Effect of Trifluoromethyl and Other Substituents on Activity of Xanthines at Adenosine Receptors

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An aryl *p*-(trifluoromethyl) substituent increases the affinity of 1,3-disubstituted 8-phenylxanthines at A_{2a}-adenosine receptors, while having little effect on affinity at A_1-adenosine receptors. In contrast, an aryl *p*-(trifluoromethyl) substituent has little effect on affinity of 3,7-disubstituted and 1,3,7-trisubstituted 8-phenylxanthines. An aryl *p*-sulfo substituent reduces affinity of all 8-phenylxanthines at A_1- and A_{2a}-adenosine receptors. An 8-(trifluoromethyl) substituent markedly reduces affinity of 1,3-dialkylxanthines at both A_1- and A_{2a}-adenosine receptors. In contrast, 8-(trifluoromethyl)caffeine retains affinity for A_{2a}-adenosine receptors, but does lose affinity for A_1-adenosine receptors. 8-Bromo-, 8-acryl-, and 8-pent-1-enylcaffeines are also selective for A_2-adenosine receptors, while 8-cyclobutylcaffeine is nonselective. 8-[*trans*-2-(*tert*-butyloxycarbonyl)vinylcaffeine is 20-fold selective for Aza vs A_1 receptors.

Structure–activity relationships for xanthines as adenosine receptor antagonists have been studied extensively over the last 2 decades.[1] High potency in xanthines that retain moderate water solubility and, hence, bioavailability and high selectivity for different classes of adenosine receptors have been the goals of such studies. Addition of an 8-phenyl substituent, particularly for 1,3-dipropylxanthines, yields extremely potent compounds with high selectivity for A_1-adenosine receptors.[2–13] Unfortunately, many of these 8-phenylxanthines have extremely low water solubility and hence poor bioavailability.[14] The 8-cycloalkylxanthines proved to be more water soluble and to be both very potent and selective for A_1-adenosine receptors. Xanthines with high selectivity for A_2-adenosine receptors had not been forthcoming, although certain 1,3,7-trisubstituted xanthines exhibited modest selectivity for A_2-adenosine receptors.[15,16] Recently certain 8-styryl-1,3,7-trisubstituted xanthines were reported to be highly selective for A_2-adenosine receptors.[17,18]

The effects of aryl substituents on the potency and selectivity of 8-phenyltheophylline have been analyzed. In one study on bovine brain A_1 receptors a quantitative structure–activity analysis for 45 aryl-substituted 8-phenyltheophyllines was presented.[4] This study was preceded by a more limited exploration of structure–activity relationships for aryl substituted 8-phenyltheophyllines.[3] Small electron-donating substituents at the ortho-position increased potency, while effects of para-substituents on activity were not readily correlated with electronic or steric effects or lipophilicity. Meta-substituents tended to decrease activity. Polar substituents such as *p*-sulfo or *p*-carboxy that are electron-withdrawing reduced potency at both A_1- and A_2-adenosine receptors, while conferring high water solubility.[5] Such xanthines have proven useful as peripheral adenosine receptor antagonists.[16,19]

The effects of xanthine substituents other than aryl at the 8-position have not been studied extensively. 8-Cycloalkyl-1,3-dialkylxanthines are potent and selective antagonists for A_1-adenosine receptors.[9,10,11,13] 8-Cycloalkyl-1,3,7-trialkylxanthines[11] and 8-styryl-1,3,7-trialkylxanthines[17,18] are selective antagonists for A_2-adenosine receptors.

The present study examines the effects at adenosine receptors of the electron-withdrawing trifluoromethyl group, either in the 8-position or in the para-position of 8-phenylxanthines and various other groups, such as halo, alkyl, or vinyl at the 8-position. Increases in potency at A_2-adenosine receptors occur on aryl *p*-(trifluoromethyl) substitution of certain 8-phenylxanthines. Various 8-substituted caffeines, including 8-(trifluoromethyl)caffeine and 8-vinylcaffeines are somewhat selective for A_2-adenosine receptors.

Chemistry

Synthesis of xanthines substituted at 1-, 3-, 7-, and 8-positions (Tables I and II) involved the acylation of appropriate 5,6-diaminouracil to afford 5-(acylamino)-6-aminouracils (e.g. **40–44**), which were then cyclized to the 8-arylxanthines (**2**, **5**, **8**, **9**, **11**), and 8-cycloalkylxanthine (**25**), or an 8-vinylxanthine (**26**) by sodium hydroxide. The 8-(*p*-sulfonamidophenyl)xanthine **11** was converted to the corresonding 8-(*p*-sulfophenyl)xanthine **10** with $NaNO_2$ in trifluoroacetic acid. Certain 1,3,7-trisubstituted 8-phenylxanthines (**13**, **15–19**) were prepared by alkylation of the appropriate disubstituted 8-phenylxanthine. 8-(Trifluoromethyl)-1,3-di-*n*-propylxanthine (**29**) and the corresponding theophylline derivative (**22**) were obtained directly from the diaminouracil after refluxing with trifluoroacetic acid and subsequent cyclization under basic conditions. An 8-acrylcaffeine derivative (**39**) was synthesized from 8-bromocaffeine and *tert*-butyl acrylate using the Heck reaction (Scheme I).[25] The *tert*-butyl ester was cleaved in trifluoroacetic acid to provide a carboxylic congener (**38**).

