Synthesis of Paraxanthine Analogs (1,7-Disubstituted Xanthines) and Other Xanthines Unsubstituted at the 3-Position: Structure–Activity Relationships at Adenosine Receptors

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Synthetic procedures for the preparation of various 3-unsubstituted xanthines, including paraxanthine analogs (1,7-disubstituted xanthines) and 1,8-disubstituted xanthines, were developed. Silylation of 1-substituted xanthines followed by alkylation at the 7-position provides a facile route to paraxanthine analogs. Regioselective alkylation of tris(trimethylsilyl)-6-aminouracil provides 3-substituted 6-aminouracils, which are converted to 1,8-disubstituted xanthines by standard procedures. The ring closure of 3-substituted 5-cyclopentanecarboxamido- and 5-(benzoylamino)-6-aminouracils requires drastic reaction conditions. Affinity for brain A1 and A2 adenosine receptors was determined in binding assays for these and other xanthines with substituents in 1-, 3-, 7-, 8-, and 9-positions. Substitution at the 1-position was necessary for high affinity at adenosine receptors. 1,3-Disubstituted xanthines generally had higher affinity than 1,7-disubstituted xanthines. 1,8-Disubstituted xanthines had high affinity for adenosine receptors; some were highly selective for A1 receptors.

Introduction

The development of potent and selective adenosine receptor ligands as pharmacological tools and as potential drugs[1,2] has been an active area of research. Potent and selective agonists have been developed for the two major subclasses of adenosine receptors, A1 and A2a (generally referred to as "A2") adenosine receptors (ARs). All AR agonists are derivatives of the physiological receptor ligand, adenosine. The most important class of AR antagonists are the xanthines.[3] Numerous xanthine derivatives, mainly 1,3-disubstituted (theophylline analogs), 1,3,7-trisubstituted (caffeine analogs), and 1,3,8-trisubstituted (8-phenyltheophylline analogs), have been synthesized and investigated in terms of affinity for A1 and A2 receptors and A1/A2AR selectivity. Potent xanthines as well as other heterocyclic AR antagonists[4–12] have been developed that are either nonselective for A1/A2 ARs or selective for the A1AR subtype. Only a few A2 selective AR antagonists are known, most of which are limited by low affinity, low selectivity, and/or unfavorable pharmacokinetic properties, including low water solubility. Only recently, some 8-(methoxystyryl)xanthine derivatives were reported to be potent and selective for the A2AR,[13] but further studies on selectivity in different systems is warranted. Certain 8-substituted caffeine derivatives were previously found to be selective in some but not all comparisons at A1 and A2ARs.[14]

Substitution in the 1-position of xanthines has appeared to be important for activity of xanthines at both receptor subtypes, with 1-propyl substitution being optimal for A1AR affinity, and 1-methyl, 1-propyl, or 1-propargyl substitution being favorable for A2AR affinity.[15] The significance of substituents in the 3-position of xanthines has been less clear. Small alkyl groups (methyl and propyl) or larger groups, such as isobutyl or 2-phenethyl, are tolerated, and large groups appear to favor A1 selectivity.[16,17] A recent study has compared the effects of methyl versus propyl substitution on N1 and N3 of 8-substituted xanthines, and it was found that a 3-propyl substituent was more important for A2AR affinity than for A1AR affinity of those compounds.[18]

Substituents, such as phenyl and cycloalkyl in the 8-position, enhance activity of 1,3-disubstituted xanthines at adenosine receptors to a great extent leading to potent, unselective, or A1 selective compounds.[19] Introduction of the *p*-sulfophenyl moiety in that position has led to relatively unselective compounds that are charged at physiologic pH and therefore do not penetrate the blood brain barrier or cell membranes.[20] Substitution in the 7-position is generally unfavorable for binding of xanthines to adenosine receptors. Substitution by a methyl group, however, appears to be better tolerated by A2 than by A2ARs and thus may contribute to the A2 selectivity of some xanthines, such as 3,7-dimethyl-1-propargylxanthine (DMPX) and 8-substituted caffeine derivatives.[14,15] 9-Substitution drastically reduces AR affinity.[17,21]

Although many xanthines with substitution variations in the 1-, 3-, 7-, and 8-position have been synthesized, only a few xanthines with no substituent in the 3-position were included in the studies.[14,22,23] This appears to be due to the lack of convenient synthetic procedures for this class of xanthines.

The present study focused on the development of appropriate syntheses for a broad range of 3-unsubstituted xanthines, an evaluation of their affinity for A1 and A2ARs, and a comparison with analogous xanthines in order to gain more insight into the structure–activity relationships of xanthines at adenosine receptors.

Chemistry

Monosubstituted Xanthines. The monomethylated xanthines were obtained from commercial sources. The synthesis of the 1-monosubstituted xanthines from 3-substituted 6-aminouracils[24] has been described elsewhere.[25]

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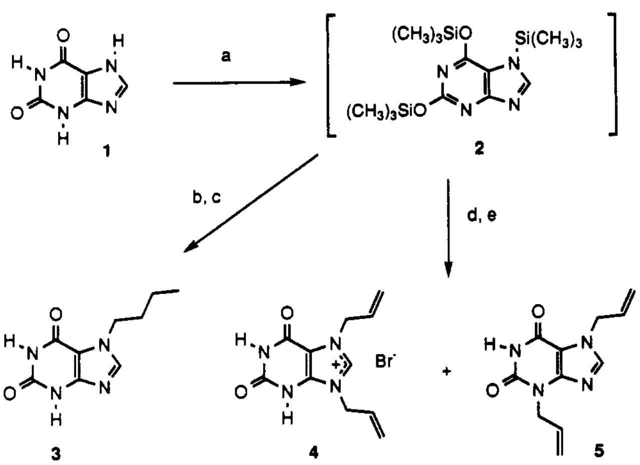
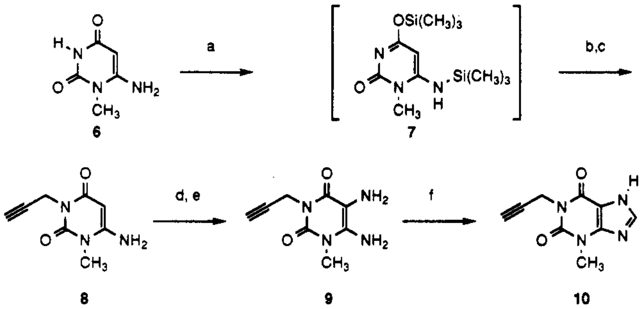
Scheme I[a]



[a] (a) HMDS, $(NH_4)_2SO_4$; (b) $CH_3CH_2CH_2CH_2I$; (c) MeOH; (d) $CH_2{=}CHCH_2Br$; (e) H_2O.

Scheme II[a]



[a] (a) HMDS, $(NH_4)_2SO_4$; (b) $HC{\equiv}CCH_2Br$, I_2; (c) $NaHCO_3$ (aqueous); (d) $NaNO_2$, HOAc; (e) $Na_2S_2O_4$, NH_4OH; (f) $HC(OEt)_3$.

The 3-monosubstituted xanthines were commercially available as were the 7-monosubstituted xanthines with the exception of 7-*n*-butylxanthine.

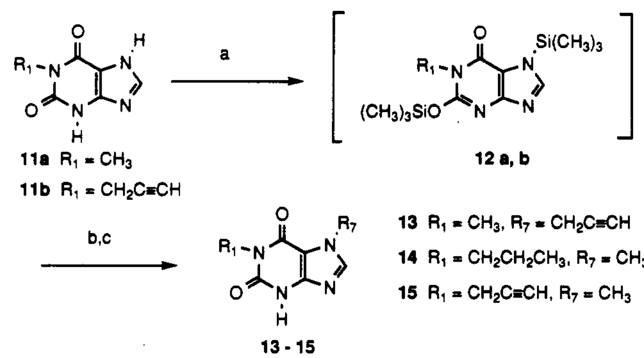
7-*n*-Butylxanthine 3 was prepared according to the procedure of Birkhofer *et al.*[26] for 7-methylxanthine by reaction of tris(trimethylsilyl)xanthine with butyl iodide (see Scheme I).

Disubstituted Xanthines. The dimethylxanthines were obtained from commercial sources. 1,3-Disubstituted xanthines were prepared by standard procedures[27] as previously described,[15,28] with the exception of 3-methyl-1-propargylxanthine 10.

3-Methyl-1-propargylxanthine 10 was prepared as outlined in Scheme II. The alkylation of 1-methyl-6-aminouracil (8) by propargyl bromide under basic conditions failed to afford the desired 1-methyl-3-propargyl-6-aminouracil, due to the high reactivity of the propargyluracil under these conditions. Therefore, 1-methyl-6-aminouracil 6[29] was silylated with hexamethyldisilazane (HMDS). Subsequent reaction with propargyl bromide, catalyzed by iodine, yielded 1-methyl-3-propargyl-6-aminouracil, 8, which was used to prepare the desired xanthine by the standard Traube procedure.

