3)_3$). Anal. Calcd for $C_{29}H_{32}N_4O_7$: C, 63.49; H, 5.88; N, 10.21. Found: C, 63.56; H, 5.72; N, 10.36.

5.1.15.4. 7-Pivaloyloxymethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-noradamantylxanthine (13d). Yellow crystals (66%); mp 127 °C. IR (KBr) v: 3450 (OH), 3120 (NH), 1730, 1695 and 1675 (CO). ^{1}H NMR (DMSO-d_6) δ: 10.77 (s, 1H, N_1-H), 7.20 (t, 2H, J = 7.40 Hz, H-3′ and H-5′), 6.82 (t, 1H, J = 7.40 Hz, H-4′), 6.78 (d, 2H, J = 7.40 Hz, H-2′ and H-6′), 6.08 (s, 2H, CH_2 pival.), 5.45 (sl, 1H, OH), 4.25 (m, 1H, CH), 4.08 (m, 2H, NCH_2), 3.93 (m, 2H, OCH_2), 2.48 (m, 1H, CH nor.), 2.26 (m, 2H, CH nor.), 1.98 (m, 2H, CH_2 nor.), 1.81 (m, 4H, CH_2 nor.), 1.59 (m, 4H, CH_2 nor.), 1.12 (s, 9H, CH_3). Anal. Calcd for $C_{29}H_{36}N_4O_6$: C, 64.91; H, 6.76; N, 10.44. Found: C, 64.77; H, 6.84; N, 10.30.

5.1.15.5. 7-Pivaloyloxymethyl-3-{1-[2-hydroxy-3-(4-methoxyphenoxy)propyl]}xanthine (13e). Yellow crystals (35%); mp 54 °C. IR (KBr) v: 3440 (OH), 3240 (NH), 1725, 1685 and 1670 (CO). ^{1}H NMR (DMSO-d_6) δ: 11.26 (sl, 1H, N_1-H), 8.16 (s, 1H, H-8), 6.85 (d, 2H, J = 8.60 Hz, H-3′ and H-5′), 6.79 (d, 2H, J = 8.60 Hz, H-2′ and H-6′), 6.10 (s, 2H, CH_2 pival.), 5.29 (d, 1H, J = 5.10 Hz, OH), 4.25 (m, 1H, CH), 4.03 (m, 3H, OCH_2 and NCH_2), 3.86 (m, 1H, OCH_2), 3.67 (s, 3H, OCH_3), 1.10 (s, 9H, $C(CH_3)_3$). Anal. Calcd for $C_{21}H_{26}N_4O_7$: C, 56.49; H, 5.87; N, 12.55. Found: C, 56.62; H, 5.73; N, 12.60.

5.1.16. General procedure for 1-alkyl-7-pivaloyloxymethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-alkyl- or -arylxanthines (14a–e). A solution of xanthines **13a–e** (1 mmol) in dry DMF (6 ml) was treated with K_2CO_3 (1.05 mmol) and propyl iodide or propargyl chloride (2 mmol). The reaction mixture was heated at 60–70 °C for 2 h, then stirred overnight at room temperature, diluted with 15 ml of water and extracted with methylene chloride. The combined extracts were washed with water and brine, dried over Na_2SO_4 and evaporated to dryness.

5.1.16.1. 1-Propargyl-7-pivaloyloxymethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]xanthine (14a). Yellow oil (71%). IR (KBr) v: 3450 (OH), 1730, 1690 and 1670 (CO). ^{1}H NMR (DMSO-d_6) δ: 8.29 (s, 1H, H-8), 7.24 (t, 2H, J = 7.75 Hz, H-3′ and H-5′), 6.91 (d, 2H, J = 7.75 Hz, H-2′ and H-6′), 6.85 (t, 1H, J = 7.75 Hz, H-4′), 6.14 (s, 2H, CH_2 pival.), 5.37 (d, 1H, J = 4.90 Hz, OH), 4.59 (m, 2H, N_1-CH_2), 4.48 (m, 1H, CH), 4.20 (m, 1H, NCH_2), 4.10 (m, 2H, OCH_2 and NCH_2), 3.94 (m, 1H, OCH_2), 3.09 (m, 1H, ≡CH), 1.12 (s, 9H, $C(CH_3)_3$). Anal. Calcd for $C_{23}H_{26}N_4O_6$: C, 60.78; H, 5.76; N, 12.33. Found: C, 60.65; H, 5.84; N, 12.22.

5.1.16.2. 1-Propyl-7-pivaloyloxymethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-cyclopentylxanthine (14b). Yellow oil (67%). IR (KBr) v: 3430 (OH), 1730, 1685 and 1660 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.21 (t, 2H, J = 7.70 Hz, H-3′ and H-5′), 6.90 (t, 1H, J = 7.70 Hz, H-4′), 6.74 (d, 2H, J = 7.70 Hz, H-2′ and H-6′), 6.18 (s, 2H, CH_2 pival.), 5.37 (d, 1H, J = 5.45 Hz, OH), 4.29 (m, 1H, CH), 4.12 (m, 2H, NCH_2), 3.92 (m, 2H, OCH_2), 3.79 (t, 2H, J = 7.15 Hz, N_1-CH_2), 3.36 (m, 1H, CH cycl.), 1.91 (m, 2H, CH_2 cycl.), 1.65 (m, 6H, CH_2 cycl.), 1.52 (m, 2H, CH_2 propyl), 1.09 (s, 9H, $C(CH_3)_3$), 0.82 (t, 3H, J = 7.15 Hz, CH_3 propyl). Anal. Calcd for $C_{28}H_{38}N_4O_6$: C, 63.86; H, 7.27; N, 10.64. Found: C, 64.02; H, 7.13; N, 10.73.