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Table I. Effect of Aryl Trifluorometyl and Sulfo Substituents on Activity of 8-Phenylxanthines at Adenosine Receptors of Rat Brain Membranes

no.	xanthine substituents	K_i (μM) or % inhibn[a]	
		A_1-binding, [^{3}H]PIA	A_{2a}-binding, [^{3}H]CGS 21680
1	1,3-dimethyl-8-phenyl	0.076 ± 0.012	0.97 ± 0.06
2	1,3-dimethyl-8-[*p*-(trifluoromethyl)phenyl]	0.15 ± 0.02	0.21 ± 0.02
3	1,3-dimethyl-8-(*p*-sulfophenyl)	1.0 ± 0.23	5.8 ± 0.7
4	1,3-dipropyl-8-phenyl	0.010 ± 0.004	0.14 ± 0.01
5	1,3-dipropyl-8-[*p*-(trifluoromethyl)phenyl]	0.0075 ± 0.0005	0.042 ± 0.004
6	1,3-dipropyl-8-(*p*-sulfophenyl)	0.14 ± 0.04	0.79 ± 0.08
7	1,3-dipropyl-8-(*p*-sulfonamidophenyl)	0.0085 ± 0.0011	0.075 ± 0.009
8	3,7-dimethyl-8-phenyl	3.4 ± 0.2	12 ± 1
9	3,7-dimethyl-8-[*p*-(trifluoromethyl)phenyl]	3.7 ± 0.2	10% (20 mM)
10	3,7-dimethyl-8-(*p*-sulfophenyl)	1.8% (250 μM)	0% (250 μM)
11	3,7-dimethyl-8-(*p*-sulfonamidophenyl)	33% (250 μM)	42 (250 μM)
12	8-phenyl-1,3,7-trimethyl	15 ± 3	16 ± 1
13	8-[*p*-(trifluoromethyl)phenyl]-1,3,7-trimethyl	17 ± 2	16 ± 1
14	8-(*p*-sulfophenyl)-1,3,7-trimethyl	3.3% (250 μM)	20 ± 1
15	1-allyl-3,7-dimethyl-8-phenyl	9.0 ± 0.1	12 ± 1
16	1-allyl-3,7-dimethyl-8-[*p*-(trifluoromethyl)phenyl]	5.7 ± 0.9	11 ± 1
17	1-allyl-3,7-dimethyl-8-(*p*-sulfophenyl)	35% (250 μM)	27 ± 4
18	1,7-diallyl-3-methyl-8-phenyl	0.66 ± 0.15	7.7 ± 0.5
19	7-allyl-1,3-dipropyl-8-[*p*-(trifluoromethyl)phenyl]	2.9 ± 0.1	4.2 ± 0.5

[a] Values are means ± SEM (n = 3) or are percent inhibition at highest concentration tested. The highest concentration is given in parentheses. In some cases higher concentrations could not be tested because of solubility.

Table II. Effect of 8-(Trifluorometbyl), 8-Methyl, 8-Halo, and 8-Vinyl Substituents on Affinity of Xanthines at Adenosine Receptors of Rat Brain Membranes

no.	substituents	K_i (μM) or % inhibn[a]	
		A_1 binding, [^{3}H]PIA	A_{2a}-binding, [^{3}H[CGS 21680
	Substituted Theophylline		
20	none	14 ± 3	8.0 ± 1.3
21	8-methyl	8.8 ± 3.0	34% (250 μM)
22	8-(trifluoromethyl)	0% (250 μM)	0% (250 μM)
23	8-chloro	39% (250 μM)	34 (100 μM)
24	8-bromo	10.2 ± 0.2	36% (100 μM)
25	8-cyclobutyl	0.19 ± 0.01	2.8 ± 0.1
26	8-pent-1-enyl	0.38 ± 0.05	0.44 ± 0.03
	Substituted Xanthine		
27	3-isobutyl-1-methyl	7 ± 21	5.8 ± 1.1
28	8-bromo-3-isobutyl-1-methyl	65 ± 21	10% (100 μM)
29	1,3-dipropyl	0.7 ± 0.3	2.6 ± 0.2
30	1,3-dipropyl-8-methyl	0.6 ± 0.1	2.8 ± 0.2
31	1,3-dipropyl-8-(trifluoromethyl)	4.5% (20 μM)	4.3% (20 μM)
	Substituted Caffeine		
32	none	29 ± 6	23 ± 2
33	8-methyl	4.9 ± 0.3	7.6 ± 0.8
34	8-(trifluoromethyl)	8% (100 μM)	29 ± 2
35	8-bromo	49 ± 5	12 ± 1
36	8-cyclobutyl	30 ± 2	19 ± 1
37	8-pent-1-enyl	9.1 ± 0.4	1.6 ± 0.1
38	8-(*trans*-2-carboxyvinyl)	3% (100 μM)	42 ± 7
39	8-[*trans*-2-(*tert*-butyloxycarbonyl)vinyl]	12 ± 2	0.61 ± 0.09

[a] Values are means ± SEM (n = 3) or are percent inhibition at highest concentration tested. See legend of Table I.

