16b, 138787-20-9; 16f N^6-isomer, 138787-14-1; 16g, 138787-21-0; 17g, 138787-15-2; 17i, 138787-16-3; 18b, 61241-10-9; 18d, 138787-17-4; 18f, 138787-18-5; 18g, 138787-19-6; 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose, 6974-32-9.

Supplementary Material Available: Table I, analytical and spectral data (^{1}H NMR) of compounds **7a-e,g, 8g,i, 13f,h,k**, and **14f**; Table II, spectral data, ^{13}C NMR and ^{1}H NMR (anomeric protons), of compounds **9a-g, 10g,i, 17g,i, 18b,d,f,g, 19**, and **20**; Table III, spectral data, ^{13}C NMR and ^{1}H NMR (anomeric protons), of compounds **15f-i,k, 16b,f,g, 21**, and **22**; Table IV, cytostatic activity for all tested compounds; and Table V, antiviral activity for all tested compounds (9 pages). Ordering information is given on any current masthead page.

8-Polycycloalkyl-1,3-dipropylxanthines as Potent and Selective Antagonists for A_1-Adenosine Receptors

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With the aim of characterizing the hydrophobic interactions between xanthines and the A_1 receptor site, 1,3-dipropyl-8-substituted xanthines were synthesized. Introduction of a quaternary carbon and the conformationally restricted cyclopentyl moiety into the 8-position of xanthines enhanced the adenosine A_1 antagonism. 1,3-Dipropyl-8-(3-noradamantyl)xanthine (**42**) was identified to be a selective and the most potent A_1 receptor antagonist reported to date. Under our structure-activity relationship, the 8-substituent of xanthine antagonists and the N^6-substituent of adenosine agonists appears to bind to the same region of the A_1 receptor.

Introduction

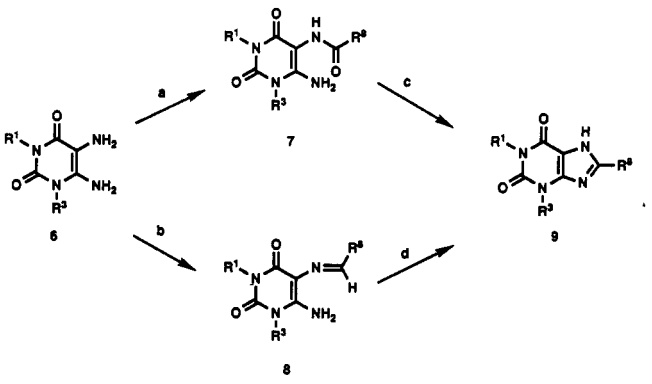
Adenosine elicits a wide variety of physiological responses[1] via interactions with two major subtypes of extracellular receptors, designated as A_1 and A_2. The two receptor subtypes were originally defined in terms of different effects on adenylate cyclase.[2,3] The A_1 receptor inhibits adenylate cyclase, whereas the A_2 receptor is stimulatory to this enzyme.

Considerable efforts to search for selective antagonists have been invested in order to elucidate the physiological role of adenosine and develop therapeutic agents.[4,5] Theophylline (**1**) and caffeine (**2**) (Figure 1) exert pharmacological effects primarily through blockade of adenosine receptors.[6] However, they are virtually nonselective antagonists and have weak affinity for A_1 and A_2 receptors. Studies of structure-activity relationships of xanthines[7-13] revealed that alkyl substitution such as propyl group at the 1- and 3-positions markedly increased affinity to A_1 and A_2 receptors. On the other hand, introduction of a hydrophobic substituent into the 8-position resulted in potent and selective A_1 antagonists such as 8-cyclopentyl-1,3-dipropylxanthine (**4**)[10,13,14] and 8-(dicyclopropylmethyl)-1,3-dipropylxanthine (**5**).[15] Although cycloalkyl or phenyl substitution at the 8-position of 1,3-dialkylxanthines was discovered to increase affinity to adenosine receptors, it is still uncertain what kinds of hydrophobic space at the 8-position are needed for the activity and selectivity.[16] As part of a program to develop adenosine A_1 antagonists as therapeutic agents, we synthesized a series of xanthines bearing a 5-membered heterocyclic, bulky alkyl, or cycloalkyl group at the 8-position and examined effects of substituents on A_1 and A_2 adenosine receptor binding.