5.1.16.3. 1-Propargyl-7-pivaloyloxymethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-(3-methoxystyryl)xanthine (14c). Orange crystals (75%); mp 62 °C. IR (KBr) v: 3430 (OH), 1715, 1660 and 1635 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.67 (d, 1H, J = 15.70 Hz, =CH), 7.48-7.20 (m, 6H, H-2″, H-4″, H-5″, H-6″, H-3′ and H-5′), 6.99–6.84 (m, 4H, =CH, H-2′, H-4′ and H-6′), 6.43 (s, 2H, CH_2 pival.), 5.35 (d, 1H, J = 5.35 Hz, OH), 4.61 (m, 2H, N_1-CH_2), 4.27 (m, 1H, CH), 4.21 (m, 2H, NCH_2), 4.02 (m, 2H, OCH_2), 3.82 (s, 3H, OCH_3), 3.07 (m, 1H, ≡CH), 1.11 (s, 9H, $C(CH_3)_3$). Anal. Calcd for $C_{32}H_{34}N_4O_7$: C, 65.51; H, 5.84; N, 9.55. Found: C, 65.43; H, 5.98; N, 9.67.

5.1.16.4. 1-Propyl-7-pivaloyloxymethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-noradamantylxanthine (14d). Yellow oil (69%). IR (KBr) v: 3410 (OH), 1735, 1700 and 1675 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.22 (t, 2H, J = 7.35 Hz, H-3′ and H-5′), 6.87 (t, 1H, J = 7.35 Hz, H-4′), 6.73 (d, 2H, J = 7.35 Hz, H-2′ and H-6′), 6.12 (s, 2H, CH_2 pival.), 5.36 (sl, 1H, OH), 4.30 (m, 1H, CH), 4.13 (m, 2H, NCH_2), 3.93 (m, 2H, OCH_2), 3.82 (t, 2H, J = 7.20 Hz, CH_2), 2.49 (m, 1H, CH nor.), 2.28 (m, 2H, CH nor.), 1.98 (m, 2H, CH_2 nor.), 1.76 (m, 4H, CH_2 nor.), 1.59 (m, 4H, CH_2 nor.), 1.54 (sext, 2H, J = 7.20 Hz, CH_2), 1.10 (s, 9H, CH_3), 0.85 (t, 3H, J = 7.20 Hz, CH_3). Anal. Calcd for $C_{32}H_{42}N_4O_6$: C, 66.41; H, 7.31; N, 9.68. Found: C, 66.25; H, 7.48; N, 9.82.

5.1.16.5. 1-Propyl-7-pivaloyloxymethyl-3-{1-[2-hydroxy-3-(4-methoxyphenoxy)propyl]}xanthine (14e). Yellow oil (72%). IR (KBr) v: 3440 (OH), 1730, 1680 and 1670 (CO). ^{1}H NMR (DMSO-d_6) δ: 8.23 (s, 1H, H-8), 6.82 (d, 2H, J = 8.45 Hz, H-3′ and H-5′), 6.76 (d, 2H, J = 8.45 Hz, H-2′ and H-6′), 6.14 (s, 2H, CH_2

pival.), 5.31 (d, 1H, J = 5.20 Hz, OH), 4.15 (m, 1H, CH), 4.07-3.76 (m, 6H, CH_2), 3.66 (s, 3H, OCH_3), 1.51 (m, 2H, CH_2), 1.08 (s, 9H, $C(CH_3)_3$), 0.80 (t, 3H, J = 7.25 Hz, CH_3). Anal. Calcd for $C_{24}H_{32}N_4O_7$: C, 59.00; H, 6.60; N, 11.47. Found: C, 58.87; H, 6.52; N, 11.63.

5.1.17. General procedure for 1-alkyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-alkyl- or -arylxanthines (3c–g). To 0.8 mmol of xanthine **14a–e** dissolved in DMSO (5 ml) was added 4 N aqueous solution of NaOH (4 ml). The solution was stirred at 50 °C for 30 min and then stirred at room temperature for 1 h. Slow dilution with water and acidification with 2 N aqueous solution of hydrochloric acid precipitated the 7*H*-xanthine. Extraction with methylene chloride (2× 25 ml), drying of the combined organic phases over Na_2SO_4 and evaporation of the solvent gave an oily residue. Crystallization from diethyl ether gave xanthines **3c–g** as white solids.

5.1.17.1. 1-Propargyl-3-[1-(2-hydroxy-3-phenoxypropyl)]xanthine (3c). White crystals (24%); mp 197 °C. IR (KBr) ν: 3330 (OH), 3240 (NH), 1690 and 1630 (CO). ^{1}H NMR (DMSO-d_6) δ: 13.61 (sl, 1H, N_7-H), 8.05 (s, 1H, H-8), 7.24 (t, 2H, J = 8.00 Hz, H-3′ and H-5′), 6.89 (t, 1H, J = 8.00 Hz, H-4′), 6.85 (d, 2H, J = 8.00 Hz, H-2′ and H-6′), 5.33 (m, 1H, OH), 4.59 (m, 1H, N_1-CH_2), 4.32 (m, 1H, CH), 4.20 (m, 2H, NCH_2), 3.95 (m, 2H, OCH_2), 3.09 (m, 1H, ≡CH). Anal. Calcd for $C_{17}H_{16}N_4O_4$: C, 59.99; H, 4.74; N, 16.46. Found: C, 59.87; H, 4.83; N, 16.32.