Results and Discussion

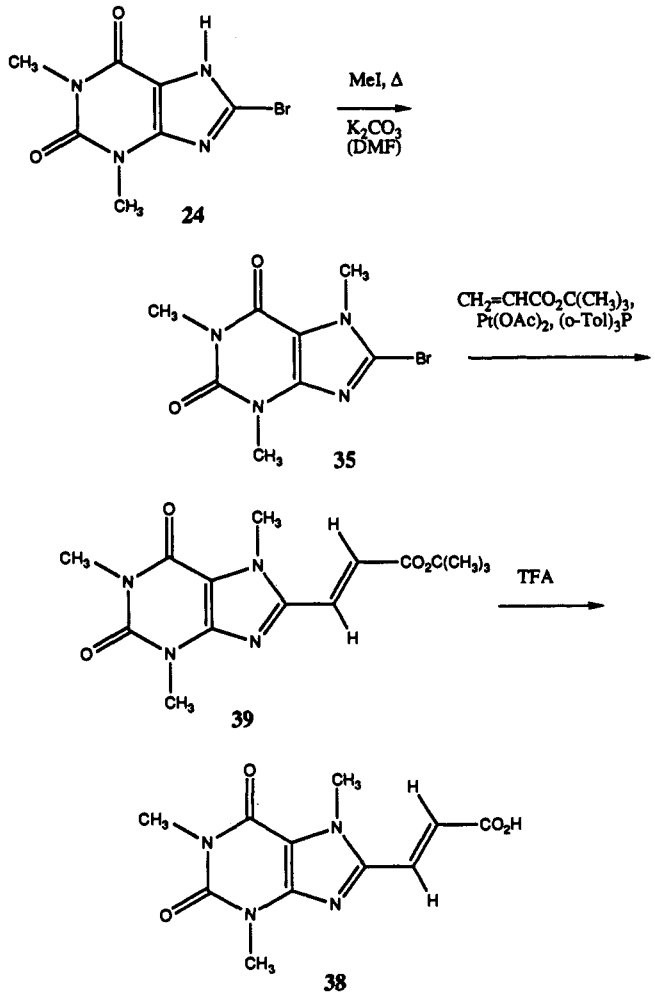
1,3-Dimethyl-8-phenylxanthine (8-phenyltheophylline, **1**) is widely used as a potent adenosine receptor antagonist, which is somewhat selective (~13-fold) for A_1-receptors. The presence of an electron-withdrawing *p*-(trifluoromethyl) substituent has little effect on affinity at rat brain A_1-receptors, but increases activity at rat brain A_{2a}-receptors by about 5-fold (Table I), resulting in a potent, but now nonselective, antagonist (**2**).

The effect of aryl substituents on the activity of 1,3-dimethyl-8-phenylxanthines at A_1-receptors has been studied.[3,4] Electron-donating substituents (hydroxy, amino) in the ortho-position appear to increase activity at A_1-receptors.[4] Correlations of activity with electronic or steric effects or lipophilicity of para-substituents were not clear.[4] At rat striatal A_{2a}-receptors *p*-amino, *p*-chloro, and *p*-methoxy substituents all increased the potency of 1,3-dimethyl-8-phenylxanthine by about 2-fold.[9] At both A_1- and A_{2a}-receptors, an anionic para-substituent (COO^-, $-SO_3^-$) markedly decreased potency.[4,7,9] In the present study, a *p*-(trifluoromethyl) group had the same effects on activity for 1,3-dipropyl-8-phenylxanthine (**5** vs **4**) as it had for 8-phenyltheophylline (**2** vs **1**), namely little effect on affinity at A_1-receptors and about a 3-fold increase in affinity at A_{2a} receptors (Table I).

3,7-Dimethyl-8-phenylxanthine, **8**, proved to be relatively weak, compared to 1,3-disubstituted 8-phenylxanthines (e.g. **1**) as an adenosine receptor antagonist (Table I). A *p*-(trifluoromethyl) substituent decreased affinity at A_{2a}-receptors (**9** vs **8**).

1,3,7-Trisubstituted 8-phenylxanthines, such as 8-phenylcaffeine, **12**, are relatively weak, compared to 1,3-

Scheme I. Synthesis of 8-Acrylxanthine Derivatives via the Heck Reaction



disubstituted 8-phenylxanthines, as adenosine receptor antagonists.[11] The effects of aryl substituents on activity have not been probed. In the present study, an electron-withdrawing *p*-(trifluoromethyl) group had little effect on affinity of either 8-phenyl-1,3,7-trimethylxanthine (8-phenylcaffeine) (**13** vs **12**) or of 1-allyl-3,7-dimethyl-8-phenylxanthine (**16** vs **15**). A *p*-(trifluoromethyl) substituent did decrease affinity of 1,7-diallyl-3-methyl-8-phenylxanthine (**19** vs **18**) at A_1-receptors by about 4-fold.

