8-Aryl- and 8-Cycloalkyl-1,3-dipropylxanthines: Further Potent and Selective Antagonists for A_1-Adenosine Receptors

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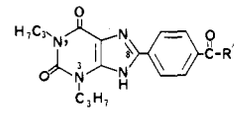
A series of 1,3-dipropylxanthines were prepared with a variety of substituents at the 8-position. These included 8-aryl and 8-cycloalkyl groups. Polar carboxylate and carboxamide moieties were introduced as aryl substituents to increase water solubility. 1,3-Dipropyl-8-[2-hydroxy-4-[(carboxymethyl)oxy]phenyl]xanthine provided a functionalized congener with high potency (K_i = 37 nM) and selectivity (54-fold) for A_1-adenosine receptors. This congener was used for preparation of a series of other analogues, some with higher potency and some with higher selectivity. 8-Cyclopentyl- and 8-cyclohexyl-1,3-dipropylxanthines were both very potent (K_i = 1–1.5 nM) and selective for A_1 receptors, while 8-cycloalkylmethyl analogues were 10-fold less potent, but still very selective for A_1 receptors. 8-Piperidinyl and 8-pyrazinyl analogues had very low activities as adenosine receptor antagonists.

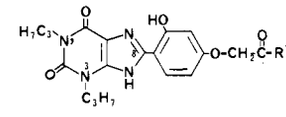
Adenosine modulates a variety of physiological functions through interaction with extracellular receptors.[1] There are at least two classes of adenosine receptors that have been characterized mainly through rank order of potencies of adenosine analogues: Activation of A_1-adenosine receptors causes inhibition of adenylate cyclase, while activation of A_2-adenosine receptors causes stimulation of adenylate cyclase. Other classes of adenosine receptors may exist, and such adenosine receptors may interact with potassium or calcium channels.[2]

Xanthines exert pharmacological effects primarily through blockade of adenosine receptors. For example, caffeine and theophylline, which are nonselective for A_1 or A_2 receptors, exert antiasthmatic, diuretic, respiratory-stimulant, cardiac-stimulant, and analgesic-adjuvant activities.[1] A number of xanthine antagonists with in vitro selectivity for A_1 and A_2 receptors have been developed.[3-11] Certain xanthines that are selective in vitro for A_1-adenosine receptors have been shown to selectively antagonize cardiodepressant effects compared to hypotensive effects of adenosine analogues in vivo.[12,13] A caffeine analogue that is selective in vitro for A_2-adenosine receptors has slightly selective antagonistic effects versus the hypotensive effects of adenosine analogues in vivo.[13] Further, much more selective antagonists are, however, needed.

Chart I. Functionalized Congener (**2**, **10**) Approach to Synthesis of Analogues (**4**, **5**, **11**–**14**, **21**, **22**)



4 R′ = -NH_2
5 R′ = -$NHCH_2CO_2CH_3$



11 R″ = -OC_2H_5
12 R″ = -NH_2
13 R″ = -$NHCH_2CH_2N(CH_3)_2$
14 R″ = -$NHCH_2CH_2NH_2$
21 R″ = -$NHCH_2CH_2$-(imidazole)
22 R″ = -$NHCH_2CH_2$-(4-hydroxyphenyl)

1,3-Dipropyl-8-phenylxanthines are moderately potent and selective A_1-receptor antagonists, and a variety of aryl substituents are well-tolerated at A_1 receptors. A *p*-hydroxy analogue (**6**) and a *p*-methoxy analogue (**7**) are both potent and selective for A_1 receptors,[4] but with low bioavailability due to very low water solubility. A 4-carboxymethyl ether of **6** has provided the basis for a "functionalized congener" approach to adenosine antagonists in which a functionalized "chain" is incorporated at a point on the primary xanthine pharmacophore that does not reduce pharmacological activity: The resultant "functionalized congener" can then be readily joined covalently to various moieties.[5,6,8,11] Such moieties can not only alter potency and selectivity, but can provide for enhanced water solubility. Certain amide and amino acid derivatives of the 4-(carboxymethyl)ethyl ether of **6** that were developed in this approach proved to be both potent and selective for A_1 receptors and to have enhanced water solubilities.[6] In the present study, we have applied the functionalized congener approach to 8-*p*-(carboxyphenyl)-1,3-dipropylxanthine (**3**) and to 8-(2,4-dihydroxyphenyl)-1,3-dipropylxanthine (**8**). The latter is a highly potent and selective antagonist for A_1 receptors, but with limited water solubility.[3] It (**8**) was converted to an 8-[2-hydroxy-4-[(carboxymethyl)oxy]phenyl] derivative (**10**) that served as a functionalized congener for preparation of various analogues (see Chart I). Certain analogues prepared from **3** and **8** proved to be highly potent and selective antagonists and to have intermediate to high water solubilities. Replacement of the 8-phenyl ring with an 8-cycloalkyl group also resulted in analogues with high potency and selectivity for A_1 receptors.