5.1.17.2. 1-Propyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-cyclopentylxanthine (3d). White crystals (32%); mp 121 °C. IR (KBr) ν: 3420 (OH), 3250 (NH), 1685 and 1645 (CO). ^{1}H NMR (DMSO-d_6) δ: 13.47 (sl, 1H, N_7-H), 7.21 (t, 2H, J = 7.50 Hz, H-3′ and H-5′), 6.87 (t, 1H, J = 7.50 Hz, H-4′), 6.76 (d, 2H, J = 7.50 Hz, H-2′ and H-6′), 5.49 (m, 1H, OH), 4.27 (m, 1H, CH), 4.12 (m, 2H, NCH_2), 3.92 (m, 2H, OCH_2), 3.80 (t, 2H, J = 7.30 Hz, N_1-CH_2), 3.05 (m, 1H, CH cycl.), 1.89 (m, 2H, CH_2 cycl.), 1.66 (m, 6H, CH_2 cycl.), 1.47 (m, 2H, CH_2 propyl), 0.84 (t, 3H, J = 7.30 Hz, CH_3). Anal. Calcd for $C_{22}H_{28}N_4O_4$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.95; H, 6.92; N, 13.61.

5.1.17.3. 1-Propargyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-(3-methoxystyryl)xanthine (3e). Yellow crystals (20%); mp 148 °C. IR (KBr) ν: 3430 (OH), 3240 (NH), 1660 and 1635 (CO). ^{1}H NMR (DMSO-d_6) δ: 13.48 (sl, 1H, N_7-H), 7.59 (d, 1H, J = 16.40 Hz, =CH), 7.37-7.16 (m, 5H, H-4″, H-5″, H-6″, H-3′ and H-5′), 7.02 (d, 1H, J = 16.40 Hz, =CH), 6.99–6.81 (m, 4 H, H-2″, H-2′, H-4′ and H-6′), 5.31 (m, 1H, OH), 4.63 (m, 2H, N_1-CH_2), 4.40 (m, 1H, CH), 4.29 (m, 1H, NCH_2), 4.19 (m, 1H, NCH_2), 4.02 (m, 2H, OCH_2), 3.82 (s, 3H, OCH_3), 3.07 (m, 1H, ≡CH). Anal. Calcd for $C_{26}H_{24}N_4O_5$: C, 66.09; H, 5.12; N, 11.96. Found: C, 65.87; H, 5.24; N, 12.09.

5.1.17.4. 1-Propyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-noradamantylxanthine (3f). White crystals (11%); mp 220 °C. IR (KBr) ν: 3400 (OH), 3040 (NH), 1695 and 1650 (CO). ^{1}H NMR (DMSO-d_6) δ: 12.91 (s, 1H, N_7-H), 7.19 (t, 2H, J = 7.30 Hz, H-3′ and H-5′), 6.86 (t, 1H, J = 7.30 Hz, H-4′), 6.73 (d, 2H, J = 7.30 Hz, H-2′ and H-6′), 5.31 (sl, 1H, OH), 4.28 (m, 1H, CH), 4.15 (m, 2H, NCH_2), 3.91 (m, 2H, OCH_2), 3.82 (t, 2H, J = 7.10 Hz, NCH_2 prop.), 2.48 (m, 1H, CH nor.), 2.24 (m, 2H, CH nor.), 2.03 (m, 2H, CH_2 nor.), 1.81 (m, 4H, CH_2 nor.), 1.56 (m, 6H, CH_2 nor. and CH_2 prop.), 0.83 (t, 3H, J = 7.10 Hz, CH_3 prop.). ^{13}C NMR (DMSO-d_6) δ: 160.6 (C-8), 159.2 (C-1′), 154.8 (C-6), 151.9 (C-2), 148.7 (C-4), 130.2 (C-3′ and C-5′), 121.3 (C-4′), 115.0 (C-2′ and C-6′), 107.6 (C-5), 71.3 (OCH_2), 66.6 (OCH), 49.7 (C-1″), 49.1 (C-2″), 48.9 (C-2″), 47.2 (NCH_2), 46.0 (C-5″), 44.0 (C-6″), 42.9 (NCH_2 prop.), 37.8 (C-3″), 35.0 (C-4″), 21.7 (CH_2 prop.), 12.2 (CH_3 prop.). Anal. Calcd for $C_{26}H_{32}N_4O_4$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.45; H, 6.73; N, 12.19.

5.1.17.5. 1-Propyl-3-{1-[2-hydroxy-3-(4-methoxyphenoxy)propyl]}xanthine (3g). White crystals (21%); mp 131 °C. IR (KBr) ν: 3350 (OH), 3250 (NH), 1690 and 1630 (CO). ^{1}H NMR (DMSO-d_6) δ: 13.50 (sl, 1H, N_7-H), 8.00 (s, 1H, H-8), 6.81 (d, 2H, J = 9.00 Hz, H-3′ and H-5′), 6.74 (d, 2H, J = 9.00 Hz, H-2′ and H-6′), 5.27 (m, 1H, OH), 4.29 (m, 1H, CH), 4.16–3.81 (m, 6H, CH_2), 3.67 (s, 3H, OCH_3), 1.53 (sext, 2H, J = 7.30 Hz, CH_2 prop.), 0.84 (t, 3H, J = 7.30 Hz, CH_3 prop.). Anal. Calcd for $C_{18}H_{22}N_4O_5$: C, 57.74; H, 5.92; N, 14.97. Found: C, 57.82; H, 5.79; N, 15.08.

5.1.18. General procedure for 1-alkyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-7-methyl-8-alkyl- or -arylxanthines (3h-j). Xanthine **3c–e** (0.6 mmol) was dissolved in 5 ml of DMF, K_2CO_3 (0.9 mmol) and methyl iodide (9.1 mmol) were added, and the mixture was stirred at room temperature for 24 h. The product was precipitated by addition of H_2O, collected by filtration, washed with H_2O and extracted with CH_2Cl_2. The organic layer was then dried over Na_2SO_4 and evaporated to dryness. Crystallization from diethyl ether gave xanthines **3h,j**.