Among the 8-[*p*-(trifluoromethyl)phenyl]xanthines in this study, no compounds were developed that have any particular advantage in A_1-selectivity or potency over the corresponding 8-phenylxanthine, and the trifluoromethyl group would be expected to cause an undesirable reduction in water solubility.

In contrast, the high water solubility conferred by an aryl sulfo substituent has made 1,3-dimethyl-8-(*p*-sulfophenyl)xanthine [8-(*p*-sulfophenyl)theophylline, **3**] and 1,3-dipropyl 8-(*p*-sulfophenyl)xanthine, **6**, useful research tools since they do not penetrate into cells[20] or cross the blood–brain barrier.[21] Both are relatively weak, compared to the parent 8-phenylxanthines, as adenosine receptor antagonists, and both (**3** and **6**) are only modestly A_1-selective (Table I). An aryl sulfonamido substituent does not decrease activity of 1,3-dipropyl-8-phenylxanthine (**7** vs **9**). The resulting xanthine, **7**, is nearly as A_1-selective as the parent xanthine and might be more water soluble. In the 3,7-disubstituted and 1,3,7-trisubstituted 8-phenylxanthines, an aryl sulfo (or sulfonamido) substituent (**10**, **14**, **17**) also markedly reduces affinity at adenosine receptors. The 8-(*p*-sulfophenyl)-1,3,7-trimethylxanthine [8-(*p*-sulfophenyl)caffeine, **14**] is somewhat selective for the rat brain A_{2a}-receptor, compared to the rat brain A_1-receptor (Table I). However, in other A_1- and A_2-receptor comparisons the selectivity for **14** for A_{2a}-receptors was not apparent.[11]

Effects of substituents other than aryl, cycloalkyl, or aralkyl at the 8-position on activity of xanthines at adenosine receptors have received little attention.[2,13] An 8-methyl group (**21**, **30**, **33**) slightly increases the affinity of theophylline, 1,3-dipropylxanthine, and caffeine at rat brain A_1-receptors, while either reducing (**21**), increasing (**33**), or having little effect (**30**) on affinity at rat brain A_{2a}-receptors (Table I). An 8-(trifluoromethyl) substituent (**22**, **31**) nearly eliminates affinity of theophylline and 1,3-dipropylxanthine at both A_1- and A_2-receptors. 3-Isobutyl-1-methyl-8-(trifluoromethyl)xanthine was previously reported to have very low potency at A_1- and A_{2a}-receptors.[13] An 8-(trifluoromethyl) substituent (**34**) also reduces the affinity of caffeine at A_1-receptors, while having virtually no effect on its affinity at A_{2a}-receptors (Table II). 8-Halo substituents (Cl, Br) markedly reduce affinity of 1,3-disubstituted xanthines at adenosine receptors with the exception of 8-bromotheophylline (**24**), which has a slightly higher affinity at A_1 receptors than theophylline (Table II). 8-Bromocaffeine, **35**, has a slightly higher affinity than caffeine at both A_1 and A_{2a} receptors. An 8-cyclobutyl substituent (**25**) markedly increases affinity of theophylline for adenosine receptors (Table II), as was the case for 8-cyclopentyl- and 8-cyclohexyltheophyllines,[9,10,13] but the degree of A_1-selectivity (15-fold) is not as large as for 8-cyclopentyltheophylline.[9] 8-Pent-1-enyltheophylline, **26**, is a potent antagonist, but unlike the 8-cycloalkyltheophyllines, is not selective for A_1 receptors (Table II). In contrast, an 8-cyclobutyl substituent (**36**) has virtually no effect on the affinity of caffeine at adenosine receptors, and the 8-pent-1-enylcaffeine, **37**, shows a slight selectivity (6-fold) for A_{2a} receptors (Table II). In view of the marked A_2-selectivity of 8-styrylcaffeines,[17,18] two 8-acryl derivatives of caffeine, namely the water soluble 8-(*trans*-2-carboxyvinyl)caffeine, **38**, and 8-[*trans*-2-(*tert*-butyloxycarbonyl)vinyl]caffeine **39** were prepared. Both were A_2-selective (Table II). The 20-fold selectivity of **39** suggests that the functionalized congener approach[6] could be applied to such caffeines to develop a range of selective A_2-antagonists, e.g. esters and other derivatives of the carboxylic congener **38**. The A_2-selectivity of 8-vinylcaffeine derivatives demonstrates that a phenyl group, as in the structurally similar, A_2-selective 1,3,7-trialkyl-8-styrylxanthines,[17,18] is not required for this selectivity. The Pd-catalyzed Heck reaction[25] represents a new approach to 8-substitution, especially 8-vinyl substitution, of xanthines.