1,7-Disubstituted Xanthines. Several approaches toward the preparation of paraxanthine or its analogs have been undertaken by different groups.[30-36] No general convenient procedure has been reported so far, and few 1,7-disubstituted xanthines have been described. Some of the published syntheses result in very low yields; others use protection strategies that circumscribe the scope of xanthine substitution. Thus, the use of a benzyl group as a protecting group[34,35] necessitates removal by catalytic hydrogenation and precludes the preparation of paraxanthine analogs with unsaturated substituents, such as propargyl derivatives. Our approach was as follows: The starting compounds were 1-monosubstituted xanthines, for which we recently developed a convenient synthetic procedure.[25] Silylation and subsequent alkylation of the xanthines led to 1,7-disubstituted xanthines in good yields (see Scheme III). This new approach to the preparation of 1,7-disubstituted xanthines is based on the procedure of Birkhofer *et al.* for the preparation of 7-methylxanthine.[26] The synthesis, however, appears to be limited to certain 7-substituents. Alkylation with allyl bromide, for example, yielded predominantly the 7,9-diallylxanthinium derivatives.

Scheme III[a]



[a] (a) HMDS, $(NH_4)_2SO_4$; (b) R_7–X; X = Br, I; (c) $NaHCO_3$ (aqueous) or MeOH.

The structures of xanthines 13–15 were confirmed by ^1H and ^{13}C NMR spectroscopy. In the ^1H NMR spectra, the chemical shifts for the methyl protons allow the assignment of the position of the methyl group.[35,37] The sequence is as follows: N1–CH_3 (ca. 3.2 ppm), N3–CH_3 (ca. 3.5 ppm), and N7–CH_3 (ca. 3.8 ppm) (see Table I). Xanthines 14 and 15, obtained by methylation of 1-substituted xanthines, were clearly assigned as 1,7-disubstituted compounds (see Table I). The shifts for the N–H protons also allow assignments between regioisomers to be made, since N1–H is at higher field compared to N3–H, while N7–H appears at the lowest field (ca. 13–14 ppm).

The ^{13}C chemical shifts for the methyl carbons also can be used for assignment (see Table II). The same sequence of the shifts for the N1-, N3-, and N7-methyl carbons are observed as for the hydrogen shifts: N1–CH_3 (ca. 27 ppm), N3–CH_3 (ca. 29–30 ppm), and N7–CH_3 (ca. 33 ppm).

If no methyl groups are present, ^{13}C NMR spectroscopy is a convenient method to distinguish between regioisomers. The shifts for C-8 are most sensitive to substitution at the neighboring N7 nitrogen; in case of N7-substitution, the resonance for C8 is shifted ca. 2 ppm downfield (see Table II).

3,7-Diallylxanthine 5. Because of the high reactivity of allyl bromide, disubstituted products were obtained when silylated xanthine was alkylated in a reaction which with butyl iodide provided mainly 7-butylxanthine (Scheme III). The main product was 7,9-diallylxanthinium bromide (4), although 3,7-diallylxanthine was isolated as a byproduct in ca. 20% yield (see Scheme I).

8-Substituted Xanthines. 8-Phenylxanthine 71 was synthesized as described.[38]

3,8-Disubstituted Xanthines. These xanthines were synthesized according to standard procedures as described.[14,39]

Table I. Selected ^{1}H NMR Spectral Data of 8-Unsubstituted Xanthines

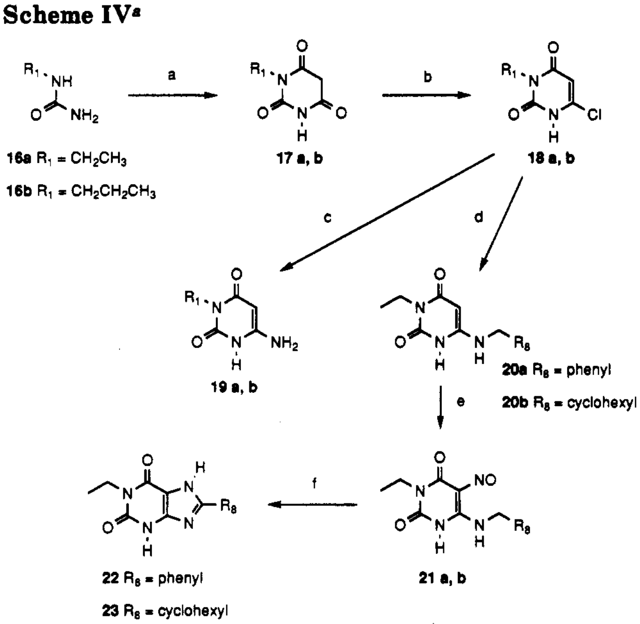
	chemical shifts (δ) in DMSO-d_6 (ppm)				
xanthine (X)	N1–CH$_3$	N3–CH$_3$	N7–CH$_3$	N–H[a]	C8–H
1-methylX	3.18			12.42 (N3–H)	7.95
3-methylX		3.37		11.10 (N1–H)	8.01
7-methylX			3.82	10.85 (N1–H) 11.50 (N3–H)	7.88
9-methylX			[3.60][b]	10.74 (N1–H) 11.92 (N3–H)	7.61
1,3-dimethylX	3.22	3.42		13.5 (N7–H)	8.01
1,7-dimethylX	3.15		3.84	11.82 (N3–H)	7.90
3,7-dimethylX		3.33	3.84	11.10 (N1–H)	7.97
1,3,7-trimethylX	3.18	3.37	3.85		7.98
1-methyl-3-propylX	3.23			13.54 (N7–H)	8.01
1-methyl-7-propargylX	3.18			11.92 (N3–H)	8.07
3-methyl-1-propargylX		3.46			8.07
7-methyl-1-propylX			3.83	11.74 (N3–H)	7.87
7-methyl-1-propargylX			3.84	11.97 (N3–H)	7.92
7-*n*-butylX				10.84 (N1–H) 11.53 (N3–H)	7.96
3,7-diallylX				11.19 (N1–H)	8.08

[a] N7–H appears as a very broad signal and, therefore, could not be seen in some spectra. [b] N9–CH$_3$.

Table II. Selected ^{13}C NMR Data of 8-Unsubstituted Xanthines

	chemical shifts (δ) in DMSO-d_6 (ppm)							
xanthine (X)	N1–CH$_3$	N3–CH$_3$	N7–CH$_3$	C2	C4	C5	C6	C8
1-methylX	27.0			151.2	147.0	106.4	155.2	140.6
3-methylX		28.8		151.2	149.4	106.9	154.7	140.5
1,3-dimethylX	27.7	29.7		151.2	147.8	106.4	154.4	140.5
1,7-dimethylX	26.7		32.9	151.1	147.4	106.5	155.3	143.0
1,3,7-trimethylX	27.5	29.3	33.1	151.0	148.1	106.6	154.5	142.8
1-methyl-3-propylX	27.5			150.7	147.5	106.2	154.3	140.4
1-methyl-7-propargylX	26.8			151.0	147.4	106.2	155.0	142.8
3-methyl-1-propargylX		30.1		150.4	148.8	106.4	153.4	141.1
7-methyl-1-propylX			32.9	150.9	147.4	106.5	155.2	143.0
7-methyl-1-propargylX			32.9	150.2	147.6	106.3	154.2	143.4
3,7-diallylX				150.5	149.4	106.4	154.6	142.3

Scheme IV[a]



[a] (a) Malonic acid, Ac$_2$O; (b) H$_2$O, POCl$_3$; (c) 12% NH$_4$OH, 180 °C; (D) R$_8$CH$_2$NH$_2$; (e) NaNO$_2$, HCl; (f) xylene, reflux.

1,8-Disubstituted Xanthines. The synthesis of 1-methyl-8-phenylxanthine and 8-phenyl-1-propylxanthine has been described.[14] 1-Ethyl-8-phenylxanthine (**22**) and 8-cyclohexyl-1-ethylxanthine (**23**) were synthesized in analogy to the described procedures with minor modifications (see Scheme IV).

All other 1,8-disubstituted xanthines were prepared from appropriately substituted 6-aminouracils. The 3-substituted 6-aminouracils **19a–c** were obtained by treating 3-substituted 6-chlorouracils **18a–c** with aqueous ammonia at high temperatures in a pressure tube (see Scheme IV). The overall yields for 3-substituted 6-aminouracils starting from monosubstituted ureas and malonic acid were moderate to low.