5.1.18.1. 1-Propargyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-7-methylxanthine (3h). White crystals (43%); mp 62 °C. IR (KBr) ν: 3350 (OH), 1700 and 1660 (CO). ^{1}H NMR (DMSO-d_6) δ: 8.00 (s, 1H, H-8), 7.25 (t, 2H, J = 7.60 Hz, H-3′ and H-5′), 6.90 (t, 1H, J = 7.60 Hz, H-4′), 6.82 (d, 2H, J = 7.60 Hz, H-2′ and H-6′), 5.34 (d, 1H, J = 5.40 Hz, OH), 4.57 (m, 1H, N_1-CH_2), 4.32 (m, 1H, CH), 4.24 (m, 1H, NCH_2), 4.12 (m, 2H, NCH_2 and OCH_2), 3.93 (m, 1H, OCH_2), 3.86 (s, 3H, N_7-CH_3), 3.10 (m, 1H, ≡CH). Anal. Calcd for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12; N, 15.81. Found: C, 60.90; H, 5.02; N, 15.93.

5.1.18.2. 1-Propyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-7-methyl-8-cyclopentylxanthine (3i). Yellow crystals (65%); mp 45 °C. IR (KBr) ν: 3430 (OH), 3040 (NH), 1700 and 1670 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.26 (t, 2H, J = 7.70 Hz, H-3′ and H-5′), 6.88 (t, 1H, J = 7.70 Hz, H-4′), 6.73 (d, 2H, J = 7.70 Hz, H-2′ and H-6′), 5.35 (d, 1H, J = 5.45 Hz, OH), 4.25 (m, 1H, CH), 4.10 (m, 2H, NCH_2), 3.90 (m, 2H, OCH_2), 3.80 (t, 2H, J = 7.20 Hz, N_1-CH_2), 3.79 (s, 3H, N_7-CH_3),

3.19 (m, 1H, CH cycl.), 1.90 (m, 2H, CH_2 cycl.), 1.58 (m, 6H, CH_2 cycl.), 1.51 (m, 2H, CH_2 prop.), 0.84 (t, 3H, $J = 7.20$ Hz, CH_3 prop.). Anal. Calcd for $C_{23}H_{30}N_4O_4$: C, 64.77; H, 7.09; N, 13.14. Found: C, 64.50; H, 7.22; N, 13.33.

5.1.18.3. 1-Propargyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-7-methyl-8-(3-methoxystyryl)xanthine (3j). Pale-yellow crystals (76%); mp 76 °C. IR (KBr) *v*: 3440 (OH), 1680 and 1655 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.58 (d, 1H, $J = 15.50$ Hz, =CH), 7.35–7.21 (m, 6H, H-2″, H-4″, H-5″, H-6″, H-3′ and H-5′), 6.97–6.85 (m, 4H, =CH, H-2′, H-4′ and H-6′), 5.35 (d, 1H, $J = 5.40$ Hz, OH), 4.61 (m, 2H, N_1-CH_2), 4.38 (m, 1H, CH), 4.29 (m, 1H, NCH_2), 4.17 (m, 1H, NCH_2), 4.06 (s, 3H, N_7-CH_3), 4.03 (m, 2H, OCH_2), 3.83 (s, 3H, OCH_3), 3.09 (m, 1H, ≡CH). Anal. Calcd for $C_{27}H_{26}N_4O_5$: C, 66.66; H, 5.38; N, 11.52. Found: C, 66.53; H, 5.44; N, 11.63.

5.1.19. 7-Amino-2-phenoxymethyl-5*H*-oxazolo[3,2-*a*]-pyrimidine-5-one (15). To a solution of ethyl 3-amino-ethoxyacrylate (26 mmol) in ethanol (100 ml) was added at room temperature the 2-amino-2-oxazoline **5a**, and the mixture was stirred at reflux for 8 h. After filtration, ethanol was removed by distillation and the mixture was triturated in a minimum of warm ethanol. The resulting precipitate was collected by filtration, washed with ethanol then petroleum ether and dried. White crystals (31%); mp 188 °C. IR (KBr) *v*: 3470–3210 (NH_2), 1680 (CO), 1640 (C=N). ^{1}H NMR (DMSO-d_6) δ: 7.28 (t, 2H, $J = 6.05$ Hz, H-3′ and H-5′), 6.94 (t, 1H, $J = 6.05$ Hz, H-4′), 6.92 (d, 2H, $J = 6.05$ Hz, H-2′ and H-6′), 6.50 (s, 2H, NH_2), 5.26 (m, 1H, H-2), 4.73 (s, 1H, H-6), 4.28 (m, 2H, OCH_2), 4.14 (dd, 1H, $J = 10.70$ and 9.45 Hz, H-3a), 3.85 (dd, 1H, $J = 10.70$ et 6.75 Hz, H-3b). ^{13}C NMR (DMSO-d_6) δ: 165.6 (C-5), 161.0 (C-1′), 159.9 (C-8a), 158.4 (C-7), 130.1 (C-3′ and C-5′), 121.7 (C-4′), 115.1 (C-2′ and C-6′), 78.8 (C-6), 77.0 (OCH_2), 68.4 (C-2), 43.9 (C-3). Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.37; H, 4.92; N, 16.34.