Chemistry

Synthetic methods are outlined in Scheme I. Acylation of the appropriate 5,6-diaminouracil[17] (**6**) with a carboxylic acid or its acid chloride, followed by treatment with aqueous sodium hydroxide or phosphorous oxychloride

Scheme I[a]



[a] (a) R^8COCl, Py or R^8CO_2H, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride, dioxane-H_2O. (b) R^8CHO, AcOH, EtOH. (c) NaOH (aq), dioxane, reflux or $POCl_3$, reflux. (d) $FeCl_3$, EtOH, reflux.

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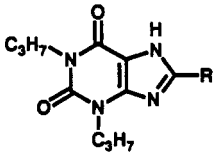
Table I. A_1 and A_2 Adenosine Receptor Binding of Reference Compounds

no.		K_i,[a] nM A_1	K_i,[a] nM A_2	K_i ratio A_2/A_1
1	(theophylline)	23000 ± 330 (8470)[b] (13000)[d] (4800)[e]	16000 ± 2200 (25300)[c] (5700)[f]	0.70
2	(caffeine)	100000 ± 2000 (29100)[b]	27000 ± 1700 (48100)[c]	0.27
3	(1,3-dipropylxanthine)	1400 ± 120 (450)[b] (1000)[d] (940)[e]	2400 ± 420 (5160)[c] (1900)[f]	1.7
4	(8-cyclopentyl-1,3-dipropylxanthine)	6.4 ± 0.35 (0.46)[b] (0.47)[e] (0.23)[g]	590 ± 48 (410)[c] (69)[f] (230)[h]	92
5	(8-(dicyclopropylmethyl)-1,3-dipropylxanthine)	3.0 ± 0.21	430 ± 5.8	140

[a] A_1 binding was carried out with N^6-[^{3}H]cyclohexyladenosine in guinea pig forebrain membranes as described,[20] and A_2 binding was carried out with N-[^{3}H]ethyladenosin-5′-uronamide in the presence of 50 nM cyclopentyladenosine in rat striatal membranes.[8] Concentration–inhibition curves were carried out in duplicate with five or more concentrations of each test agent, and IC_{50} values were calculated from computerization of logit log curve. IC_{50} values were converted to K_i values as described.[30] When the assays were carried out three or more times, standard errors (SEM) are given in the table. [b] A_1 binding measured as inhibition of N^6-[^{3}H]cyclohexyladenosine to rat whole brain (minus cerebellum and brainstem) membranes.[8,14a] [c] A_2 binding measured as inhibition of N-[^{3}H]ethyladenosin-5′-uronamide to rat striatal membranes.[8,13c] [d] A_1 binding measured as inhibition of N^6-[^{3}H]cyclohexyladenosine to guinea pig membranes.[20] [e] K_B values for reversal of adenylate cyclase inhibition by (*R*)-N^6-(2-[^{3}H]phenyl-1-methylethyladenosine in rat adipocytes.[10,13b] [f] K_B values for inhibition of adenylate cyclase stimulation by N-[^{3}H]ethyladenosin-5′-uronamide in human platelet membranes.[10,13b] [g] A_1 binding measured as inhibition of N^6-[^{3}H]cyclohexyladenosine to rat cortical membranes.[13d] [h] A_2 binding measured as inhibition of N-[^{3}H]ethyladenosin-5′-uronamide to rat striatal membranes.[13d]

under reflux, gave the corresponding xanthine (**9**). Condensation of 5,6-diaminouracil (**6**) with an aldehyde, followed by oxidative cyclization,[18] also gave the desired xanthine (**9**).