Results and Discussion

1,3-Diphenyl-8-phenylxanthine (**2**) is a potent and selective (210-fold) A_1 receptor antagonist with limited water

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0022-2623/88/1831-0613$01.50/0

Table I. Activity of 8-Substituted 1,3-Dipropylxanthines as Antagonists at A_1- and A_2-Adenosine Receptors

no.	8-substituent	K_B or K_i, nM: rat brain A_1 receptor[a]	human platelet A_2 receptor[b]	ratio A_2/A_1
1	hydrogen	710 (670–750)	7400 (1700–32000)	10
2	phenyl	10 (5.5–18)	2100 (1300–3600)	210
3	*p*-carboxyphenyl	200 (170–240)	320 (230–440)	1.6
4	*p*-carbamoylphenyl	12 (9.7–19)	54 (32–91)	4.5
5	*p*-[(carbomethoxymethyl)carbamoyl]phenyl	38 (26–55)	240 (190–310)	6.3
6	*p*-hydroxyphenyl	3.5 (1.5–8.3)	48 (21–110)	14
7	*p*-methoxyphenyl	3.7 (1.8–7.8)	2900 (2200–3900)	780
8	2,4-dihydroxyphenyl	2.5 (1.2–5.3)	820 (290–2300)	330
9	2-hydroxy-4-methoxyphenyl	4.6 (2.2–9.9)	180 (42–800)	39
10	2-hydroxy-4-[(carboxymethyl)oxy]phenyl	37 (12–110)	2000 (1400–2700)	54
11	2-hydroxy-4-[(carbethoxymethyl)oxy]phenyl	31 (23–43)	3800 (1700–8400)	120
12	2-hydroxy-4-[(carbamoylmethyl)oxy]phenyl	6.5 (5.8–7.4)	1200 (600–2500)	190
13	2-hydroxy-4-[[[2-(dimethylamino)ethyl]carbamoyl]methyl]oxy]phenyl	8.4 (6.1–12)	77 (60–94)	9
14	2-hydroxy-4-[[[(2-aminoethyl)carbamoyl]methyl]oxy]phenyl	2.4 (0.74–7.4)	140 (130–190)	58
15	cyclopentyl	0.9 (0.8–1.1)	140 (120–170)	160
16	cyclohexyl	1.5 (1.1–2.1)	190 (170–210)	130
17	4-piperidinyl	620 (510–760)	6900 (1500–24000)	9.5
18	pyrazinyl	600 (440–820)	3600 (1400–8900)	6
19	cyclopentylmethyl	16 (10–28)	1900 (220–16000)	120
20	cyclohexylmethyl	39 (19–82)	2700 (1500–5100)	69
21	2-hydroxy-4-[[[(2-imidazol-4-ylethyl)carbamoyl]methyl]oxy]phenyl	100 (70–150)	2400 (1900–2800)	24
22	2-hydroxy-4-[[[[2-(*p*-hydroxyphenyl)ethyl]carbamoyl]methyl]oxy]phenyl	16 (5–45)	4400 (3900–5100)	270

[a] Values are means (95% confidence limits) versus N^6-([^{3}H]phenylisopropyl)adenosine binding to rat brain membranes as described.[5] [b] Values are means (95% confidence limits) for inhibition of 5′-(*N*-ethylcarbamoyl)adenosine-elicited stimulation of adenylate cyclase in human platelet membranes as described.[11]

Table II. Comparison of Activity of 1,3-Dipropylxanthines as Antagonists of A_2 Receptors in Human, Rat, and Guinea Pig Preparations and Solubility in Water

no.	A_2 receptors: K_B, μM, for inhibition of stimulation of adenylate cyclase: human platelet membranes[a]	rat PC12 cell membranes[a]	guinea pig brain slices[b]	solubility in water,[c] μM
1	7.4 (1.7–32)	5.4 (4.0–7.3)	2.7 ± 0.8	1600
2	2.1 (1.3–3.6)	2.3 (0.6–8.7)	0.3 ± 0.08	18
3	0.32 (0.23–0.44)	0.64 (0.37–1.1)	0.11 ± 0.02	180
4	0.054 (0.032–0.091)	0.17 (0.16–0.19)	0.072 ± 0.011	5
7	2.9 (2.2–3.9)	0.10 (0.066–0.16)[d]	0.95 ± 0.07	14
8	0.82 (0.29–2.3)	2.0 (1.2–3.1)	0.4 ± 0.08	11
9	0.18 (0.042–0.8)	0.13 (0.08–0.21)	0.98 ± 0.01	18
10	2.0 (1.4–2.7)	1.1 (0.6–1.9)		1100
12	1.2 (0.6–2.5)	0.43 (0.19–0.93)		5600
14	0.14 (0.13–0.19)	0.10 (0.018–0.59)		710
15	0.14 (0.12–0.17)	0.25 (0.10–0.59)		31
16	0.19 (0.17–0.21)	0.21 (0.062–0.71)		74

[a] Values are means (95% confidence limits) for inhibition of 5′-(*N*-ethylcarbamoyl)adenosine-elicited stimulation of adenylate cyclase in membranes as described.[11] [b] Values are IC_{50} ± SEM versus 2-chloroadenosine-elicited accumulations of cyclic AMP from ref 3 and 7. [c] Tris·HCl buffer, pH 7.4. [d] The K_B value is significantly lower than that reported in the literature.[11] It appears likely that the literature value is in error, perhaps due to solubility problems.