5.1.20. 5-Amino-6-nitroso-2-phenoxymethyl-5*H*-oxazolo[3,2-*a*]pyrimidine-5-one (16). Sodium nitrite (43.5 mmol) in acetic acid (12 ml) was added with stirring to compound **15** (14.5 mmol) in water (100 ml). The reaction mixture was stirred 1 h at room temperature and then heated at 60 °C for 30 min. The precipitate was separated by filtration, washed with water and dried in air to give oxazolopyrimidinone **16**. Blue crystals (96%); mp 229 °C. IR (KBr) *v*: 3470 (NH_2), 1670 (CO). ^{1}H NMR (DMSO-d_6) δ: 11.36 (sl, 1H, NH_2), 9.17 (sl, 1H, NH_2), 7.29 (t, 2H, $J = 7.75$ Hz, H-3′ and H-5′), 6.96 (m, 3H, H-2′, H-4′ and H-6′), 5.48 (m, 1H, CH), 4.38 (m, 2H, OCH_2), 4.34 (m, 1H, NCH_2), 4.08 (dd, 1H, $J = 10.00$, $J = 6.55$ Hz, NCH_2). Anal. Calcd for $C_{13}H_{12}N_4O_4$: C, 54.17; H, 4.19; N, 19.44. Found: C, 54.23; H, 4.01; N, 19.18.

5.1.21. 6-Amino-5-nitroso-3-(2-hydroxy-3-phenoxypropyl)uracil (17). To a solution of sodium (20 mmol) in dry ethanol (100 ml) was added **16** (10 mmol). The resulting solution was refluxed for 5 min. The solvent was then removed in vacuo. The solid residue was solubilized in water and the obtained solution was acidified until pH = 5–6 with a diluted aqueous solution of HCl. The precipitate was collected by filtration, washed with ethanol then petroleum ether and then dried. Orange crystals (71%); mp 245 °C. IR (KBr) *v*: 3380 (NH), 3320 (OH), 3200 (NH_2), 1740 and 1695 (CO). ^{1}H NMR (DMSO-d_6) δ: 11.45 (m, 2H, NH and NH_2), 8.01 (sl, 1H, NH_2), 7.25 (t, 2H, $J = 7.75$ Hz, H-3′ and H-5′), 6.88 (t, 1H, $J = 7.75$ Hz, H-4′), 6.86 (d, 2H, $J = 7.75$ Hz, H-2′ and H-6′), 5.27 (m, 1H, OH), 4.19 (m, 1H, CH), 4.05 (m, 1H, CH_2), 3.94 (m, 3H, CH_2). Anal. Calcd for $C_{13}H_{14}N_4O_5$: C, 50.98; H, 4.61; N, 18.29. Found: C, 50.79; H, 4.72; N, 18.34.

5.1.22. 5,6-Diamino-3-(2-hydroxy-3-phenoxypropyl)-uracil (18). To a suspension of the nitroso compound **17** (5 mmol) in 25 ml of boiling water, sodium dithionite (15 mmol) was added in small portions until the blue colour disappeared. After refluxing for 45 min, the reaction mixture was filtered and cooled at 0 °C. The oily residue which separated was extracted with hot ethanol. The solvent was then evaporated to yield **18** as yellow crystals. Yellow crystals (39%); mp 119 °C. IR (KBr) *v*: 1700 and 1635 (CO). ^{1}H NMR (DMSO-d_6) δ: 10.52 (sl, 1H, NH), 7.24 (t, 2H, $J = 7.65$ Hz, H-3′ and H-5′), 6.90 (t, 1H, $J = 7.65$ Hz, H-4′), 6.83 (d, 2H, $J = 7.65$ Hz, H-2′ and H-6′), 5.65, (sl, 2H, NH_2), 5.16 (d, 1H, $J = 5.40$ Hz, OH), 4.06 (m, 1H, CH), 3.92 (m, 1H, NCH_2), 3.83 (m, 3H, NCH_2 and OCH_2), 3.23 (sl, 2H, NH_2). Anal. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.67; H, 5.43; N, 19.31.

5.1.23. General procedure for 6-amino-5-arylideneamino-3-(2-hydroxy-3-phenoxypropyl)uracils (19a,b). A mixture of arylaldehyde (3.10 mmol), 5,6-diaminouracil **18** (2.7 mmol) and 0.10 ml of acetic acid was refluxed for 4 h in 15 ml of ethanol. Upon cooling of the mixture, the precipitate was filtered and washed with ethanol then diethyl ether to give the imine **19a**,**b** as a pale yellow solid, which was used directly in the next step.

5.1.23.1. 6-Amino-5-benzylideneamino-3-(2-hydroxy-3-phenoxypropyl)uracil (19a). Yellow crystals (41%); mp 162 °C. IR (KBr) *v*: 3345 (NH_2), 1685 and 1625 (CO). ^{1}H NMR (DMSO-d_6) δ: 10.81 (s, 1H, NH), 9.64 (s, 1H, N=CH), 7.85 (d, 2H, $J = 6.85$ Hz, H-2″ and H-6″), 7.35 (m, 3H, H-3″, H-4″ and H-5″), 7.24 (t, 2H, $J = 7.90$ Hz, H-3′ and H-5′), 6.89 (t, 1H, $J = 7.90$ Hz, H-4′), 6.85 (d, 2H, $J = 7.90$ Hz, H-2′ and H-6′), 6.66 (sl, 2H, NH_2), 5.17 (d, 1H, $J = 5.45$ Hz, OH), 4.13 (m, 1H, CH), 3.99 (m, 1H, NCH_2), 3.86 (m, 3H, NCH_2 and OCH_2). ^{13}C NMR (DMSO-d_6) δ: 158.8 (C-4), 158.6 (C-1′), 152.1 (C-6), 149.5 (C-2), 149.1 (N=CH), 139.4 (C-1″), 129.5 (C-3′ and C-5′), 129.1 (C-4″), 128.5 (C-3″ and C-5″), 127.2 (C-2″ and C-6″), 120.5 (C-4′), 114.4 (C-2′ and C-6′), 98.4 (C-5), 70.9 (OCH_2), 66.3 (CH), 42.6 (NCH_2). Anal. Calcd for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.26; H, 5.21; N, 14.88.