We also developed an alternative, convenient method for the general synthesis of 3-substituted 6-aminouracils **19** by regioselective alkylation of tris(trimethylsilyl)-6-aminouracil **25**,[24] as shown in Scheme V. The 3-substituted 6-aminouracils were converted to the corresponding 5,6-diaminouracils as described.[25]

1-Substituted 8-phenylxanthine derivatives were obtained by reaction of the diaminouracils with benzaldehyde and subsequent oxidative ring closure.

For the preparation of 8-cyclopentyl- and 8-(*p*-sulfophenyl)xanthines, diaminouracils were reacted with cyclopentane carboxylic acid, or *p*-sulfobenzoic acid, respectively, by means of a water-soluble carbodiimide, to yield the 5-cyclopentanecarboxamidouracils (**29b,e**) and the 5-(*p*-sulfobenzoylamino)uracil (**30**) in excellent yields.

In prior preparations of xanthines that bear a substituent at the 3-position, the ring closure to the xanthines was usually performed in aqueous or alcoholic sodium hydroxide solution under mild conditions.[19,20] Aminouracils without a 1-substituent, however, need much more drastic conditions to undergo ring closure to the desired 3-unsubstituted xanthines.[25,34] 8-Cyclopentyl-1-propylxanthine (**34**) could be obtained in low yield by refluxing of **29b** in 20% solution of NaOH in water or ethanol for 20 h. There was no reaction with lower concentrations.

Table III. Adenosine Receptor Affinities of Monosubstituted Xanthines

xanthine (X)	$K_i{}^a$ (μM) A$_1$ receptors vs [^{3}H]*R*-PIA rat cortex	A$_2$ receptors vs [^{3}H]NECA rat striatum
	1-Substituted	
39 1-methylX	36 ± 8	47 ± 6
40 1-propylX	13 ± 3	33 ± 7
41 1-butylX	9.0 ± 0.1	61 ± 4
42 1-allylX	9.2 ± 0.6	10 ± 3
43 1-propargylX	20 ± 1	26 ± 3
44 1-cyclopentylX	11 ± 0	13 ± 3
45 1-benzylX	2.8 ± 1.1	22 ± 4
46 1-*m*-chlorobenzylX	4.9 ± 1.1	26 ± 7
47 1-(2-phenylethyl)X	12 ± 2	0% (20 μM)^b
	3-Substituted	
48 3-methylX	24% (100 μM)	59 ± 7
49 3-propylX	32 ± 2	137 ± 7
50 3-isopropylX	34% (100 μM)	53 ± 8
	7-Substituted	
51 7-methylX	33 ± 5	59 ± 2
52 7-propylX	18 ± 6	40% (200 μM)
3 7-butylX	27 ± 3	66 ± 6
	9-Substituted	
53 9-methylX	1% (250 μM)	18% (250 μM)
54 9-propylX	42% (250 μM)	15% (250 μM)

^{a} In some cases the percent inhibition at the highest tested concentration is given. ^{b} Insoluble at higher concentrations.

Table IV. Adenosine Receptor Affinities of Disubstituted Xanthines

xanthine (X)	$K_i{}^a$ (μM) A$_1$ receptors vs [^{3}H]*R*-PIA rat cortex	A$_2$ receptors vs [^{3}H]NECA rat striatum
	1,3-Disubstituted	
55 1,3-dimethylX	14 ± 3	22 ± 3
56 1-methyl-3-propylX	6.3 ± 1.4	19 ± 1
57 3-isopropyl-1-methylX	12 ± 4	16 ± 1
58 3-isobutyl-1-methylX	7 ± 2	16 ± 1
59 1-ethyl-3-methylX	15 ± 4	23 ± 3
60 3-methyl-1-propylX	5.7 ± 0.7	37 ± 6
10 3-methyl-1-propargylX	0.82 ± 0.09	4.8 ± 1.7
61 1,3-diethylX	3.7 ± 0.2	31 ± 7
62 1,3-dipropylX	0.7 ± 0.3	6.6 ± 0.5
63 1,3-diallylX	10 ± 2	20 ± 1
64 1,3-diisobutylX	4 ± 2	15 ± 4
65 3-isobutyl-1-isoamylX	13 ± 5	11 ± 1
	1,7-Disubstituted	
66 1,7-dimethylX	21 ± 2	32 ± 3
13 1-methyl-7-propargylX	9.9 ± 1.9	14 ± 1
14 7-methyl-1-propylX	21 ± 3	29 ± 6
15 7-methyl-1-propargylX	22 ± 3	16 ± 4
	3,7-Disubstituted	
67 3,7-dimethylX	105 ± 6	40% (250 μM)
5 3,7-diallylX	36 ± 2	36 ± 3
	1,9-Disubstituted	
68 1,9-dimethylX	11% (200 μM)	14% (200 μM)
	3,9-Disubstituted	
69 3,9-dimethylX	42% (250 μM)	11% (200 μM)
	7,9-Disubstituted	
70 7,9-dimethylX	5% (250 μM)	6% (200 μM)

^{a} In some cases the percent inhibition at the highest tested concentration is given.

Subsequently, a wide range of condensing reagents was investigated. Finally, 30% solution of sodium methoxide in methanol was found to be optimal for the preparation of **34**, affording high yields within a short reaction time. However, when the same conditions were applied to the ring closure of the propargyl derivative **29e**, ring closure occurred, but in addition there was hydration of the triple bond, and 8-cyclopentyl-1-(2-oxopropyl)xanthine (**36**) was obtained in excellent yield. The desired 8-cycloalkyl-1-propargylxanthine could be obtained by a different route. Reaction of 3-propargyl-5,6-diaminouracil (**26e**) with a large excess of cyclohexanecarboxaldehyde and subsequent oxidative ring closure led to the desired 8-cyclohexyl-1-propargylxanthine **35**.

Ring closure of the (*p*-sulfobenzoyl)aminouracil derivative **30b** could neither be achieved in sodium hydroxide nor in sodium methoxide solution. Finally, it was found that 1-propyl-8-(*p*-sulfophenyl)xanthine (**37**) could be obtained in good yield by heating **30b** with polyphosphoric acid trimethylsilyl ester, a mild, acidic condensing agent.[40]

1,3,7,8-Substituted Xanthines. 3,7-Dimethyl-8-phenyl-1-propargylxanthine (**38**) was obtained in excellent yield by methylation of 8-phenyl-1-propargylxanthine **31** with excess methyl iodide (see Scheme V).

Table V. Adenosine Receptor Affinities of 8-Substituted Xanthines

xanthine (X)	$K_i{}^a$ (μM) A$_1$ receptors vs [^{3}H]*R*-PIA rat cortex	A$_2$ receptors vs [^{3}H]NECA rat striatum
	8-Monosubstituted	
71 8-PhenylX	2.5 ± 0.1	21 ± 0.6
	1,8-Disubstituted	
72 1-methyl-8-phenylX	0.26 ± 0.01	2.2 ± 0.2
22 1-ethyl-8-phenylX	0.15 ± 0.03	1.8 ± 0.3
73 1-propyl-8-phenylX	0.067 ± 0.02	1.9 ± 0.15
31 1-propargyl-8-phenylX	0.21 ± 0.07	0.73 ± 0.30
32 1-(*m*-chlorobenzyl)-8-phenylX	0.068 ± 0.018	32% (1 μM)^b
33 1-(2-phenethyl)-8-phenylX	0.19 ± 0.04	0% (1 μM)^b
23 1-ethyl-8-cyclohexylX	0.076 ± 0.010	2.3 ± 0.4
34 1-propyl-8-cyclopentylX	0.014 ± 0.003	0.58 ± 0.18
35 1-propargyl-8-cyclohexylX	0.17 ± 0.04	1.7 ± 0.13
36 1-(2-oxopropyl)-8-cyclopentylX	2.5 ± 0.3	9.7 ± 2.3
37 1-propyl-8-*p*-sulfophenylX	2.2 ± 0.3	24 ± 5
	3,8-Disubstituted	
74 3-methyl-8-phenylX	3.4 ± 0.2	17% (250 μM)
75 3-propyl-8-phenylX	9.8 ± 1.8	61 ± 9
76 3-propyl-8-cyclohexylX	0.85 ± 0.51	24 ± 1
77 3-methyl-8-*p*-sulfophenylX	5% (250 μM)	16% (250 μM)
78 3-propyl-8-*p*-sulfophenylX	40% (250 μM)	44% (250 μM)
	1,3-8-Trisubstituted	
79 1-allyl-3-methyl-8-phenylX	0.10 ± 0.00	2.1 ± 0.14
	1,3,7,8-Tetrasubstituted	
38 1-propargyl-3,7-dimethyl-8-phenylX	6.1 ± 0.5	6.4 ± 0.5

^{a} In some cases the percent inhibition at the highest tested concentration is given. ^{b} Insoluble at higher concentrations.