Table II. A_1 and A_2 Adenosine Receptor Binding of 8-(Five-membered heteroaryl)-1,3-dipropylxanthines



no.	R	K_i,[a] nM A_1	K_i,[a] nM A_2	K_i ratio A_2/A_1
10	2-furyl	560 (37)[b]	530 (640)[c]	0.95
11	4-sulfo-2-furyl	>10000	>10000	
12	2-thienyl	210 (16.1)[b]	1900 (381)[c]	9.0
13	*N*-methylpyrrol-2-yl	140	6000	43
14	1,2,3-thiadiazol-5-yl	4400	>10000	
15	1,2,5-thiadiazol-3-yl	5400	>10000	
16	2-methylthiazol-4-yl	410	2300	5.7
17	5-tetrazolyl	>10000	>100000	
18	2-indanyl	220	1700	7.7
19	9-fluorenyl	2900	>100000	>34
20	benzo[*b*]furan-2-yl	>10000	1200	
21	benzo[*b*]thiophen-2-yl	>100000	>100000	
22	*N*-methyl-2-indolyl	>100000	>100000	

[a] See footnote *a* in Table I. [b] A_1 binding measured as inhibition of (*R*)-N^6-2-[^{3}H]phenyl-1-methylethyladenosine to rat cortical membranes.[13c] [c] See footnote *c* in Table I.

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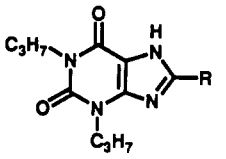
Table III. A_1 and A_2 Adenosine Receptor Binding of 8-Substituted-1,3-dipropylxanthines

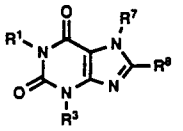


no.	R	K_i,[a] nM A_1	K_i,[a] nM A_2	K_i ratio A_2/A_1
23	2-propyl	49 ± 9.4	1500 ± 150	31
24	2-butyl	25 ± 0.58	1200 ± 73	48
25	3-pentyl	19 ± 1.0	570 ± 44	30
26	4-heptyl	78 ± 4.1	590 ± 49	7.6
27	*tert*-butyl	31	2300	74
28	2-methyl-2-butyl	23	1000	43
29	2-methyl-2-pentyl	25	2200	88
30	2-hydroxy-2-butyl	240	21000	88
31	3-hydroxy-3-pentyl	170	12000	71
32	cyclopropylmethyl	120	1200	10
33	2,2-dimethyl-1-propyl	49	6000	120
34	1-methylcyclohexyl	11	1200	110
35	2,2,5,5-tetramethylcyclopentyl	22	>100000	>4500
36	(1*R**,2*R**,5*R**)-bicyclo[3.3.0]octan-2-yl	3.5 ± 0.20	330 ± 4.7	94
37	(1*R**,2*S**,5*R**)-bicyclo[3.3.0]octan-2-yl	5.6 ± 0.19	560 ± 26	100
38	2-*endo*-norbornen-5-yl	4.3 ± 0.62	480 ± 18	110
39	2-*exo*-norbornen-5-yl	3.4 ± 0.41	210 ± 12	62
40	2-*endo*-norbornyl	3.8 ± 0.32	440 ± 42	120
41	2-*exo*-norbornyl	4.4 ± 0.13	290 ± 54	66
42	3-noradamantyl	1.3 ± 0.12	380 ± 30	290
43	(2-*exo*-norbornyl)methyl	80 ± 9.5	1000	13
44	1-adamantyl	13 ± 2.8 (82)[b]	5100 ± 1100 (>5000)[c]	390
45	(1-adamantyl)methyl	880	>100000	>110

[a] See footnote *a* in Table I. [b] See footnote *e* in Table I. [c] See footnote *f* in Table I.