5.1.23.2. 6-Amino-5-(4-hydroxybenzylideneamino)-3-(2-hydroxy-3-phenoxypropyl)uracil (19b). Orange crystals (92%); mp 87 °C. IR (KBr) *v*: 1675 and 1630

(CO). ^{1}H NMR (DMSO-d_6) δ: 10.74 (s, 1H, NH), 9.68 (sl, 1H, OH), 9.55 (s, 1H, N=CH), 7.76 (d, 2H, J = 8.45 Hz, H-2″ and H-6″), 7.26 (t, 2H, J = 7.70 Hz, H-3′ and H-5′), 6.93 (m, 3H, H-3″, H-5″ and H-4′), 6.78 (d, 2H, J = 7.70 Hz, H-2′, and H-6′), 6.51 (sl, 2H, NH_2), 5.12 (sl, 1H, OH), 4.14 (m, 1H, CH), 3.98 (m, 1H, NCH_2), 3.90 (m, 3H, NCH_2 and OCH_2). Anal. Calcd for $C_{20}H_{20}N_4O_5$: C, 60.60; H, 5.08; N, 14.13. Found: C, 60.73; H, 5.01; N, 14.18.

5.1.24. 6-Amino-5-cyclopentylcarboxamido-3-(2-hydroxy-3-phenoxypropyl)uracil (20). A suspension of 2.4 mmol of **18** in 12 ml of dry pyridine was cooled to 0 °C, and acid chloride (2.76 mmol) was added dropwise with stirring. The mixture was stirred overnight and then evaporated to dryness. The residue was treated with water, collected by filtration and dried to yield **20**. Yellow crystals (23%); mp 259 °C. IR (KBr) v: 1675, 1660 and 1645 (CO). ^{1}H NMR (DMSO-d_6) δ: 10.42 (s, 1H, N_1-H), 8.28 (s, 1H, CONH), 7.25 (m, 2H, H-3′ and H-5′), 6.87 (m, 3H, H-2′, H-4′ and H-6′), 5.84 (sl, 2H, NH_2), 5.14 (sl, 1H, OH), 4.05 (m, 1H, CH), 3.82 (m, 4H, NCH_2 and OCH_2), 2.73 (m, 1H, CH cycl.), 1.59 (m, 8H, CH_2 cycl.). ^{13}C NMR (DMSO-d_6) δ: 175.9 (CO amide), 161.0 (C-1′), 158.6 (C-6), 150.2 (C-2), 150.0 (C-4), 129.5 (C-3′ and C-5′), 120.5 (C-4′), 114.4 (C-2′ and C-6′), 87.6 (C-5), 70.8 (OCH_2), 66.6 (OCH), 44.0 (NCH_2), 42.9 (CH cycl.), 30.0 (CH_2 cycl.), 25.8 (CH_2 cycl.) Anal. Calcd for $C_{19}H_{24}N_4O_5$: C, 58.75; H, 6.23; N, 14.43. Found: C, 58.92; H, 6.17; N, 14.33.

5.1.25. 1-[1-(2-Hydroxy-3-phenoxypropyl)]xanthine (4a). A solution of **18** (1.7 mmol) in $HC(OEt)_3$ (3 ml) and DMF (five drops) was refluxed for 4 h. The solvent was then removed under reduced pressure. The solid residue was triturated in Et_2O, filtered and the filtrate evaporated to dryness. The solid was triturated in ethanol, collected by filtration, washed with ethanol and dried to give **4a**. Pale-yellow crystals (6%); mp 264 °C. IR (KBr) v: 3350 (OH), 3170 and 3015 (NH), 1680 and 1660 (CO). ^{1}H NMR (DMSO-d_6) δ: 13.35 (sl, 1H, N_7-H), 11.81 (sl, 1H, N_3-H), 7.93 (s, 1H, H-8), 7.23 (t, 2H, J = 7.70 Hz, H-3′ and H-5′), 6.88 (t, 1H, J = 7.70 Hz, H-4′), 6.80 (d, 2H, J = 7.70 Hz, H-2′ and H-6′), 5.18 (d, 1H, J = 5.65 Hz, OH), 4.15 (m, 1H, CH), 4.05 (m, 1H, NCH_2), 3.92 (m, 3H, NCH_2 and OCH_2). ^{13}C NMR (DMSO-d_6) δ: 158.5 (C-1′), 155.3 (C-6), 151.3 (C-2), 147.1 (C-4), 140.6 (C-8), 129.3 (C-3′ and C-5′), 120.4 (C-4′), 114.3 (C-2′ and C-6′), 106.4 (C-5), 70.8 (OCH_2), 66.0 (CH), 43.2 (NCH_2). Anal. Calcd for $C_{14}H_{14}N_4O_4$: C, 55.62; H, 4.67; N, 18.53. Found: C, 55.43; H, 4.71; N, 18.68.

5.1.26. General procedure for 1-[1-(2-hydroxy-3-phenoxypropyl)]-8-phenylxanthines (4b,c). The imine **19a**,**b** (1.2 mmol) was heated in 10 ml of glyme. As the mixture began to reflux, the imine dissolved. Diethylazodicarboxylate (DEAD) (2.4 mmol) was added through the condenser. Within 10 min a white solid was formed. After an additional 45 min, the reaction mixture was filtered, and the precipitate was washed with ethanol and diethyl ether to give **4b**,**c**.