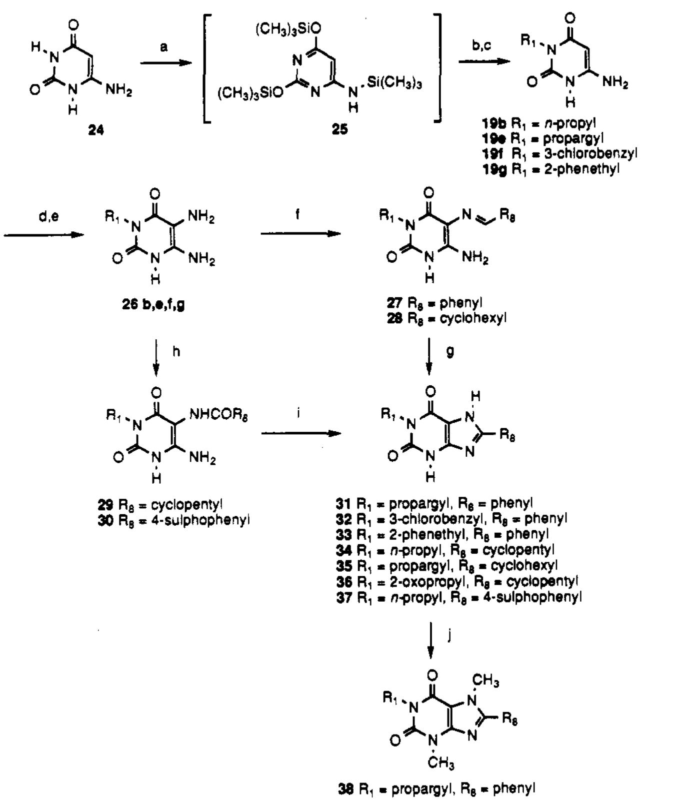
Biological Evaluation

The xanthines were tested in radioligand binding assays for affinity at A1 and A2a adenosine receptors in rat brain cortical membranes and rat striatal membranes, respectively. [^{3}H]N^6-*R*-Phenylisopropyladenosine (*R*-PIA) was used as the A1 ligand and [^{3}H]-5′-*N*-ethylcarboxamidoadenosine (NECA) as the A2a ligand in the presence of 50 nM N^6-cyclopentyladenosine, the latter to block A1 receptors present in the striatal tissue.

Results and Discussion

Monosubstituted Xanthines. A series of 1-monosubstituted xanthines has been evaluated in binding studies at A1 and A2 adenosine receptors and compared to 3-, 7-, and 9-monosubstituted xanthines.

Scheme V[a]



[a] (a) HMDS, $(NH_4)_2SO_4$; (b) R_1X, I_2; (C) $NaHCO_3$ (aqueous) (d) $NaNO_2$, H^+; (e) $Na_2S_2O_4$, NH_4OH; (f) R_8CHO; (g) $FeCl_3$; (h) R_8COOH, EDC; (i) $NaOCH_3$ or PPSE; (j) CH_3I, K_2CO_3.

The 1-monosubstituted xanthines were more potent at both receptor subtypes compared to any other monosubstituted xanthines. All of the 1-substituted compounds were either nonselective or selective for the A1AR. Different substituents, ranging from small alkyl, to propargyl, and to benzyl residues had little effect on the affinity of the compounds for the A2AR. 1-Methyl- and 1-propylxanthine were about equipotent at the A2AR. 1-Allyl- and 1-cyclopentylxanthine were the most potent at the A2 receptor subtype, being about 3-fold more potent than 1-propyl- or 1-methylxanthine. Large substituents, such as benzyl and *m*-chlorobenzyl, were well tolerated by both receptors. A 2-phenethyl substituent in the 1-position, however, was less favorable, particularly for binding to the A2AR. At the A1 receptor, 1-benzylxanthine **45** was the most potent compound of the entire series of monosubstituted xanthines, with a K_i value of 2.8 μM and 8-fold A1 selectivity.

The 3-monosubstituted xanthines had relatively low affinity for ARs. The 3-methyl- (**48**) and the 3-isopropyl derivative (**50**) were somewhat A2-selective. The 3-propylxanthine **49** (enprofylline) was about 4-fold A1-selective. It was slightly more potent than caffeine at the A1AR.

7-Monosubstituted compounds **3**, **51**, and **52** showed moderate affinity for the A1AR, with 7-methyl-, 7-propyl-, and 7-butylxanthine being somewhat more potent than caffeine. 7-Methyl- and 7-butylxanthine were about 2-fold A1 selective, while 7-propylxanthine, the most potent compound in the series at A1ARs, showed >10-fold A1 selectivity.

9-Substituted compounds **53** and **54** exhibited the lowest affinity for adenosine receptors being virtually inactive.

Disubstituted Xanthines. The most potent disubstituted xanthines were the 1,3-disubstituted analogs of theophylline, particularly at the A1 adenosine receptor. Some 1,3-disubstituted xanthines exhibited 10-fold selectivity for that receptor subtype. The replacement of a methyl group in theophylline with propyl enhanced (about 2-fold) binding to A1 receptors, while A2 receptor affinity was either unaltered (3-propyl, **56**) or decreased (1-propyl, **60**, 3-fold). The replacement of 1-methyl with ethyl had no effect on activity, while replacement with propargyl (in **10**) increased A1 affinity 17-fold and A2 affinity 5-fold, resulting in one of the most potent A1AR antagonists with a K_i value of 0.82 μM. It was also the most potent A2AR antagonists in the present series of 8-unsubstituted xanthines. Unlike the structurally related 3,7-dimethyl-1-propargylxanthine, which is somewhat A2 selective,[15,28,41] compound **10** is somewhat A1 selective and may prove a useful research tool.

Several compounds with identical substituents in the 1- and 3-position were investigated (**61–64**). Affinity for A1ARs was increased by replacing the methyl groups in theophylline by larger substituents from ethyl to propyl and to isobutyl. Substitution of the methyl groups by allyl did not alter A1AR affinity. At the A2 receptor, the effect of replacement of methyl groups in theophylline was less pronounced.

1,7-Disubstituted xanthines are analogs of paraxanthine **67** (1,7-dimethylxanthine), which is a major metabolite of caffeine in humans.[42] Paraxanthine itself is slightly more potent than 1-methylxanthine at A1 and A2 adenosine receptors. It is somewhat weaker than 1,3-dimethylxanthine (theophylline). 7-Methyl-1-propylxanthine (**14**) is weaker than 1-propylxanthine (**40**) at A1ARs and about equipotent with **40** at A2ARs. The 7-methyl-1-propargylxanthine **15** is equipotent at A1ARs and somewhat more potent at A2ARs compared to 1-propargylxanthine **43**. 1-Methyl-7-propargylxanthine **13** is relatively active at both receptors, being somewhat more potent than theophylline.

The 3,7-disubstituted xanthines had relatively low affinities for ARs, again indicating the importance of a 1-substituent. 3,7-Dimethylxanthine **67** (theobromine) is a much weaker A1 and A2AR antagonist compared to 1,3-dimethylxanthine **66** (theophylline). 3,7-Diallylxanthine **5** also showed lower affinity for the receptors compared to 1,3-diallylxanthine.

Among the disubstituted xanthines, 9-substitution also nearly abolished activity in ARs. 1,9-, 3,9-, and 7,9-dimethylxanthine (**68**, **69**, and **70**) showed very low affinity with K_i values well above 200 μM.

8-Substituted Xanthines. Phenyl, cyclopentyl, or cyclohexyl and *p*-sulfophenyl substituents in the 8-position were combined with various 1-, 3-, and/or 7-substituents.

The 1,8-disubstituted xanthines were much more potent at A1 and A2ARs compared to the 3,8-disubstituted xanthines, emphasizing again the crucial role of 1-substitution for affinity of the compounds at both receptors. All of the investigated compounds were either nonselective or selective, in some cases highly selective, for the A1AR.

Introduction of a 1-methyl group to 8-phenylxanthine (**71**) resulted in a 10-fold increase in affinity at A1- and A2ARs (compound **72**). Replacement of 1-methyl by an ethyl or propyl group had virtually no effect of A2AR affinity but increased A1AR affinity. 8-Phenyl-1-propylxanthine **73** was one of the most potent A1AR antagonists among the 8-phenyl substituted compounds in this series

(K_i = 0.067 μM) and was 28-fold A1-selective. The 1-(*m*-chlorobenzyl) derivative **32** was also very potent. The replacement of the 1-methyl substituent with 1-propargyl- or 1-(2-phenethyl) substituents did not alter A1AR affinity compared to the 1-methyl-8-phenylxanthine. The phenethyl substituent, however, was much less tolerated by the A2AR. In the 8-phenyl series, the compound with the highest affinity for A2ARs was the 8-phenyl-1-propargylxanthine **31** (K_i value of 0.73 μM), which was about 3-fold A1-selective.