solubility (Table I). The effect of ortho and para substituents on the potency and selectivity of 8-phenyl xanthine as an A_1-receptor antagonist has been previously reported: A binding assay with N^6-[^{3}H]cyclohexyladenosine to rat cerebral cortical membrane was used to assess interaction with A_1 receptors and antagonism of 2-chloroadenosine-elicited cyclic AMP accumulation in guinea pig cerebral cortical slices was used to assess interaction with A_2 receptors.[3,7] In the present study, potency at A_1 receptors was based on a binding assay of N^6-([^{3}H]phenylisopropyl)adenosine to rat brain membranes, while potency at A_2 receptors was based on antagonism of 5′-(*N*-ethylcarbamoyl)adenosine-induced stimulation of adenylate cyclase activity in human platelet membranes (Table I) and in some cases rat pheochromocytoma PC12 cell membranes (Table II). It was noted that the activities of certain xanthine analogues at A_2 receptors in human platelet membranes proved to be different from the activities of the same xanthines versus 2-chloroadenosine-elicited cyclic AMP accumulation in guinea pig brain slices (Table II). Such differences in A_2-receptor activity can result in marked changes in apparent selectivities of certain analogues for A_1 versus A_2 receptors. Such differences in activities of xanthines at the A_2 receptors of human platelet membranes and guinea pig brain slices might be due to the differences in species, to differences in type of assay (slice versus membrane), or to differences in receptors of the A_2 subtype in different tissues. Differences between potencies of certain xanthines as antagonists of 5′-(*N*-ethylcarbamoyl)adenosine-elicited activation of adenylate cyclase in membranes from rat PC-12 cells or human platelets have been noted previously[11] and in the present study (Table II). The potencies for several xanthines in the three A_2 receptor assay systems are given in Table II together with water solubilities.

Earlier studies demonstrated that an anionic para substituent (CO_2^-, SO_3^-) on the 8-phenyl ring increased water solubility of 8-phenylxanthines, while lowering activity at an A_1 receptor and slightly increasing activity at an A_2 receptor:[3,7] The water-soluble 8-(*p*-carboxyphenyl)-1,3-

dipropylxanthine (**3**, solubility 180 μM) and 8-(*p*-sulfophenyl)-1,3-dipropylxanthine (solubility 16 mM) are relatively nonselective as adenosine receptor antagonists. But conversion of these anionic para substituents to neutral amides results in an increase in potency as well as selectivity.[3] Thus, the 8-(*p*-carbamoylphenyl)-1,3-dipropylxanthine (**4**) is a potent, somewhat selective A_1 antagonist (Table I). However, water solubility is reduced many fold to less than 10 μM (Table II). 8-(*p*-Sulfamoylphenyl)-1,3-dipropylxanthine is also a potent, somewhat selective A_1 antagonist.[3] The potency and selectivity of **4** suggested that the 8-*p*-carboxy compound (**3**) could serve as a functionalized congener for preparation of various N-substituted carboxamides. An initial study on this approach involved the coupling of a glycyl methyl ester to the 8-*p*-carboxy compound (**3**) to yield a derivative (**5**) more potent and selective than **3** at the A_1 receptor. The conversion of **3** to **5** proceeded in 60% yield, but efforts to prepare other derivatives of **3** such as the aminoethylamide did not prove successful. A similar approach from 8-(*p*-sulfophenyl)-1,3-dipropylxanthine and 8-(*p*-sulfophenyl)-1,3-dimethylxanthine has been utilized by others to prepare a variety of N-substituted 8-*p*-sulfonamides,[14] many of which are potent adenosine receptor antagonists.

Earlier studies,[3] demonstrated that disubstitution on the 8-phenyl ring can result in an increase in A_1 selectivity. Thus, the 2,4-dihydroxy-8-phenyl-1,3-dipropylxanthine (**8**) has slightly higher activity at A_1 receptors compared to the monosubstituted *p*-hydroxyphenyl analogue (**6**) and has a much higher selectivity for the A_1 receptor (Table I). A 2-hydroxy-4-methoxy analogue (**9**) is also a potent and selective (39-fold) A_1-antagonist (Table I). The water solubilities of both **8** and **9** are, however, low (Table II). On the basis of the application of the functionalized congener approach to the monosubstituted 8-(*p*-hydroxyphenyl)xanthines,[5,6,8,10,11] it appeared likely that coupling of a polar moiety to the highly potent and selective 8-(2,4-dihydroxyphenyl)xanthines could be used to increase the water solubility, while retaining the potency and selectivity. A functionalized congener approach was, therefore, applied to 8-(2,4-dihydroxyphenyl)xanthine (**8**). Substitution of a *p*-(carboxymethyl)oxy group for the *p*-methoxy group of 8-(2-hydroxy-4-methoxyphenyl)-1,3-dipropylxanthine (**9**) slightly decreases the activity at the A_1 receptor, while decreasing activity much more at the A_2 receptor, and yields a 54-fold selective A_1 antagonist (**10**) with a water solubility of 1.1 mM (Table I, II). Conversion of the functionalized congener **10** to 8-[2-hydroxy-4-[[(carbethoxy)methyl]oxy]phenyl]-1,3-dipropylxanthine (**11**) has little effect on potency at the A_1 receptor while decreasing it significantly at the A_2 receptor, resulting in a potent, 120-fold selective A_1 antagonist (Table I). The water solubility of the ester **11** would be expected to be low. A 2-hydroxy-4-(carbamoylmethyl)oxy analogue (**12**) displays a high activity and 190-fold selectivity for A_1 receptor (Table I). The water solubility is 0.56 mM (Table II). The coupling of *N*,*N*-dimethylethylenediamine moiety to the carbomethoxy group yields analogue **13**, with a selective increase in activity at the A_2 receptor: Analogue **13** is only 9-fold selective for the A_1 receptor (Table I). The coupling of an ethylenediamine moiety to the carbomethoxy group results in a marked increase in activity at the A_1 receptor, while causing only a modest increase in activity at A_2 receptors, yielding a potent and 58-fold selective A_1 antagonist (**14**) (Table I). Thus, analogues **10**, **12**, and **14** are very potent and selective A_1 antagonists (Table I) and have high water solubilities (Table II).