5.1.26.1. 1-[1-(2-Hydroxy-3-phenoxypropyl)]-8-phenylxanthine (4b). Orange (71%); mp 334 °C. IR (KBr) v: 3405 (OH), 3350 and 3030 (NH), 1710 and 1630 (CO). ^{1}H NMR (DMSO-d_6) δ: 13.65 (s, 1H, N_7-H), 11.92 (s, 1H, N_3-H), 8.08 (d, 2H, J = 6.30 Hz, H-2″ and H-6″), 7.49 (t, 1H, =6.30 Hz, H-4″), 7.45 (t, 2H, J = 6.30 Hz, H-3″ and H-5″), 7.22 (t, 2H, J = 7.65 Hz, H-3′ and H-5′), 6.88 (t, 1H, J = 7.65 Hz, H-4′), 6.82 (d, 2H, J = 7.65 Hz, H-2′ and H-6′), 5.22 (d, 1H, J = 5.45 Hz, OH), 4.20 (m, 1H, CH), 4.06 (m, 1H, NCH_2), 3.94 (m, 3H, NCH_2 and OCH_2). ^{13}C NMR (DMSO-d_6) δ: 158.6 (C-1′), 155.2 (C-6), 151.4 (C-2), 149.9 (C-8), 147.8 (C-4), 130.2 (C-1″), 129.4 (C-3′ and C-5′), 129.0 (C-3″ and C-5″), 126.3 (C-2″ and C-6″), 120.3 (C-4″), 120.5 (C-4′), 114.4 (C-2′ and C-6′), 107.8 (C-5), 70.8 (OCH_2), 66.1 (CH), 43.3 (NCH_2). Anal. Calcd for $C_{20}H_{18}N_4O_4$: C, 63.48; H, 4.79; N, 14.81. Found: C, 64.62; H, 4.72; N, 14.88.

5.1.26.2. 1-[1-(2-Hydroxy-3-phenoxypropyl)]-8-(4-hydroxyphenyl)xanthine (4c). Yellow crystals (42%); mp 306 °C. IR (KBr) v: 3410 (OH), 3220 and 3045 (NH), 1690 and 1650 (CO). ^{1}H NMR (DMSO-d_6) δ: 13.27 (sl, 1H, N_7-H), 11.75 (s, 1H, N_3-H), 10.05 (s, 1H, OH ar), 7.93 (d, 2H, J = 7.65 Hz, H-2″ and H-6″), 7.24 (t, 2H, J = 7.00 Hz, H-3′ and H-5′), 6.85 (m, 5H, H-3″, H-5″, H-2′, H-4′ and H-6′), 5.18 (m, 1H, OH), 4.20 (m, 1H, CH), 4.09 (m, 1H, NCH_2), 3.99 (m, 3H, NCH_2 and OCH_2). Anal. Calcd for $C_{20}H_{18}N_4O_5$: C, 60.91; H, 4.60; N, 14.21. Found: C, 60.77; H, 4.73; N, 14.08.

5.1.27. 1-[1-(2-Hydroxy-3-phenoxypropyl)]-8-cyclopentylxanthine (4d). A suspension of **20** (0.6 mmol) in 6 ml of a CH_3ONa solution in methanol (18 mmol of Na) was prepared and refluxed for 10 h. After evaporation of the solvent, the residue was dissolved in water and acidified with diluted hydrochloric acid until pH = 2. The formed precipitate was then filtered, washed with water and ethanol and dried to give **4d**. White crystals (47%); mp 308 °C. IR (KBr) v: 3420 (OH), 3250 and 3015 (NH), 1690 et 1660 (CO). ^{1}H NMR (DMSO-d_6) δ: 12.92 (sl, 1H, N_7-H), 11.70 (sl, 1H, N_3-H), 7.21 (t, 2H, J = 7.65 Hz, H-3′ and H-5′), 6.87 (t, 1H, J = 7.65 Hz, H-4′), 6.78 (d, 2H, J = 7.65 Hz, H-2′ and H-6′), 5.16 (d, 1H, J = 5.55 Hz, OH), 4.15 (m, 1H, CH), 3.98 (m, 1H, NCH_2), 3.91 (m, 3H, NCH_2 and OCH_2), 3.06 (m, 1H, CH cycl.), 1.97 (m, 2H, CH_2 cycl.), 1.65 (m, 6H, CH_2 cycl.). Anal. Calcd for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99; N, 15.13. Found: C, 61.53; H, 6.06; N, 15.28.

5.1.28. General procedure for 3,7-dimethyl-3-[1-(2-hydroxy-3-phenoxypropyl)]-8-phenylxanthines (4e,f). Xanthines **4b**,**c** (0.9 mmol) were dissolved in 6 ml DMF, K_2CO_3 (3 mmol) and methyl iodide (27 mmol) were added and the mixture was heated at 60 °C for 2 h and then allowed at room temperature overnight. The product was precipitated by addition of H_2O collected by filtration, washed with H_2O and extracted with CH_2Cl_2. The organic layer was then dried over Na_2SO_4 and evaporated to dryness to give xanthines **4e**,**f**.