1-Monosubstituted 8-cyclohexyl and 8-cyclopentylxanthines were more potent at the A1AR compared to 8-phenyl derivatives and exhibited somewhat greater A1-selectivity. This is also true for comparisons of 8-phenyl and 8-cycloalkyl-1,3-dimethyl- and 1,3-dipropylxanthines. The polar 1-(2-oxopropyl) substituent in **36** was not well tolerated by both receptor subtypes. This was also true for 1-(2-oxopropyl) substituted caffeine analogs.[28]

3,8-Disubstituted xanthines were considerably less potent compared to the 1,8-disubstituted isomers at both A1 and A2ARs. Compared with 1,3-unsubstituted 8-phenylxanthine (**71**), 3-methyl substitution reduced affinity slightly at the A1AR, but considerably (>10-fold) at the A2AR (compound **74**). Replacement of the 3-methyl substituent by 3-propyl in **75** reduced affinity for the A1AR about 3-fold, while enhancing A2AR affinity. 3-Propyl-8-phenylxanthine was about 3-fold less potent at A1 and A2ARs than unsubstituted 8-phenylxanthine.

With compound **38**, we investigated the effect of introducing an 8-phenyl substituent to the A2-selective antagonist 3,7-dimethyl-1-propargylxanthine (DMPX).[15,28,41] The introduction of a phenyl group increased A1 and A2AR affinity, A1 affinity to a greater extent, leading to a nonselective, moderately potent compound (**38**).

Experimental Section

Melting points were measured with a Büchi 510 apparatus and are uncorrected. Mass spectra were determined with Finnegan 1015 quadrupole (chemical ionization with CH_4 or NH_3) and VG 70/70 (electron impact, 70 eV) mass spectrometers. NMR spectra were run on a Bruker WP-80 spectrometer or a Bruker AC-200 spectrometer; DMSO-d_6 was used as solvent, unless otherwise noted. IR spectra were determined with a Perkin-Elmer 1750 FT-IR spectrometer. All compounds were checked for purity by TLC on 0.2 mm aluminum sheets with silica gel 60 F_{254} (Merck); as eluent CH_2Cl_2/MeOH = 9:1, or 3:1, for the more polar compounds, was used.

Elemental analyses were performed by the Institute of Chemistry, University of Tübingen.

7-*n*-Butylxanthine (3). Xanthine 1 (1.52 g, 10 mmol) is refluxed in 10 mL of hexamethyldisilazane (HMDS) with a catalytic amount of $(NH_4)_2SO_4$ for 12 h. A clear solution is obtained. Excess HMDS is removed *in vacuo*, and the product is used without further purification.

Tris(trimethylsilyl)xanthine **2** is treated with 3.4 mL (30 mmol) of *n*-butyl iodide at room temperature for 2 days. The mixture is solvolyzed by the addition of methanol, diluted with acetone, and the precipitate collected by filtration. The product is extracted with hot isopropanol, insoluble material (xanthine) is filtered off, and the isopropyl alcohol solution is evaporated to dryness. The residue is recrystallized from H_2O: yield 38%; mp 210 °C. Anal. ($C_9H_{12}N_4O_2$) C: Calcd 51.9. Found 51.3, H, N.

7,9-Diallylxanthinium Bromide (4). Xanthine (3.0 g, 19.7 mmol) is silylated as described for the preparation of **3**, treated with 3.5 mL (41 mmol) of allyl bromide, and stirred over night at room temperature. The solution is cooled in an ice bath and treated with H_2O. The solvent is removed by rotary evaporation, and the residue is extracted with hot acetone and filtered. The residue contains 3,7-diallylxanthine **5**, while the main product, 7,9-diallylxanthinium bromide **4** is soluble in acetone. Compound **4** is obtained by evaporation of the solvent and is purified by recrystallization from acetone/H_2O: yield 63%; mp 228 °C dec; ^1H NMR δ 4.73 (d, 2H, CH_2-N), 4.94 (d, 2H, CH_2-N), 5.17–5.26 (dd, 4H, 2 × CH_2=CH), 5.88–6.09 (m, 2H, 2 × CH_2=*CH*), 9.37 (s, 1H, C8-H), 10.84 (br s, 1H, NH); ^{13}C NMR δ 46.9, 50.0 (2 × N-CH_2), 105.0 (C5), 119.8, 120.0 (2 × CH_2=CH), 130.9, 131.4 (2 × CH_2=CH), 136.2 (C8), 147.6 (C4), 155.2, 155.6 (C2, C6). Anal. ($C_{12}H_{14}BrN_4O_2$) C, H, N.

3,7-Diallylxanthine (5). The residue of 3,7-diallylxanthine obtained as described for the preparation of **4** is purified by recrystallization from DMF/H_2O: yield 21%; mp 163 °C. Anal. ($C_{11}H_{12}N_4O_2$) C, H: calcd, 5.21; found, 5.01, N.

3-Methyl-1-propargylxanthine (10). 1-Methyl-6-aminouracil **6**[29] (5.0 g, 35.5 mmol) and 100 mg of $(NH_4)_2SO_4$ is suspended in 150 mL of HMDS. The mixture is refluxed for ca. 30 h until a clear solution is obtained. Excess HMDS is removed by rotary evaporation, and a few crystals of iodine and 5.5 mL (62 mmol) of propargyl bromide is added. An exothermic reaction takes place, and the brown iodine color disappears within 15 min. Then, the mixture is refluxed for 15 min until the iodine color reappears. Methanol (250 mL) is added slowly.

After cooling, the precipitate of unreacted 1-methyl-6-aminouracil is removed by filtration. The solvent is removed in vacuo, affording 1.1 g (6.15 mmol, 17%) of 1-methyl-3-propargyl-6-aminouracil (**8**) which is used without further purification.

Compound **8** is dissolved in a mixture of water and acetic acid (30 mL + 30 mL) and heated to 80 °C. $NaNO_2$ (0.85 g, 12.3 mmol) is added in small portions over a period of 30 min. The mixture is cooled, filtered, and washed with water to afford pure 1-methyl-5-nitroso-3-propargyl-6-aminouracil as dark pink crystals.

Reduction of the nitroso function is performed by dissolving the compound in 100 mL of 12% NH_4OH, heating to 70–80 °C, and adding $Na_2S_2O_4$ in small portions, until the dark orange color has disappeared. Part of the solvent is removed by rotary evaporation until the product starts to crystallize. The mixture is then cooled in the refrigerator, and crystals of **9** are collected by filtration and dried in a desiccator (yield: 620 mg, 58%).

A suspension of 470 mg (2.4 mmol) of 1-methyl-3-propargyl-5,6-diaminouracil **9** and 15 mL of triethyl orthoformate is refluxed. The solution becomes clear, then the product starts to separate.

After 90 min, the mixture is cooled, and the precipitate is collected by filtration and washed with diethyl ether.

Dissolution in 2 N NaOH and precipitation with 2 N HCl affords pure 3-methyl-1-propargylxanthine (**10**): yield 340 mg (69%); mp 325 °C. Anal. ($C_9H_8N_4O_2$) C: calcd, 52.9; found, 53.7; H: calcd, 3.95; found, 3.78, N.

1,7-Disubstituted Xanthines (Paraxanthine Analogs). General Procedure. 1-Monosubstituted xanthine **11**[25] (100 mg) is refluxed with 10 mL of HMDS and a catalytic amount of $(NH_4)_2SO_4$ for 1–2 h until a clear solution is obtained. Refluxing is continued for an additional 0.5 h. Excess HMDS is removed *in vacuo*. A 10-fold excess of the appropriate halogenide (methyl iodide or propargyl bromide, respectively) is added to the 1-substituted bis(trimethylsilyl)xanthine **12**, and the solution is stirred at room temperature over night. The volatiles are removed by evaporation, H_2O is slowly added with cooling, and the precipitate is collected by filtration.

1-Methyl-7-propargylxanthine (13). The product is purified by dissolution in DMF and precipitation with H_2O: glittering crystals; yield 86%; mp 230 °C dec; CIMS 205 (59%), 147 (100%). Anal. ($C_9H_8N_4O_2$ × $1H_2O$) C: calcd, 48.6; found, 49.4, H: calcd, 4.54; found, 4.49, N: calcd, 25.1; found, 25.5.

7-Methyl-1-propylxanthine (14). The product is recrystallized several times from H_2O. It takes several days of cooling in the refrigerator to crystallize the compound: long needles, soluble in methanol; yield 68%; mp 215 °C. Anal. ($C_9H_{12}N_4O_2$ × 0.5 H_2O) C: calcd, 49.7; found, 48.9, H, N: calcd, 25.8; found, 25.5.

7-Methyl-1-propargylxanthine (15). Purification is achieved by recrystallization from H_2O: yield 73%; mp 264 °C; IR (KBr) 3588, 3495, 3276, 1713, 1666, 1573, 1442, 764, 703, 565 cm^{-1}. Anal. ($C_9H_8N_4O_2$ × $1H_2O$) C, H, N.