The present study indicates that the presence of 8-substituents, including a *p*-(trifluoromethyl) group on an 8-phenyl and 8-methyl, 8-(trifluoromethyl), 8-halo, 8-cycloalkyl, 8-pent-1-enyl and 8-acryl groups, can have markedly different effects on affinity for adenosine receptors when the xanthine is a caffeine analog (1,3,7-substituted) rather than a theophylline analog (1,3-substituted). Such differences suggest either that caffeine analogs bind differently than theophylline analogs to adenosine receptors or that the conformational effects of 7- and 8-position substituents are interdependent. 8-Substituted caffeine analogs, including the 8-styryl com-

pounds[7,18] and the present 8-acryl compounds (Table II), appear likely to provide long-sought potent and selective A_2-receptor antagonists.

Experimental Section

Chemistry. Compounds **1**, **3**, **4**, **6**, **7**, **14** were synthesized as reported[5,10,11] or were obtained from Research Biochemicals International (Natick MA). CHN analysis (±0.4% acceptable) were obtained for new compounds synthesized (**2**, **5**, **8**, **9–11**, **13**, **15–19**, **22**, **25**, **26**, **29**, **32**, **36**, **37–39**, **40–44**). All melting points were determined without correction using a Gallenkamp apparatus. UV/vis spectra were done with a Perkin-Elmer, Lambda 5 spectrometer; λ_{max} is reported in nanometers (log ϵ). ^{1}H-NMR spectra were determined with a Bruker WM-250 and are reported as δ in ppm relative to TMS as internal standard.

8-[4-(Trifluoromethyl)phenyl]-1,3-dimethylxanthine (2). 6-Amino-5-[[4-(trifluoromethyl)benzoyl]amino]-1,3-dimethyluracil (**40**, 2.5 g) was refluxed in 40 mL of 1 N NaOH and 10 mL of EtOH for 1 h. The hot solution was acidified with AcOH, and the precipitate was collected after cooling. Recrystallization from MeOH gave 1.68 g (71%) of colorless crystals. Mp: >350 °C. UV (MeOH): 225 sh (4.25), 236 (4.32), 264 sh (3.70), 318 (4.32).

8-[4-(Trifluoromethyl)phenyl]-1,3-di-*n*-propylxanthine (5). 6-Amino-5-[[4-(trifluoromethyl)benzoyl]amino]-1,3-di-*n*-propyluracil (**41**, 2.0 g) was refluxed in 50 mL of 2 N NaOH and 10 mL of EtOH for 1 h. The hot solution was acidified with AcOH, and after cooling, the precipitate was collected, washed with water, and dried at 100 °C to give 1.48 g (78%) of chromatographically pure crystals. Mp: 259–261 °C. UV (MeOH): 202 (4.32), 238 (4.29), 318 (4.29).

3,7-Dimethyl-8-phenylxanthine (8). 6-Amino-5-benzoyl-*N*-(methylamino)-1-methyluracil (**43**, 17 g, 70 mmol) was refluxed in 150 mL of 2 N NaOH and 50 mL of EtOH for 1 h. The hot solution was diluted with 200 mL of H_2O and then acidified with AcOH to give a colorless precipitate. After drying at 100 °C, 15.6 g (93%) of a chromatographically pure solid (mp: >300 °C) was obtained. UV (MeOH): 205 (4.33), 229 (4.23), 2.93 (4.11).

8-[4-(Trifluoromethyl)phenyl]-3,7-dimethylxanthine (9). 6-Amino-5-(4-trifluoromethylbenzoyl)-*N*-(methylamino)-1-methyluracil (**42**, 6.84 g, 20 mmol) was refluxed in 100 mL of 2 N NaOH and 20 mL of EtOH for 1 h. The hot solution was acidified with AcOH, and after cooling, the solid was collected to give 5.6 g (86%) of chromatographically pure crystals. Mp: 304–305 °C. UV (MeOH): 205 (4.36), 222 (4.31), 230 sh (4.28), 303 (4.15).

3,7-Dimethyl-8-(4-sulfophenyl)xanthine (10). 3,7-Dimethyl-8-(4-sulfonamidophenyl)xanthine (**11**, 16.75 g, 0.05 mol) was dissolved in 300 mL of trifluoroacetic acid, and then at room temperature a solution of 5 g of $NaNO_2$ in 10 mL of water was added dropwise with stirring. The reaction was diluted with 200 mL of H_2O and then stirred for another 2 h to form a crystalline precipitate. The chromatographically pure product was dried to provide 16.1 g (95%) of a crystalline powder. Mp: >300 °C. UV (pH 2): 228 sh (4.32), 235 (4.33), 297 (4.24).

3,7-Dimethyl-8-(4-sulfoamidophenyl)xanthine (11). 6-Amino-5-(4-sulfonamidobenzoyl)-*N*-(methylamino)-1-methyluracil (**44**, 25 g, 71 mmol) was refluxed in 150 mL of 2 N NaOH and 50 mL of EtOH for 1 h. The hot solution was diluted with 200 L of H_2O and then acidified with AcOH to form a colorless precipitate. After drying, 21.4 g (90%) of a chromatographically pure, crystalline powder (mp: >300 °C) was obtained. UV (pH 1): 228 (4.31), 235 sh (4.31), 301 (4.21).