5.1.28.1. 3,7-Dimethyl-1-[1-(2-hydroxy-3-phenoxypropyl)]-8-phenylxanthine (4e). Yellow crystals (52%); mp 157 °C. IR (KBr) *v*: 3430 (OH), 1715 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.78 (m, 2H, H-2″ and H-6″), 7.55 (m, 3H, H-3″, H-4″ and H-5″), 7.22 (t, 2H, J = 7.65 Hz, H-3′ and H-5′), 6.87 (t, 1H, J = 7.65 Hz, H-4′), 6.77 (d, 2H, J = 7.65 Hz, H-2′ and H-6′), 5.22 (d, 1H, J = 5.45 Hz, OH), 4.17 (m, 1H, CH), 4.07 (m, 1H, NCH_2), 3.98 (m, 3H, NCH_2 and OCH_2), 3.92 (s, 3H, N_7-CH_3), 3.41 (s, 3H, N_3-CH_3). Anal. Calcd for $C_{22}H_{22}N_4O_4$: C, 65.01; H, 5.45; N, 13.78. Found: C, 64.93; H, 5.54; N, 13.62.

5.1.28.2. 3,7-Dimethyl-1-[1-(2-hydroxy-3-phenoxypropyl)]-8-(4-methoxyphenyl)xanthine (4f). Yellow crystals (53%); mp 138 °C. IR (KBr) *v*: 3450 (OH), 1685 and 1655 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.75 (d, 2H, J = 8.70 Hz, H-2″ and H-6″), 7.24 (t, 2H, J = 7.70 Hz, H-3′ and H-5′), 7.11 (d, 2F, J = 8.70 Hz, H-3′ and H-5′), 6.90 (t, 1H, J = 7.70 Hz′, H-4′), 6.82 (d, 2H, J = 7.70 Hz, H-2′ and H-6′), 5.18 (d, 1H, J = 5.40 Hz, OH), 4.19 (m, 1H, CH), 4.09 (m, 1H, NCH_2), 3.99 (m, 3H, NCH_2 and OCH_2), 3.93 (s, 3H, N_7-CH_3), 3.85 (s, 3H, OCH_3), 3.43 (s, 3H, N_3-CH_3). ^{13}C NMR (DMSO-d_6) δ: 160.7 (C-4″), 158.5 (C-1′), 154.8 (C-6), 151.3 (C-2), 151.1 (C-8), 147.8 (C-4), 130.7 (C-3″ and C-5″), 129.4 (C-3′ and C-5′), 120.6 (C-4′), 120.5 (C-1″), 114.4 (C-2′ and C-6′), 114.3 (C-2″ and C-6″), 107.7 (C-5), 70.9 (OCH_2), 66.0 (CH), 55.4 (OCH_3), 43.9 (NCH_2), 33.6 (N_7-CH_3), 29.4 (N_3-CH_3). Anal. Calcd for $C_{23}H_{24}N_4O_5$: C, 63.29; H, 5.54; N, 12.84. Found: C, 63.45; H, 5.48; N, 12.93.

5.2. X-ray crystallography

Colourless single crystals were obtained from a chloroform–methanol (80:20) solution of **2c** or **4f**. Diffraction data were collected using an Enraf-Nonius CAD-4 diffractometer. An empirical absorption correction was applied. The data were also corrected for Lorentz and polarization effect. The program PLATON[46,47] was used for analysis and drawing figures. The positions of non-H atoms were easily determined by the program SHELXS86[48] and the positions of the H atoms were deduced from coordinates of the non-H atoms and confirmed by Fourier synthesis. The non-H atoms were refined with anisotropic temperature parameters. H atoms were included for structure factor calculations but not refined. Full crystallographic results have been deposited at the Cambridge Crystallographic Data Centre (CCDC-262106 and CCDC-262107), UK, as supplementary material.[49]

5.3. Adenosine binding assays

Radioligand binding assays were performed as previously described using rat brain cortical membrane preparations for adenosine A_1 receptor assays and rat brain striatal membrane preparations for adenosine A_{2A} receptor assays.[50–54] Frozen rat brains (unstripped) obtained from Pel Freez®, Rogers (Arkansas, USA), were thawed and the striata were dissected. For assays at human adenosine A_3 receptors, Chinese hamster ovary (CHO) cell membranes expressing the human adenosine A_3 receptor were used as described.[50,53,55] [^{3}H]2-Chloro-N^6-cyclopentyladenosine ([^{3}H]CCPA) was used as the A_1 radioligand, [^{3}H]3-(3-hydroxypropyl)-7-methyl-8-(*m*-methoxystyryl)-1-propargylxanthine ([^{3}H]MSX-2) as the A_{2A} ligand[41] and [^{3}H]2-phenyl-8-ethyl-4-methyl-(8*R*)-4,5,7,8-tetrahydro-1*H*-imidazo[2,1-*i*]purine-5-one ([^{3}H]PSB-11) as the adenosine A_3 receptor radioligand.[43,44] Initially, a single high concentration of compound (10 μM at A_1, A_{2A} and A_3 receptors) was tested in three (A_1 and A_{2A}) or two (A_3) independent experiments. For potent compounds, which showed greater than 50% inhibition of radioligand binding at the test concentration, curves were determined at the adenosine A_1 and A_{2A} receptors using 6–7 different concentrations of test compounds spanning 3 orders of magnitude. At least three separate experiments were performed each in triplicate. Data were analyzed using GraphPad Prism™, version 3.0 (GraphPad, San Diego, CA, USA). For non-linear regression analysis, the Cheng–Prusoff equation and K_D values of 0.5 nM (rat A_1) and 0.61 nM (human A_1) for [^{3}H]CCPA, 8.0 nM (rat A_{2A}) and 7.3 nM (human A_{2A}) for [^{3}H]MSX-2 and 4.9 nM for [^{3}H]PSB-11 were used to calculate K_i values from IC_{50} values.

Acknowledgments

D.C.G.B., S.L. and C.E.M. were supported by the Deutsche Forschungsgemeinschaft (GRK677). We thank Sonja Hinz for expert technical assistance.

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