N-Monosubstituted Barbituric Acids (17). N-Monosubstituted barbituric acids were prepared according to the method of Biltz and Wittek.[43]

N-Alkylurea **16** (113.5 mmol) and malonic acid (120 mmol) are dissolved in 25 mL of acetic acid with heating at 70–80 °C. Then 25 mL of acetic acid is slowly added within 2 h. The temperature is raised to 90 °C. After 8 h, 5 mL of water is added to remove unreacted acetic anhydride. Then, 20 mL of hot ethanol is added with vigorous stirring, and the solution is cooled in the refrigerator for several hours. The precipitate is collected by filtration. Additional precipitate is obtained by evaporation of the filtrate, addition of hot ethanol, and precipitation of the product by cooling. Depending on the substituent on the nitrogen, various amounts of 5-acetylated barbituric acids are formed as byproducts which crystallize more readily compared to the desired barbituric acids.

1-Ethyl barbituric acid (17a): white crystals from ethanol: yield 70%; mp 121 °C (lit. mp 124 °C[43]); CIMS 157 (10%), 131 (100%); ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 3H, CH_3), 3.65 (s, 2H, C5-H), 3.91 (q, 2H, CH_2-N), 8.95 (br s, 1H, N3-H).

1-Propyl barbituric acid (17b): yield 73%; mp 100 °C (lit. mp 104 °C[44]); ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3H, CH_3), 1.65 (sext, 2H, CH_3-CH_2-), 3.62 (s, 2H, C5-H), 3.79 (t, 2H, CH_2-N), 8.98 (br s, 1H, N3-H), ^{13}C NMR ($CDCl_3$) δ 11.0 (CH_3), 21.1 (CH_3-CH_2-), 39.2 (C5), 42.7 (CH_2-N), 150.9 (C2), 165.5, 165.6 (C4, C6).

3-Substituted 6-Chlorouracils (18). Chlorouracils are prepared according to the method of Pfleiderer.[45,46] N-Monosubstituted barbituric acid **17** (48 mmol) is humidified with 2.4 mL of H_2O. Then, 65 g (39.4 mL) of $POCl_3$ is slowly added in such a way that the solution keeps boiling. After 1 h, the mixture is cooled, excess $POCl_3$ is removed *in vacuo*, and ice is slowly added. The precipitate is collected by filtration and recrystallized from acetone.

3-Ethyl-6-chlorouracil (18a): yield 36%; mp 159 °C (lit. mp 220 °C[46]); CIMS 175 (100%); ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3H, CH_3), 3.98 (q, 2H, CH_2), 5.86 (s, 1H, C5-H), 10.59 (br s, 1H, N1-H); ^{13}C NMR ($CDCl_3$) δ 12.7 (CH_3), 36.1 (CH_2), 101.4 (C5), 142.7 (C6), 151.8 (C2), 161.6 (C4).

3-Propyl-6-chlorouracil (18b). Yield 63%; mp 165 °C (lit. mp 194 °C[46]); ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3H, CH_3), 1.62 (sext, 2H, CH_3-CH_2-), 3.82 (t, 2H, CH_2-N), 5.86 (s, C5-H), 11.09 (br s, 1H, N1-H), ^{13}C NMR ($CDCl_3$) δ 11.3 (CH_3); 20.9 (CH_3-CH_2-), 42.5 (CH_2-N), 101.4 (C5), 143.1 (C6), 152.4 (C2), 162.0 (C4).

3-Substituted 6-Aminouracils (19). Method A. 3-Substituted 6-chlorouracils **18** (1.0 g) and 7 mL of 12.5% aqueous ammonia are heated in a sealed tube at 180 °C for 10–30 h. The solution is cooled to room temperature, evaporated to dryness, taken up in a small amount of cold water, and the residue is collected by filtration and washed with cold water. Yields are ranging from 44 to 63%.

Method B. 3-Substituted 6-aminouracils are prepared by alkylation of silylated 6-aminouracil **25** with the appropriate halogenides as described elsewhere.[24]

Identical products were obtained by both independent methods. The new method B proved to be superior to method A. Starting from an inexpensive precursor, 6-aminouracil, the desired products are obtained in a one-pot procedure with high yields, while method A is a three-step procedure with the chlorination of the barbituric acids being the critical step. In some cases, the monosubstituted ureas are not commercially available and have to be prepared also.

6-(Benzylamino)-3-ethyluracil (20a). A mixture of 0.94 g (5.4 mmol) of 3-ethyl-6-chlorouracil (**18a**), 5 mL of butanol, 2 mL of benzylamine, and a catalytic amount of benzylamine hydrochloride is gently refluxed for 3 h. The solution is cooled, 10 mL of ethanol is added, and the precipitate is collected by filtration and washed with ethanol: white glittering crystals, insoluble in ethanol, soluble in DMSO; yield 87%; mp 276 °C; CIMS 246 (100%); ^{1}H NMR δ 1.00 (t, 3H, CH_3), 3.68 (q, 2H, CH_3-CH_2-), 4.25 (d, 2H, benzyl-CH_2), 4.51 (s, 1H, C5-H), 6.64 (s, 1H, exocyclic N-H), 7.31 (m, 5H, aromatic), 10.23 (br s, 1H, N3-H). Anal. ($C_{13}H_{14}N_3O_2$) C, H, N.

6-(Benzylamino)-3-ethyl-5-nitrosouracil (21a). A solution of 0.9 g (3.7 mmol) of **20a** in 20 mL of DMF is prepared with heating at 80 °C. $NaNO_2$ (0.5 g, 100% excess), dissolved in 5 mL of H_2O, is added. The solution is acidified by a few drops of HCl concentrated and turns red. After stirring for 30 min, it is cooled, and H_2O is added until an orange precipitate is formed which is collected by filtration. The product is purified by recrystallization from acetone/H_2O to afford purple crystals: yield 83%; mp 205 °C dec; ^{1}H NMR δ 1.12 (t, 3H, CH_3), 3.82 (q, 2H, CH_3-CH_2-), 4.67 (d, 2H, benzyl CH_2), 7.33 (m, 5H, aromatic), 9.07 (br s, 1H, N3-H). Anal. ($C_{13}H_{14}N_4O_3$) C, H, N.

1-Ethyl-8-phenylxanthine (22). A solution of 0.5 g (1.8 mmol) of **21a** in 10 mL of xylene is refluxed for 2.5 h. After cooling, the precipitate is collected by filtration and washed with ethanol. Purification is achieved by dissolution in DMF and precipitation with H_2O: yield 86%; mp > 350 °C; ^{1}H NMR δ 1.13 (t, 3H, CH_3), 3.92 (q, 2H, CH_3-CH_2), 7.48 (m, 3H, phenyl-C3′, C4′, C5′-H), 8.08 (m, 2H, phenyl-C2′, C6′-H), 11.90 (br s, 1H, N3-H), 13.68 (br s, 1H, N7-H); ^{13}C NMR δ 13.3 (CH_3), 35.0 (CH_2), 107.8 (C5), 126.3, 128.9, 130.1 (aromatic), 147.7 (C4), 149.9 (C8), 150.8 (C2), 154.6 (C6). Anal. ($C_{13}H_{12}N_4O_2$) C, H, N.

6-((Cyclohexylmethyl)amino)-3-ethyluracil (20b). Compound **20** is prepared from 3-ethyl-6-chlorouracil (**18a**) and cyclohexylmethylamine as described for the preparation of **20a**: yield 84%; mp 251 °C; ^{1}H NMR δ 0.90–1.65 (m, 11H, cyclohexyl), 1.01 (t, 3H, CH_3), 2.84 (t, 2H, cyclohexyl-CH_2-N), 3.67 (q, 2H, CH_3-CH_2-), 4.53 (s, 1H, C5-H), 6.11 (s, 1H, exocyclic N-H), 9.97 (br s, 1H, N1-H). Anal. ($C_{13}H_{21}N_3O_2$) C, H, N.

6-((Cyclohexylmethyl)amino)-3-ethyl-5-nitrosouracil (21b) is prepared as described for **21a**: yield 84%.

8-Cyclohexyl-1-ethylxanthine (23) is prepared as described for **22**, except that the reaction time had to be extended to 10 h: white crystals, recrystallized from DMF/H_2O: yield 68%; mp 274 °C dec; CIMS 263 (100%). Anal. ($C_{13}H_{18}N_4O_2$) C: calcd, 59.5; found, 58.9, H: calcd, 6.92; found, 6.83, N: calcd, 21.4; found, 20.9.