Histamide (**21**) and tyramide (**22**) derivatives of **10** were prepared as possible precursors for iodinated radioligands. The tyramide derivative was very potent (K_i = 16 nM) and selective (270-fold) for the A_1 receptor and thus appears to be an excellent candidate for preparation of an ^{125}I-labeled ligand.

The replacement of an 8-phenyl ring of **2** with an 8-cyclopentyl group yields a very potent xanthine (**15**) that is 160-fold selective for the A_1 receptor (Table I). Others[15-17] have now reported similar data on 8-cyclopentyl-1,3-dipropylxanthine and related 8-cycloalkyl-1,3-disubstituted-xanthines. The 8-cyclohexyl-1,3-dipropylxanthine (**16**) is also very potent and 130-fold selective for the A_1 receptor (Table I). The solubilities of the 8-cycloalkyl analogues (31 and 74 μM, respectively) are somewhat higher than that of the 8-phenyl analogue **2** (Table II). The high potency of the 8-cycloalkylxanthines suggests that nonplanar saturated 8-cycloalkyl rings can be better accommodated in a hydrophobic pocket of the A_1 and A_2 receptors than can the planar 8-aryl ring. Analogues with 8-cyclopentylmethyl and 8-cyclohexymethyl substituents (**19**, **20**) are not accommodated as well and have about 20-fold lower activities at adenosine receptors but are still highly selective for A_1 receptors (Table I). The effect of replacement of the saturated 8-cycloalkyl substituent with more polar substituents was investigated. Analogues with an 8-piperidinyl or 8-pyrazinyl substituent (**17**, **18**) have low activities at both A_1 and A_2 receptors. This indicates that the receptors cannot accommodate such polar moieties.

In summary, application of the functionalized congener approach to 8-monosubstituted arylxanthine such as 8-(*p*-carboxyphenyl)-1,3-dipropylxanthine can lead to potent A_1-selective analogues such as the 1,3-dipropyl-8-[*p*-[(carbomethoxymethyl)carbamoyl]phenyl]xanthine (**5**). Similarly, application of the functionalized congener approach to an 8-disubstituted arylxanthine such as 1,3-dipropyl-8-(2,4-dihydroxyphenyl)xanthine (**8**) has led to potent, highly selective, water soluble A_1 antagonists. Three of the analogues are the functionalized congener 1,3-dipropyl-8-[2-hydroxy-4-[(carboxymethyl)oxy]-phenyl]xanthine (**10**) and the analogues 1,3-dipropyl-8-[2-hydroxy-4-[(carbamoylmethyl)oxy]phenyl]xanthine (**12**) and 1,3-dipropyl-8-[2-hydroxy-4-[[[(2-aminoethyl)carbamoyl]methyl]oxy]phenyl]xanthine (**14**) with K_i values of 2–37 nM and selectivities of 50–200-fold for the A_1 receptor. The compounds have high water solubilities (Table II). Replacement of the 8-phenyl ring in 1,3-dipropylxanthines with 8-cycloalkyl groups resulted in highly potent and highly selective antagonists, as now reported by other groups.[15-17] Two of these compounds are 8-cyclopentyl-1,3-dipropylxanthine (**15**) and 8-cyclohexyl-1,3-dipropylxanthine (**16**) with K_i values of 0.9 and 1.5 nM and selectivities of 160- and 130-fold, respectively, for the A_1 receptor. The compounds have only moderate water solubility. Since polar groups are not tolerated in the 8-position close to the xanthine pharmacophore, a func-

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tionalized congener approach, therefore, appears necessary in developing more soluble congeners of 8-cyclopentyl- or 8-cyclohexyl-1,3-dipropylxanthine.