8-[4-(Trifluoromethyl)phenyl]-1,3,7-trimethylxanthine (13). 8-[4-(Trifluoromethyl)phenyl]-1,3-dimethylxanthine (**2**, 1.63 g, 6 mmol) was treated in 100 mL of DMF with 3 g of K_2CO_3 and 5 mL of methyl iodide for 3 h with stirring at room temperature. The inorganic salts were filtered off, the filtrate was evaporated to dryness, and the residue was treated with 15 mL of water. The crystalline solid was recrystallized from MeOH to give 1.56 g (92%) of colorless crystals. Mp: 180–182 °C. UV (MeOH): 203 (4.30), 224 (4.28), 302 (4.16).

1-Allyl-3,7-dimethyl-8-phenylxanthine (15). A solution of 3,7-dimethyl-8-phenylxanthine (**8**, 15 g, 59 mmol) in 500 mL of DMF was treated with 45 g of K_2CO_3 and allyl iodide (14.4 g, 86 mmol) at 50 °C for 4 h with stirring. After cooling, the inorganic salts were filtered off, and the filtrate was reduced in volume by evaporation in vacuo. The residue was treated with 200 mL of H_2O to give a colorless solid, which on recrystallization from H_2O/EtOH gave 14.8 g (85%) colorless crystals. Mp: 177–178 °C. UV (MeOH): 230 (4.34), 293 (4.22).

1-Allyl-8-[4-((trifluoromethyl)phenyl]-3,7-dimethylxanthine (16). A solution of 8-[4-(trifluoromethyl)phenyl]-3,7-dimethylxanthine (**9**, 1.62 g, 5 mmol) in 100 mL of DMF was treated with 3 g of K_2CO_3 and allyl iodide (1.5 g) at room temperature for 3 h with stirring. The inorganic salts were filtered off, the filtrate was evaporated to dryness, and the residue was treated with 50 mL of H_2O to give a colorless solid. Recrystallization from H_2O/EtOH gave 1.55 g (85%) of colorless crystals. Mp: 150–152 °C. UV (MeOH): 204 (4.34), 223 (4.32), 230 sh (4.30), 303 (4.17).

1-Allyl-3,7-dimethyl-8-(4-sulfophenyl)xanthine (17). A suspension of **10** (16.7 g, 0.05 mol) in 300 mL of DMF was treated with 5 g of sodium hydride and 25 g of allyl iodide at room temperature for 8 h. The inorganic salts were filtered off, and the filtrate was evaporated to dryness. The residue was treated with 100 mL of acetone, to give a solid, which was recrystallized from 50 mL of 5 N HCl to give 13.6 g (73%) of colorless crystals. Mp: >300 °C. UV (pH 13): 203 (4.42), 235 (4.36), 298 (4.26).

1,7-Diallyl-3-methyl-8-phenylxanthine (18). A mixture of 3-methyl-8-phenylxanthine (2.42 g, 10 mmol) and 9 g of K_2CO_3 was treated in 100 mL of DMF with allyl iodide (4 g) at 50 °C with stirring for 3 h. The inorganic salts were filtered off, the filtrate was evaporated to dryness, and the residue was recrystallized from H_2O/MeOH to give 2.4 g (75%) of colorless crystals. Mp: 104–106 °C. UV (MeOH): 204 (4.44), 230 (4.33), 293 (4.20).

7-Allyl-8-[4-(trifluoromethyl)phenyl]-1,3-di-*n*-propylxanthine (19). A mixture of 8-[4-((trifluoromethyl)phenyl]-1,3-di-*n*-propylxanthine (**5**, 1.62 g, 4.3 mmol) and 3 g of K_2CO_3 were treated in 100 mL of DMF with 2 g of allyl iodide at room temperature with stirring for 3 h. The inorganic salts were filtered off, the filtrate was evaporated to dryness, and the residue was treated with 50 mL of water. The precipitate was recrystallized from H_2O/EtOH to give 1.4 g (80%) of colorless crystals. Mp: 63–65 °C. UV (MeOH): 205 (4.36), 222 (4.32), 230 sh (4.29), 302 (4.11).

8-(Trifluoromethyl)theophylline (22). 5,6-Diamino-1,3-dimethyluracil (8.5 g, 0.05 mol) was refluxed in 50 mL of trifluoroacetic anhydride for 20 min. The reaction mixture was evaporated to dryness and the residue treated with 20 mL of 2 N NaOH for 30 min under reflux. The hot solution was acidified to pH 3 and the precipitate collected after cooling. The colorless crystals were recrystallized from a mixture of H_2O/EtOH (3:2) to give 9.07 g (73%) of colorless crystals. Mp: 268–270 °C. UV (pH 13): 216 (4.03), 235 sh (3.61), 274 (4.08). ^{1}H NMR (DMSO-d_6): δ 3.4 (s, 3H, NCH_3), 3.51 (s, 3H, NCH_3), 13.8 (s, 1H, NH).