6-Amino-5-(benzylideneamino)-3-propargyluracil (27e). A solution of 0.85 g (4.7 mmol) 3-propargyl-5,6-diaminouracil (**26e**) in 10 mL of ethanol is prepared. Benzaldehyde (0.6 g, 5.7 mmol) is added, and the solution is refluxed for 3 h. After cooling, water is added, and the precipitate is collected by filtration: yield 1.1 g (88%); mp 209 °C; ^{1}H NMR δ 3.03 (t, 1H, propargyl CH), 4.47 (d, 2H, CH-N), 6.73 (br s, 2H, NH_2), 7.36 (m, 3H, aromatic), 7.83 (m, 2H, aromatic), 9.65 (s, 1H, benzylidene CH), 10.94 (br s, 1H, N1-H); ^{13}C NMR δ 28.4 (N-CH_2), 72.3 (propargyl C-2′), 79.9 (propargyl CH), 98.2 (C5), 127.2, 128.4, 129.1 (aromatic), 138.5 (phenyl C-1), 149.5 (N=CH), 148.5, 152.2, 157.3 (C2, C4, C6). Anal. ($C_{14}H_{12}N_4O_2$) C, H, N.

8-Phenyl-1-propargylxanthine (31). A mixture of 0.85 g (3.25 mmol) of **27e** and 0.55 g (3.39 mmol) of anhydrous $FeCl_3$ is refluxed in 20 mL of ethanol for 3 h. The solution is cooled, H_2O is added, and the precipitate is collected by filtration. Purification is achieved by dissolution in 1 N NaOH followed by precipitation by addition of acetic acid: yield 79%; mp > 300 °C; ^{1}H NMR δ 3.06 (t, 1H, propargyl C-H), 4.61 (d, 2H, CH_2-N), 7.48 (m, 3H, aromatic), 8.06 (m, 2H, aromatic), 12.28 (br s, 1H, N3-H); ^{13}C NMR δ 29.4 (N-CH_2), 72.5 (propargyl C2′), 79.8 (propargyl CH), 107.6 (C5), 126.4, 128.8, 129.0, 130.3 (aromatic), 148.1 (C4), 150.4 C2, C8), 154.0 (C6). Anal. ($C_{14}H_{10}N_4O_2$) C, H, N.

1-(*m*-Chlorobenzyl)-8-phenylxanthine (32). A mixture of 0.71 g (2.8 mmol) of 3-(3-chlorobenzyl)-5,6-diaminouracil[25] and 0.35 g (3.3 mmol) of benzaldehyde in 20 mL of ethanol is refluxed for 1 h to yield **27f** which is subsequently cyclized by the addition of 0.5 g (3 mmol) of anhydrous $FeCl_3$ and refluxing for 1 h. Purification of **32** was achieved by dissolving the compound in a small amount of 1 N NaOH and subsequent precipitation by acetic acid. Final recrystallization from methanol yields pure crystals: soluble in ethanol; yield 47%; mp >320 °C; ^{1}H NMR δ 5.05 (s, 2H, N-CH_2), 7.30 (m, 4H, benzyl aromatic), 7.44 (m, 3H, 8-phenyl aromatic), 8.06 (m, 2H, 8-phenyl aromatic), 12.5 (br s, 1H, N3-H). Anal. ($C_{18}H_{13}N_4O_2Cl$) C, H, N.

1-(2-Phenethyl)-8-phenylxanthine (33). 3-(2-Phenethyl)-5,6-diaminouracil (**26g**)[25] is refluxed with benzaldehyde in ethanol for 2 h and subsequently cyclized as described for the preparation of **32**. Purification is achieved by dissolution of the compound in 1 N NaOH solution, filtration, and subsequent precipitation of the product by the addition of concentrated HCl. The compound is finally recrystallized from methanol: yield 52%; mp 255 °C dec; ^{1}H NMR δ 2.51 (m, 2H, phenyl-CH_2-CH_2), 3.99 (m, 2H, N-CH_2), 7.24 (m, 5H, phenethyl aromatic), 7.39 (m, 3H, 8-phenyl), 7.47 (m, 2H, 8-phenyl), 11.90 (s, 1H, N3-H); IR (KBr) 3432, 3122, 3028, 1719, 1636, 1564, 1457, 760, 712, 691 cm^{-1}. Anal. ($C_{19}H_{16}N_4O_2$) C: calcd, 68.7; found, 68.1, H: calcd, 4.85; found, 4.82, N: calcd, 16.9; found, 16.6.

6-Amino-5-cyclopentylcarboxamido-3-propyluracil (29b). A mixture of 1.0 g (5.4 mmol) of 3-propyl-5,6-diaminouracil (**26b**),[25] 0.63 g (5.5 mmol) of cyclopentanecarboxylic acid, and 0.66 g (5.5 mmol) of *N*-((dimethylamino)propyl)-*N'*-ethylcarbodiimide hydrochloride is dissolved in 30 mL of methanol and stirred at room temperature over night. The precipitate is collected by filtration and washed with H_2O: yield 93%; mp > 300 °C; EIMS 280 (24%), 69 (100%); ^{1}H NMR δ 0.82 (t, 3H, CH_3), 1.49–1.81 (m, 10 H, cyclopentyl CH_2 + CH_3-CH_2-), 2.73 (m, 1H, cyclopentyl-C1'-H), 3.62 (t, 2H, CH_2-N), 5.80 (s, 2H, NH_2), 8.25 (s, 1H, NH-CO), 10.40 (br s, 1H, N1-H); ^{13}C NMR δ 11.1 (CH_3), 20.9 (CH_2), 27.7 (cyclopentyl C3', C4'), 29.9 (cyclopentyl C2', C5'), 40.8 (CH_2-N), 43.9 (cyclopentyl-C1'), 87.3 (C5), 149.7, 150.1, 160.5 (C2, C4, C6), 175.7 (exocyclic C=O). Anal. ($C_{13}H_{20}N_4O_3$) C, H, N.

8-Cyclopentyl-1-propylxanthine (34). A suspension of **29b** (1.0 g, 3.6 mmol) in 20 mL of 30% $NaOCH_3$ solution in methanol is refluxed for 3 h. After cooling to room temperature, H_2O is added, the solution is brought to pH 5 with concentrated HCl, and the solvents are removed by rotary evaporation. The residue is suspended in H_2O, and the product is collected by filtration and washed with water: white crystals, soluble in DMSO, slightly soluble in H_2O, acetone, and diethyl ether: yield 96%; mp 270 °C dec; ^{1}H NMR δ 0.83 (t, 3H, CH_3), 1.39–1.74 (m, 10H, cyclopentyl CH_2 + CH_3-CH_2), 3.10 (m, 1H, cyclopentyl C1'-H), 3.77 (t, 2H, CH_2-N), 12.45 (br s, 1H, N3-H); ^{13}C NMR δ 11.1 (CH_3), 20.9 (CH_3-CH_2-), 25.0 (cyclopentyl C3', C4'), 31.8 (cyclopentyl C2', C5'), 38.6 (cyclopentyl C1'), 41.2 (CH_2-N), 105.9 (C5), 147.1 (C4), 151.0 (C2), 154.6 (C6), 158.0 (C8). Anal. ($C_{13}H_{18}N_4O_2$) C, H, N.

8-Cyclohexyl-1-propargylxanthine (35). A mixture of 0.60 g (3.3 mmol) of 3-propargyl-5,6-diaminouracil (**26e**), 4 mL of cyclohexanecarboxaldehyde, 3 drops of acetic acid, and 10 mL of ethanol is refluxed. After 5 h, 0.55 g (3.4 mmol) of anhydrous $FeCl_3$ is added to the solution, and the refluxing is continued for another 12 h. After cooling, H_2O is added, and the precipitate is collected by filtration, dried, and washed with diethyl ether. The product is purified by dissolution in 1 N NaOH, filtration, and precipitation by concentrated HCl. This procedure is repeated twice: yield 68%; mp 287 °C; ^{1}H NMR δ 1.32–1.94 (m, 10H, cyclohexyl-CH_2), 2.67 (m, 1H, cyclohexyl C1'-H), 2.99 (t, 1H, propargyl CH), 4.52 (d, 2H, propargyl CH_2), 11.83 (br s, 1H, N3-H), 12.93 (br s, 1H, N7-H); ^{13}C NMR δ 25.3, 30.9 (cyclohexyl CH_2), 29.2 (propargyl N-CH_2), 37.4 (cyclohexyl C1'-H), 72.3 (propargyl-C2'), 79.9 (propargyl C-H), 105.6 (C5), 147.3 (C4), 150.3 (C2), 153.7 (C6), 158.8 (C8). Anal. ($C_{14}H_{16}N_4O_2$) C: calcd, 61.8; found, 61.2, H: calcd, 5.92; found, 6.13; N: calcd 20.6; found, 19.5.