Experimental Section

Mass spectra were determined with a Finnegan 1015 quadrupole (chemical ionization with CH_4 or NH_3) and with VG 70/70 (electron-impact, 70-eV) mass spectrometers. The molecular ions with electron-impact spectra or the prominent protonated molecular ions with chemical-ionization spectra were consistent with the structures. Certain xanthine analogues, such as compounds 21 and 22, were further characterized by proton NMR spectra, which were taken on a Varian 220-MHz instrument in the Fourier transform mode. Melting points were taken on a Kofler block hot stage and are uncorrected. Thin-layer chromatographic analysis on silica gel with $CHCl_3$/MeOH mixture indicated the presence of a single compound in the final xanthine products. Elemental analysis gave results within ±0.4% of theoretical values. The synthesis of 1,3-dipropyl-8-phenylxanthine (2), 8-(*p*-carboxyphenyl)-1,3-dipropylxanthine (3), 8-(*p*-carbamoylphenyl)-1,3-dipropylxanthine (4), 1,3-dipropyl-8-(*p*-hydroxyphenyl)xanthine (6), 1,3-dipropyl-8-(*p*-methoxyphenyl)xanthine (7), 8-(2,4-dihydroxyphenyl)-1,3-dipropylxanthine (8), and 1,3-dipropyl-8-(2-hydroxy-4-methoxyphenyl)xanthine (9) has been described elsewhere.[2,5] 1,3-dipropyl-5,6-diaminouracil was prepared by standard procedures.[18,19]

1,3-Dipropyl-8-[*p*-[(carbomethoxymethyl)carbamoyl]phenyl]xanthine (5). To a mixture of 356 mg (1 mmol) of 1,3-dipropyl-8-(*p*-carboxyphenyl)xanthine (3) was added 0.28 mL (2 mmol) of Et_3N and 190 mg (1 mmol) of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride in 20 mL of DMF was added dropwise 130 mg (1 mmol) of glycine methyl ester hydrochloride in 15 mL of DMF. The reaction mixture was stirred overnight, and the solvent was removed in vacuo. H_2O was added to precipitate the product, which was removed by filtration and dried. Recrystallization with DMF/H_2O gave 257 mg (60%) of 1,3-dipropyl-8-[*p*-[(carbomethoxymethyl)carbamoyl]phenyl]-xanthine, mp 270 °C dec. Anal. ($C_{21}H_{25}N_5O_5$) C, H, N.

1,3-Dipropyl-8-[2-hydroxy-4-[(carbethoxymethyl)oxy]phenyl]xanthine (11). To a mixture of 4 g (29 mmol) of 2,4-dihydroxybenzaldehyde and 2.45 g of $NaHCO_3$ in 20 mL of DMF was added dropwise 3.4 mL (29 mmol) of ethyl iodoacetate, and the reaction mixture was heated at 70 °C for 48 h. After cooling, the reaction mixture was poured in 200 mL of H_2O. The resulting precipitate was filtered and dissolved in 100 mL of $CHCl_3$. This was extracted with saturated $NaHCO_3$ solution to remove any unreacted aldehyde. The organic layer was dried over Na_2SO_4 (anhydrous), filtered, and concentrated under reduced pressure. The product crystallized and was filtered and dried to give 4.56 g (70%) of 2-hydroxy-4-[(carboxymethyl)oxy]benzaldehyde ethyl ester.

To a solution of 192 mg (0.85 mmol) of 1,3-dipropyl-5,6-diaminouracil in 20 mL of MeOH/HOAc (5:1) was slowly added 194 mg (0.87 mmol) of 2-hydroxy-4-[(carboxymethyl)oxy]benzaldehyde ethyl ester in 15 mL of MeOH. The reaction mixture was stirred at room temperature for 15 min. A yellow precipitate was filtered, washed with MeOH, and dried to give 240 mg (65%) of 1,3-dipropyl-6-amino-5-[[2-hydroxy-4-[(carboxymethyl)oxy]-benzylidene]amino]uracil ethyl ester.

A mixture of 151 mg (0.35 mmol) of 1,3-dipropyl-6-amino-5-[[2-hydroxy-4-[(carboxymethyl)oxy]benzylidene]amino]uracil ethyl ester and 56.8 mg (0.35 mmol) of $FeCl_3$ in 10 mL of absolute EtOH was refluxed for 4 h. A precipitate, which appeared on cooling, was filtered, washed with EtOH, and dried to give 110 mg (73%) of 1,3-dipropyl-8-[2-hydroxy-4-[(carbethoxymethyl)-oxy]phenyl]xanthine: mp 251–252 °C; ^1H NMR (Me_2SO-d_6) δ 0.9 (m, 6 H), 1.2 (t, 3 H), 1.6 (m, 2 H), 1.78 (m, 2 H), 2.5 (s, 1 H), 3.82 (t, 2 H), 3.97 (t, 2 H), 4.18 (q, 2 H), 4.83 (s, 2 H), 6.52 (s, 1 H), 6.58 (d, 1 H), 8.0 (d, 1 H), 11.2 (s, 1 H). Anal. ($C_{21}H_{26}N_4O_6$) C, H, N.

1,3-Dipropyl-8-[2-hydroxy-4-[(carboxymethyl)oxy]phenyl]xanthine (10). A mixture of 76 mg (0.18 mmol) of 1,3-dipropyl-8-[2-hydroxy-4-[(carbethoxymethyl)oxy]phenyl]-xanthine and 2 mL (10%) of NaOH in 6 mL of DMF was refluxed for 20 min. The reaction mixture was allowed to cool, diluted with H_2O, and acidified with concentrated HCl. The resulting white precipitate was filtered, washed with H_2O, and dried to give 57.3 mg (80%) of 1,3-dipropyl-8-[2-hydroxy-4-[(carboxymethyl)oxy]phenyl]xanthine. Recrystallization from DMF/H_2O provided an analytical sample, mp 294 °C dec. Anal. ($C_{19}H_{22}N_4O_6$) C, H, N.