8-Cyclobutyl-1,3-dimethylxanthine (25). Compound **25** was made from cyclobutanoic acid according to the general procedure A given in ref 18 in 28% yield. Mp: >300 °C dec. ^{1}H NMR (DMSO-d_6): δ 1.8–2.1 (m, 2H, CH_2, 3 of Bu), 2.3 (m, 4H, CH_2, C2 and C4 of Bu), 3.23 (s, 3H, NCH_3), 3.43 (s, 3H, NCH_3), 3.58 (m, 1H, Cl of Bu). MS (EI): *m/e* 234, 206.

***trans*-8-Pent-1-enyl-1,3-dimethylxanthine (26).** Compound **26** was made from *trans*-2-hexenoic acid according to the general procedure A given in ref 18 in 8% yield and recrystallized from DMF/water. Mp: 218–223 °C dec. ^{1}H NMR (DMSO-d_6): δ 0.91 (t, 3H, CH_3), 1.46 (m, 2H, CH_2), 2.20 (q, 2H, CH_2, J = 7 Hz), 3.22 (s, 3H, NCH_3), 3.42 (s, 3H, NCH_3), 6.27 (d, 1H, J = 16 Hz), 6.81 (dt, 1H, J = 16 Hz, J = 7 Hz). MS (CI NH_3): *m/e* 266 (MNH_4^+, base), 241 (MH^+).

8-(Trifluoromethyl)-1,3-di-*n*-propylxanthine (29). 5,6-Diamino-1,3-di-*n*-propyluracil (4 g, 0.018 mol) was refluxed in 40 mL of trifluoroacetic anhydride for 1 h. The reaction mixture was evaporated to dryness, the residue was treated with 50 mL of 2 N NaOH under reflux for 30 min, and then acidified to pH 4, and the crystalline precipitate was collected. Recrystallization from H_2O/EtOH gave 4.3 g (80%) of colorless crystals. Mp: 172 °C. UV (pH 13): 216 (4.06), 235 sh (3.58), 275 (4.05).

8-(Trifluoromethyl)caffeine (32). 8-(Trifluoromethyl)-theophylline (**22**, 2.48 g, 0.01 mol) was dissolved in DMF (60 mL) and then K_2CO_3 (7.5 g, 0.05 mol) and methyl iodide (2.11 g, 0.015 mol) added and stirred for 2 h at room temperature. The insoluble

inorganic salts were filtered off, the filtrate was evaporated to dryness, and the residue was recrystallized from H_2O/EtOH (4:1) to give 2.18 g (83%) of colorless crystals. Mp: 131–133 °C. UV (MeOH): 207 (4.39), 232 sh (3.64), 281 (3.92). ^{1}H NMR (DMSO-d_6): δ 4.12, 3.55, 3.38 (each s, 3H, NCH_3). MS (EI): *m/e* 262, 193, 177.

8-Cyclobutyl-1,3,7-trimethylxanthine (36). Compound **36** was made from compound **25** according to procedure B given in ref 18. It was recrystallized from DMF/water (72% yield). Mp: 181–183 °C. MS (EI): *m/e* 248, 220.

***trans*-8-Pent-1-enyl-1,3,7-trimethylxanthine (37).** Compound **37** was made from compound **26** according to procedure B given in ref 18. It was recrystallized from DMF/water (64% yield). Mp: 142–143 °C. ^{1}H NMR (DMSO-d_6): δ 0.92 (t, 3H, CH_3), 1.50 (m, 2H, CH_2), 2.26 (q, 2H, J = 7 Hz), 3.21 (s, 3H, NCH_3), 3.41 (s, 3H, NCH_3), 3.89 (s, 3H, N_7CH_3), 6.57 (d, 1H, J = 16 Hz), 6.86 (dt, 1H, J = 16 Hz, J = 7 Hz). MS (EI): *m/e* 262, 247 (M – CH_3, base).

8-(*trans*-2-Carboxyvinyl)-1,3,7-trimethylxanthine (38). Compound **39** (76 mg, 238 μmol) was dissolved in 3 mL of trifluoroacetic acid and stirred for 1 h. After evaporation, the residue was triturated with ether to provide the pure product (55 mg, 88% yield). Mp: 278 °C dec. ^{1}H NMR (DMSO-d_6): δ 3.27 (s, 3H, NCH_3), 3.44 (s, 3H, NCH_3), 4.02 (s, 3H, N_7CH_3), 6.78 (d, 1 H, J = 15.4 Hz), 7.55 (d, 1 H, J = 15.4 Hz), 8.4 (br s, 1 H, COOH). MS (CI NH_3): *m/e* 265 (MH^+).

Alternately compound **38** was prepared from **39** in DMF/water (1:1) solution by saponification with sodium hydroxide in 49% yield.