6-Amino-5-cyclopentanecarboxamido-3-propargyluracil (29e). A solution of 1.0 g (5.5 mmol) of 3-propargyl-5,6-diaminouracil (**26e**),[25] 0.64 g (5.6 mmol) of cyclopentane carboxylic acid, and 1.07 g (5.6 mmol) of *N*-((dimethylamino)propyl)-*N'*-ethylcarbodiimide hydrochloride in 30 mL of methanol is prepared and stirred over night. A precipitate is formed which is collected by filtration. The filtrate is evaporated to dryness, the residue is taken up in H_2O and cooled, and additional product is collected by filtration: yield 94%; mp 244 °C; ^{1}H NMR δ 1.58 (m, 8H, cyclopentyl CH_2), 2.65 (m, 1H, cyclopentyl C1'-H), 2.98 (t, 1H, propargyl CH), 4.39 (d, 2H, propargyl CH_2), 5.91 (br s, 2H, NH_2), 8.23 (s, 1H, exocyclic NH), 10.53 (br s, 1H, N1-H). Anal. ($C_{13}H_{16}N_4O_3$) C, H, N.

8-Cyclopentyl-1-(2-oxopropyl)xanthine (36). A suspension of 1.0 g (3.6 mmol) of **29e** in 20 mL of 30% $NaOCH_3$ solution in methanol is prepared and refluxed for 1 h. The product is isolated as described for **34**: yield 93%; mp > 300 °C; ^{1}H NMR δ 1.68 (m, 8H, cyclopentyl CH_2), 2.15 (s, 3H, CH_3), 3.14 (m, 1H, cyclopentyl C1'-H), 4.65 (s, 2H, CH_2-N), 11.81 (br s, 1H, N3-H); ^{13}C NMR δ 25.1 (cyclopentyl C3', C4'), 27.0 (CH_3), 31.8 (cyclopentyl C2', C5'), 38.5 (cyclopentyl C1'), 49.2 (CH_2-N), 105.7 (C5), 147.4 (C4), 150.7 (C2), 154.0 (C6), 158.4 (C8), 202.2 (C=O). Anal. ($C_{13}H_{16}N_4O_3$) C, H, N: calcd, 20.3; found, 19.6.

6-Amino-3-propyl-5-((*p*-sulfobenzoyl)amino)uracil (30b). A solution of 2.37 g (12.9 mmol) of 3-propyl-5,6-diaminouracil (**26b**),[25] 3.24 g (13.5 mmol) of *p*-sulfobenzoic acid potassium salt, and 2.58 g (13.5 mmol) of *N*-((dimethylamino)propyl)-*N'*-ethylcarbodiimide hydrochloride in 60 mL of methanol/H_2O = 1:1 is stirred over night at room temperature. The solvent is removed by evaporation, methanol is added, and the residue is collected by filtration. The filtrate is cooled to complete the precipitation of further product: yield 96%; mp > 300 °C; ^{1}H NMR δ 0.83 (t, 3H, CH_3), 1.47 (sext, 2H, CH_2), 3.67 (t, 2H, CH_2-N), 6.20 (br s, 2H, NH_2), 7.73 (d, 2H, phenyl), 7.87 (d, 2H, phenyl), 8.88 (s, 1H, exocyclic NH), 10.36 (br s, 1H, N-H), ^{13}C NMR δ 28.9 (N-CH_2), 72.4 (propargyl C2'), 80.1 (propargyl CH), 86.8 (C5), 125.2, 127.5, 134.6, 149.3, 150.4, 150.9 (aromatic + C2, C4), 159.7 (C4), 166.2 (exocyclic C=O). Anal. ($C_{14}H_{16}N_4O_6S$) C, H, N.

1-Propyl-8-(*p*-sulfophenyl)xanthine (37). A mixture of 2.50 g (6.8 mmol) of **30b** and 15 mL of polyphosphoric acid trimethylsilyl ester is refluxed for 1 h. After cooling, methanol is added to the mixture, the precipitate is collected by filtration and washed with methanol. The filtrate is left in the freezer and yields another precipitation of product.

The product is recrystallized from H_2O: yield 86%; mp > 300 °C; ^{1}H NMR δ 0.87 (t, 3H, CH_3), 1.60 (q, 2H, CH_3-CH_2), 3.81 (t, 2H, CH_2-N), 7.69 (d, 2H, phenyl), 8.01 (d, 2H, phenyl), 11.88 (br s, 1H, N3-H); ^{13}C NMR δ 11.2 (CH_3), 20.9 (CH_3-CH_2), 41.6 (CH_2-N), 108.1 (C5), 125.8, 126.0, 129.1 (aromatic), 147.6 (C4), 149.4 (aromatic C4'), 149.7 (C8), 151.0 (C2), 154.9 (C6); IR (KBr) 3456, 3129, 3093, 2968, 1724, 1635, 1580, 1462, 1192, 1041, 759, 672, 629 cm^{-1}. Anal. ($C_{14}H_{14}N_4O_5S$) C, H, N, S.

3,7-Dimethyl-8-phenyl-1-propargylxanthine (38). 8-Phenyl-1-propargylxanthine (**31**) (0.40 g, 1.5 mmol) is dissolved in 10 mL of DMF, K_2CO_3 (0.42 g, 3 mmol), and MeI (1.9 mL, 30 mmol) is added, and the mixture is stirred at room temperature over night. The product is precipitated by the addition of 20 mL of H_2O, collected by filtration, and washed with H_2O. Recrystallization from DMF/H_2O affords pure **38**: yield 0.34 g (77%); mp 237 °C; ^{1}H NMR δ 3.12 (t, 1H, propargyl CH), 3.49 (s, 3H, N3-CH_3), 4.00 (s, 3H, N7-CH_3), 4.64 (d, 2H, propargyl CH_2), 7.59 (m, 3H, aromatic), 7.81 (m, 2H, aromatic). Anal. ($C_{16}H_{14}N_4O_2$) C: calcd, 65.3; found, 64.4, H, N.

8-Phenylxanthine (71). Compound 71 is prepared from 5,6-diaminouracil sulfate[47] as described[38] with slight modifications. 6-Aminouracil (6.0 g, 47 mmol) is dissolved in 300 mL of 2 N NaOH with heating. After cooling, 3.5 g of $NaNO_2$ (51 mmol) is added, and 2 N H_2SO_4 is slowly added with vigorous stirring until a pH value of 6–7 is obtained. After 1 h, the precipitate is collected and washed with water. The 6-amino-5-nitrosouracil is dissolved in 500 mL of 12% NH_4OH solution with heating, the solution is allowed to cool to room temperature, and $Na_2S_2O_4$ (ca. 17 g) is slowly added until the color has disappeared. The solution is neutralized with 2 N H_2SO_4 with cooling. The white precipitate of 5,6-diaminouracil sulfate is collected by filtration and washed with water: yield 5.8 g (37%).

A mixture of 3.0 g of 5,6-diaminouracil × H_2SO_4 (12.5 mmol), 1.33 g of benzaldehyde (12.5 mmol), 15 mL of nitrobenzene, and 2.45 g of barium acetate (12.5 mmol) is refluxed for 1 h. Diethyl ether (50 mL) is added, and the precipitate is collected by filtration and washed with diethyl ether. Purification is achieved by dissolution in 10% NaOH solution, filtration from an undissolved byproduct, and precipitattion by addition of concentrated HCl: yield 0.8 g (28%); mp > 300 °C; EIMS 228 (100%); ^{1}H NMR δ 7.50 (m, 3H, aromatic), 8.07 (m, 2H, aromatic), 10.90 (brs, 1H, N1-H), 11.63 (s, 1H, N3-H), 13.66 (v br s, 1H, N7-H); ^{13}C NMR δ 107.9 (C5), 126.2, 128.9, 130.1 (aromatic), 149.6, 149.9 (C4, C8), 151.4 (C2), 155.3 (C6). Anal. ($C_{11}H_8N_4O_2$) C, H, N.

Receptor Binding Assays. Inhibition of binding of [^{3}H]-(*R*)-N^6-(phenylisopropyl)adenosine (*R*-PIA) to A1 adenosine receptors of rat brain cortical membranes and inhibition of binding of [^{3}H]-5'-*N*-(ethylcarboxamido)adenosine (NECA) to A2 adenosine receptors of rat striatal membranes were assayed as described.[48-50] 2-Chloroadenosine (10 μM) was used in the A1 binding assay, and theophylline (5 mM) was used in the A2 binding assay to determine nonspecific binding. The A1-selective adenosine receptor agonist N^6-cyclopentyladenosine (N^6-CPA) was present in the A2 binding assay to block A1 adenosine receptors present in striatal membranes. Inhibition of binding by a range of concentrations of xanthines was determined in triplicate in three separate experiments. K_i values were calculated using the Cheng–Prusoff equation[51] with K_d values of 1 nM for *R*-PIA and 8.5 nM for NECA.

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