1,3-Dipropyl-8-[2-hydroxy-4-[(carbamoylmethyl)oxy]phenyl]xanthine (12). To a solution of 41.4 mg (0.1 mmol) of 1,3-dipropyl-8-[2-hydroxy-4-[(carboxymethyl)oxy]phenyl]xanthine in 2 mL of DMF was added 0.5 mL of $SOCl_2$, the reaction mixture was refluxed for 10 min, and the solvent was then removed in vacuo. The resulting oil was triturated with aqueous NH_3 and H_2O followed by extraction with several portions of $CHCl_3$. The combined organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The product that precipitated upon addition of ether was filtered and dried to afford 25 mg (62%) of 1,3-dipropyl-8-[2-hydroxy-4-[(carbamoylmethyl)oxy]-phenyl]xanthine. An analytical sample was obtained by recrystallization with DMF/Et_2O, mp 235–236 °C. Anal. ($C_{19}H_{23}N_5O_5 \cdot H_2O$) C, H, N.

1,3-Dipropyl-8-[2-hydroxy-4-[[[(2-aminoethyl)carbamoyl]methyl]oxy]phenyl]xanthine (14). To a solution of 152.7 mg (0.38 mmol) of 1,3-dipropyl-8-[2-hydroxy-4-[(carboxymethyl)oxy]phenyl]xanthine in 4 mL of DMF at 0 °C was added 0.053 mL (0.38 mmol) of Et_3N and 51.9 mg (0.38 mmol) of isobutyl chloroformate. The reaction mixture was stirred at 0 °C for 30 min followed by an addition of 0.03 mL (0.4 mmol) of ethylenediamine. After being stirred for a few minutes, the mixture was allowed to stand at 5 °C overnight. MeOH was added to precipitate the product, which was collected and dried to give 130 mg (35%) of crude 1,3-dipropyl-8-[2-hydroxy-4-[[[(2-aminoethyl)carbamoyl]methyl]oxy]phenyl]xanthine. Purification by chromatography in MeOH on Sephadex LH-20 provided an analytical sample, mp 213–214 °C. Anal. ($C_{21}H_{28}N_6O_5 \cdot {}^1/_2H_2O$) C, H, N.

1,3-Dipropyl-8-[2-hydroxy-4-[[[[2-(dimethylamino)ethyl]carbamoyl]methyl]oxy]phenyl]xanthine (13). To a solution of 64.5 mg (0.15 mmol) of 1,3-dipropyl-8-[2-hydroxy-4-[(carbethoxymethyl)oxy]phenyl]xanthine in 1 mL of DMF was added 1 mL of *N,N*-dimethylethylenediamine, and the reaction mixture was stirred for few minutes. The solvent was removed under a stream of nitrogen, and ether was added to precipitate the compound, which was filtered and dried. Recrystallization with DMF/MeOH gave 25 mg (45%) of 1,3-dipropyl-8-[2-hydroxy-4-[[[[2-(dimethylamino)ethyl]carbamoyl]methyl]oxy]-phenyl]xanthine, mp 257–258 °C. Anal. ($C_{23}H_{32}N_6O_5 \cdot {}^1/_2H_2O$) C, H, N.

1,3-Dipropyl-8-[2-hydroxy-4-[[[(2-imidazol-4-ylethyl)carbamoyl]methyl]oxy]phenyl]xanthine (21). To a solution of 15.3 mg (0.038 mmol) of 1,3-dipropyl-8-[2-hydroxy-4-[(carboxymethyl)oxy]phenyl]xanthine in 0.5 mL of DMF were added 5.3 μL (0.038 mmol) of Et_3N and 5.19 mg (0.038 mmol) of isobutyl chloroformate, and the reaction mixture was stirred at 0 °C for 30 min, followed by addition of 4.6 mg (0.04 mmol) of histamine free base in 0.4 mL of H_2O. After the mixture was stirred for few minutes, an oil separated out, which did not solidify on cooling. The oil was extracted with $CHCl_3$, and the $CHCl_3$ layer was washed with H_2O. The $CHCl_3$ layer was dried over Na_2SO_4, and the solvent was removed under vacuo to give 5.55 mg (30%) of a white solid, mp 207–208 °C. The compound was homogeneous by thin-layer chromatography and afforded a proton NMR spectrum in agreement with the expected structure: ^1H NMR (Me_2SO-d_6) δ 0.9 (m, 6 H), 1.6 (m, 2 H), 2.12 (s, 1 H), 3.29 (t, 2 H), 3.95 (m, 2 H), 4.1 (m, 2 H), 4.87 (s, 1 H), 5.0 (s, 2 H), 6.6–6.75 (m, 3 H), 7.4 (s, 1 H), 8.2 (d, 1 H), 11.0 (s, 1 H), the peaks at 1.7–1.8 (2 H) and 3.8 (2 H) are obscured by solvent peaks.