8-[*trans*-2-(*tert*-Butyloxycarbonyl)vinyl]-1,3,7-trimethylxanthine (39). A mixture of 8-bromocaffeine (450 mg, 1.65 mmol), *tert*-butyl acrylate (0.390 mL, 2.69 mmol), $Pd(AcO)_2$ (3.7 mg, 16.5 μmol), tri-o-tolylphosphine (20 mg, 66 μmol), triethylamine (2 mL), and acetonitrile (2 mL) was warmed to 100 °C for 16 h with stirring in a capped tube. After cooling to room temperature, $CHCl_3$ was added and the mixture filtered. The organic layer was extracted twice with 1 N HCl, washed with brine several times, dried ($MgSO_4$), and then evaporated to dryness. The residue was treated with MeOH (1 mL), and hexane was added, to afford 152 mg of the crystalline product. The mother liquors were evaporated, and the remaining product was purified by preparative TLC (hexane/ethyl acetate 1:1) to give 49 mg (38% overall). Mp: 214–215 °C. ^{1}H NMR DMSO-d_6: δ 1.48 (s, 9H, CH_3), 3.22 (s, 3H, NCH_3), 3.42 (s, 3H, NCH_3), 4.03 (s, 3H, N_7CH_3), 6.73 (d, 1 H, J = 15 Hz), 7.51 (d, 1 H, J = 15 Hz). MS (CI NH_3): *m/z* 321 (MH^+).

6-Amino-5-[[4-(trifluoromethyl)benzoyl]amino]-1,3-dimethyluracil (40). 5,6-Diamino-1,3-dimethyluracil (2.06 g; 10 mmol) was suspended in 20 mL of dry pyridine and then 4-(trifluoromethyl)benzoyl chloride (2 mL, 14 mmol) was added and stirred for 4 h at room temperature. The mixture was then poured into 100 mL of water and the precipitate collected and recrystallized from H_2O/EtOH (7:3) to give 2.6 g (85%) of colorless crystals. Mp: 267–269 °C. UV (MeOH): 223 (4.23), 267 (4.29).

6-Amino-5-[[4-(trifluoromethyl)benzoyl]amino]-1,3-di-*n*-propyluracil Monohydrate (41). In 10 mL of dry pyridine was dissolved 5,6-diamino-1,3-di-*n*-propyluracil (2.26 g, 10 mmol) and then after cooling 4-(trifluoromethyl)benzoyl chloride (2 mL, 11.5 mmol) was added slowly with stirring. The mixture was stirred at room temperature overnight and then evaporated and the residue treated with 100 mL of water with stirring until a precipitate was formed. The solid was collected and recrystallized from H_2O/EtOH 7:3 to give 3.63 g (90%) of colorless crystals. Mp: 121–123 °C. UV (MeOH): 202 (4.29), 221 (4.20), 268 (4.27).

6-Amino-5-[4-(trifluoromethyl)benzoyl]-*N*-(methylamino)-1-methyluracil (42). 6-Amino-1-methyl-5-(methylamino)-uracil (8.5 g, 0.05 mol) was suspended in 100 mL of dry pyridine, and the mixture was cooled in an ice bath. 4-(Trifluoromethyl)-benzoyl chloride (12 g, 58 mmol) added dropwise with stirring. After stirring for 4 h at room temperature, the mixture was evaporated and the residue treated with 100 mL of water to form a crystalline precipitate. Recrystallization from H_2O/MeOH gave 12.45 g (72%) of colorless crystals. Mp: 298–300 °C. UV (MeOH): 205 (4.22), 214 sh (4.15), 267 (4.17).

6-Amino-5-benzoyl-*N*-(methylamino)-1-methyluracil (43). A suspension of 6-amino-1-methyl-5-(methylamino)uracil (17 g, 0.1 mol) in 200 mL of dry pyridine was cooled with ice and then benzoyl chloride (16 mL, 0.115 mol) was added dropwise with stirring. The reaction was continued overnight and then evaporated to dryness, and the residue was treated with 200 mL of H_2O to form a crystalline precipitate. Recrystallization from H_2O/ethanol gave 21 g (76%) of colorless crystals. Mp: >300 °C. UV (MeOH): 203 (4.24), 222 sh (4.05), 268 (4.12).

6-Amino-5-(4-sulfonamidobenzoyl)-*N*-(methylamino)-1-methyluracil Monohydrate (44). A suspension of 6-amino-5-(methylamino)-1-methyluracil (17 g, 0.1 mol) in 600 mL of H_2O/EtOH 1:1 was treated with 4-sulfamylbenzoic acid (20.1 g, 0.10 mol) and 1,3-dicyclohexylcarbodiimide (25 g, 0.12 mol) at room temperature with stirring. The crystalline precipitate was filtered to yield 2.94 g (83%) of chromatographically pure material. Mp: >300 °C. UV (MeOH): 202 (4.25), 223 (4.22), 266 (4.15).

Biology. Inhibition of binding of 1 nM [^{3}H]-N^6-[(*R*)-phenylisopropyl]adenosine (NEN, Boston, MA) to A_1-receptors in rat brain membranes in rat brain membranes or of 4 nM [^{3}H]-CGS 21680 (NEN, Boston, MA) to A_{2a}-receptors in rat striatal membranes was measured as described.[22,23] Nonspecific binding was defined for A_1-receptors with 10 μM 2-chloroadenosine and for A_{2a}-receptors with 20 μM 2-chloroadenosine. The K_i values were calculated from IC_{50} values by the method of Cheng and Prusoff[24] with K_D values of 1 nM for [^{3}H]N^6-[(*R*)-phenylisopropyl]-adenosine and 14 nM for [^{3}H]CGS 21680.

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