1,3-Dipropyl-8-[2-hydroxy-4-[[[[2-(*p*-hydroxyphenyl)ethyl]carbamoyl]methyl]oxy]phenyl]xanthine (22). To a solution of 15.3 mg (0.038 mmol) of 1,3-dipropyl-8-[2-hydroxy-4-[(carboxymethyl)oxy]phenyl]xanthine in 0.5 mL of DMF was added 5.3 μL (0.038 mmol) of Et_3N and 5.19 mg (0.038 mmol) of isobutyl chloroformate, and the reaction mixture was stirred at 0 °C for 30 min. To this was added a mixture of 6.94 mg (0.04

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mmol) of tyramine hydrochloride and 5.56 μL (0.04 mmol) of Et_3N in 1 mL of MeOH, and the reaction mixture was stirred for few minutes. An oil separated out, which solidified on cooling. The solid was filtered and dried to give 8.51 mg (43%) of the final product, mp 275 °C dec. The compound was homogeneous by thin-layer chromatography and afforded a proton NMR spectrum in agreement with the expected structure: ^1H NMR (Me_2SO-d_6) δ 0.9 (m, 6 H), 1.55 (m, 2 H), 1.72 (m, 2 H), 2.52 (s, 1 H), 3.85–4.4 (m, 6 H), 4.73 (s, 1 H), 4.90 (s, 2 H), 6.5–7.0 (6 H), 8.0 (d, 1 H), 9.2 (s, 1 H), 11.0 (s, 1 H).

8-Cyclopentyl-1,3-dipropylxanthine (15). To a solution of 0.24 mL (2.15 mmol) of cyclopentanecarboxylic acid in 10 mL of MeOH was added 0.34 mL (2.15 mmol) of diisopropylcarbodiimide followed by 469.5 mg (2.1 mmol) of 1,3-dipropyl-5,6-diaminouracil in 15 mL of MeOH. The reaction mixture was stirred at room temperature for 30 min, and the solvent removed in vacuo to give a solid residue. The residue was washed with ether, filtered, and dried to give 410 mg (61.5%) of 1,3-dipropyl-5-cyclopentanecarboxamido-6-aminouracil. The crude amide was refluxed for 20 min in 10 mL of MeOH and 15 mL (10%) of NaOH. The solvent was removed in vacuo, and H_2O was added to give a white precipitate, which was filtered and dried. Recrystallization with DMF/H_2O gave 360 mg (93%) of 8-cyclopentyl-1,3-dipropylxanthine, mp 199–200 °C. Anal. ($C_{16}H_{24}N_4O_2$) C, H, N.

8-Cyclohexyl-1,3-dipropylxanthine (16). To a solution of 565 mg (2.5 mmol) of 1,3-dipropyl-5,6-diaminouracil in 25 mL of MeOH/HOAc (5:1) was added dropwise 0.31 mL (2.5 mmol) of cyclohexanecarboxaldehyde, and the reaction mixture was stirred at room temperature for 20 min. The solvent was allowed to evaporate to give a yellowish white residue, which was washed with a small quantity of MeOH. The resulting white solid was recrystallized with DMF/H_2O to yield 520 mg (65%) of 8-cyclohexyl-1,3-dipropylxanthine. Oxidative cyclization had occurred spontaneously, mp 159–160 °C. Anal. ($C_{17}H_{26}N_4O_2$) C, H, N.

1,3-Dipropyl-8-pyrazinylxanthine (18). To a mixture of 75 mg (0.6 mmol) of 2-pyrazinecarboxylic acid and 0.1 mL (0.6 mmol) of diisopropylcarbodiimide in 6 mL of MeOH/DMF (5:1) was added dropwise 113 mg (0.5 mmol) of 1,3-dipropyl-5,6-diaminouracil in 5 mL of MeOH. The reaction mixture was stirred for 20 min at room temperature and volume reduced by evaporation. Et_2O was added to precipitate the product, which was filtered and dried to give 150 mg (90%) of 1,3-dipropyl-6-amino-5-pyrazinecarboxamidouracil. The crude amide was refluxed in 10 mL (10%) of NaOH and 2 mL of DMF for 20 min. The reaction mixture was allowed to cool, diluted with H_2O, and acidified with concentrated HCl to give a white precipitate, which was filtered and dried to afford 110 mg (78%) of 1,3-dipropyl-8-pyrazinylxanthine. Recrystallization with DMF/H_2O provided an analytical sample, mp 274–275 °C. Anal. ($C_{15}H_{18}N_6O_2 \cdot {}^1/_4H_2O$) C, H, N.

1,3-Dipropyl-8-(4-piperidinyl)xanthine (17). A solution of 12.92 g (100 mmol) of piperidine-4-carboxylic acid in 100 mL of 2 N NaOH was cooled to 0 °C. To this was added in small portions and with vigorous stirring a cooled solution of 42.8 mL (300 mmol) of benzylchloroformate in 125 mL of 4 N NaOH. The reaction mixture was stirred for 20 min and allowed to stand overnight at 5 °C. After acidification with 5 N HCl, the reaction mixture was extracted with ether. The ethereal layer was extracted with $KHCO_3$ solution, and the basic aqueous layer was again acidified with HCl. An oil separated out, which solidified on cooling to give 22.8 g (87%) of *N*-carbobenzoxypiperidine-4-carboxylic acid.

To a mixture of 325 mg (1.24 mmol) of *N*-carbobenzoxypiperidine-4-carboxylic acid and 0.19 mL (1.24 mmol) of diisopropylcarbodiimide in 10 mL of MeOH was added dropwise 280 mg (1.24 mmol) of 1,3-dipropyl-5,6-diaminouracil in 10 mL of MeOH. The reaction mixture was stirred for 2 h, and the solvent was then removed in vacuo. Acetone was added to precipitate the product, which was filtered, washed with acetone, and dried to give 370 mg (63%) of 1,3-dipropyl-6-amino-5-(*N*-carbobenzoxypiperidine-4-carboxamido)uracil.

To a solution of 6 mg (0.00026 g-atom) of sodium in 15 mL of EtOH was added 121.5 mg (0.26 mmol) of 1,3-dipropyl-6-amino-5-(N-carbobenzoxypiperidine-4-carboxamido)uracil in 10 mL of EtOH, and the reaction mixture was refluxed for 3 h. The solvent was removed in vacuo, and the residue was dissolved in H_2O and extracted with $CHCl_3$. The organic layer was dried with Na_2SO_4 and filtered, and the solvent was removed in vacuo to give 100 mg (85%) of 1,3-dipropyl-8-(4-carbobenzoxypiperidinyl)xanthine.

A solution of 100 mg (0.22 mmol) of 1,3-dipropyl-8-(4-carbobenzoxypiperidinyl)xanthine in 25 mL of MeOH/HOAc (5:1) and 2 mg of 10% Pd on C was hydrogenated at normal pressure for 1 h. The catalyst was removed by filtration, and the solvent was reduced in vacuo. Et_2O was added to precipitate the product, which was filtered and recrystallized with MeOH/Et_2O to afford 25 mg (36%) of 1,3-dipropyl-8-(4-piperidinyl)xanthine, mp 197–198 °C. Anal. ($C_{16}H_{25}N_5O_2 \cdot 1^1/_2H_2O$) C, H, N.

8-(Cyclopentylmethyl)-1,3-dipropylxanthine (19). To a mixture of 0.32 mL (2.5 mmol) of cyclopentylacetic acid and 0.4 mL (2.5 mmol) of diisopropylcarbodiimide in 20 mL of MeOH was added dropwise 425 mg (2 mmol) of 1,3-dipropyl-5,6-diaminouracil in 20 mL of MeOH, and the reaction mixture was stirred at room temperature for 20 min. The solvent was allowed to evaporate, and Et_2O was added to precipitate the product. This was washed with a small quantity of ethyl acetate, filtered, and dried to give 650 mg (97%) of 1,3-dipropyl-6-amino-5-(cyclopentylacetamido)uracil. The crude amide was refluxed in 20 mL (20%) of NaOH and 15 mL of EtOH for 15 min. The solvent was reduced in vacuo, and H_2O was added to precipitate the product, which was collected by filtration and dried to give 520 mg (85%) of 8-(cyclopentylmethyl)-1,3-dipropylxanthine. Purification by column chromatography in MeOH with Sephadex LH-20 provided an analytical sample, mp 158–159 °C. Anal. ($C_{17}H_{26}N_4O_2$) C, H, N.

8-(Cyclohexylmethyl)-1,3-dipropylxanthine (20). To a mixture of 355.5 mg (2.5 mmol) of cyclohexylacetic acid and 0.4 mL (2.5 mmol) of diisopropylcarbodiimide in 20 mL of MeOH was added dropwise 452 mg (2 mmol) of 1,3-dipropyl-5,6-diaminouracil in 20 mL of MeOH, and the reaction mixture was refluxed for 20 min. The solvent was allowed to evaporate, and Et_2O was added to precipitate the product, which was collected by filtration, washed with ethyl acetate, filtered, and dried to give 570 mg (81%) of 1,3-dipropyl-6-amino-5-(cyclohexylacetamido)uracil.

The crude amide was refluxed for 15 min in 20 mL (20%) of NaOH and 15 mL of EtOH. The solvent was removed in vacuo, and water was added to precipitate the product, which was filtered and dried to give 350 mg (65%) of 8-(cyclohexylmethyl)-1,3-dipropylxanthine. Purification by column chromatography in MeOH with Sephadex LH-20 provided an analytical sample, mp 137–138 °C. Anal. ($C_{18}H_{28}N_4O_2$) C, H, N.

Biochemical Assay. Inhibition of binding of 1 nM N^6-([^{3}H]phenylisopropyl)adenosine to A_1-adenosine receptors in rat cerebral cortical membranes was assayed as described.[5] Inhibition of binding by a range of concentrations of xanthine was assessed in triplicate in at least two separate experiments. Inhibition of the stimulation by *N*-[(ethylcarbonyl)amino]adenosine of adenylate cyclase at A_2 receptors in human platelet or rat pheochromocytoma PC12 cell membranes was assayed as described.[11] EC_{50} values for stimulation by 5′-(*N*-ethylcarbamoyl)adenosine were obtained from concentration–response curves in the absence or presence of xanthine in three experiments. K_B values were then calculated by using the Schild equation.

Acknowledgment. M. T. Shamim was supported by a grant from the International Life Sciences Institute (Washington, DC). D. Ukena was on leave from the Pharmakologisches Institut der Universität Heidelberg with support of the Deutsche Forschungsgemeinschaft (Uk 4.1-1).