Biological Results and Discussion

The structure–activity relationships of 8-substituted xanthines as adenosine antagonists have been investigated using radioligand binding assays with several different tissues and tests of receptor-mediated functions (adenylate cyclase activity). Evidence has accumulated for distinct tissue and species differences in adenosine receptors.[19] The sites labeled by N^6-[^{3}H]cyclohexyladenosine in guinea pig brain are the most similar to those found in man. Since we would like to develop adenosine A_1 antagonists for therapeutic uses, affinity of compounds to the adenosine A_1 receptor was measured with N^6-[^{3}H]cyclohexyladenosine binding in guinea pig forebrain membranes.[20] A_2 receptor binding was performed with *N*-[^{3}H]ethyl-



	R^1	R^3	R^7	R^8
1	methyl	methyl	H	H
2	methyl	methyl	methyl	H
3	propyl	propyl	H	H
4	propyl	propyl	H	cyclopentyl
5	propyl	propyl	H	dicyclopropylmethyl

Figure 1. Xanthine derivatives.

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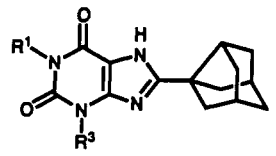
adenosin-5'-uronamide in rat striatal membranes.[8]

Our results of reference compounds such as 1–4 are presented in Table I along with comparable data from the literature. The K_i value of compound 4 in our assay was consistent with the Ukena's result (K_i = 3.9 nM).[19b] However it was larger than reported values (K_i = 0.46 or 0.23 nM) in the another assay using rat brain membranes.[13d,14a] This discrepancy might be explained by species differences.

We designed several 8-substituted xanthines bearing a 5-membered heterocyclic, alkyl, or polycycloalkyl group on the basis of compounds 4 and 5. Substitution of a furyl or thienyl group at the 8-position sparingly increased both A_1 and A_2 affinity as reported previously (compare 10 and 12 with 3).[13c,d] Thiadiazole substitution suppressed affinity (14 and 15). Five-membered heteroaromatic substitution did not alter A_1 selectivity (10, 12, and 16) except for compound 13 (43-fold A_1 selective) (Table II). This result seemed to indicate that 2'-substitution of 8-substituent had favorable effects on A_1 selectivity (compare 13 with 16). Additional fusion of a phenyl group decreased the antagonist potency (compare 18–22 with 4, 10, 12, and 13). The presence of an acidic group caused a reduction of affinity to both A_1 and A_2 receptors (11 and 17). Electrostatic effects of heteroaromatic rings did not play important roles in affinity to the A_1 receptor. Thus we examined the binding of alkyl derivatives (Table III). Alkyl substitution enhanced affinity to A_1 and A_2 receptors in general (compare 23–33 with 3). Incorporation of a quaternary carbon to 1'-position of 8-substituents enhanced A_1 selectivity (compare 27–29 with 23–26). A quaternary carbon bearing a hydroxyl group also seemed to increase A_1 selectivity (compare 30 and 31 with 24 and 26), but decrease affinity to A_1 and A_2 receptors. And furthermore, incorporation of a quaternary carbon to cycloalkyl group also seemed to enhance the selective A_1 antagonism (compare 34 and 35 with 4). Compound 35 was a highly A_1 selective antagonist (>4500-fold).

Conformation of the cyclopentyl group is not restricted at room temperature.[21] It is of great interest to examine whether interactions of the cyclopentyl group with the A_1 receptor need its optimum conformation. Thus conformation of the cyclopentyl group was fixed using bicyclo- and tricycloalkane systems which contain quaternary carbons in 1'- or 2'-position of the 8-substituent. This modification caused a remarkable enhancement of affinity to the A_1 receptor (36–42). In this series, stereoisomers had almost equipotent affinity to the A_1 receptor (compare 36, 38, and 40 with 37, 39, and 41). And furthermore, tricycloalkyl substitution resulted in a selective A_1 antagonism (42 and 44). Katsushima et al.[13b] also reported 8-(1-adamantyl)-1,3-dipropylxanthine (44) as an A_1 selective adenosine antagonist. Compound 42 (KW-3902) was 10-fold more potent than 44. Introduction of a quaternary carbon and a rigid cyclopentyl moiety to the 8-substituent contributed to the selective and potent A_1 antagonism of 42. Separation of the bicycloalkyl or tricycloalkyl substituent from the xanthines by a methylene group (43 and 45) caused much low potency and selectivity at the A_1 receptor. When the A_1 binding assay was carried out with N^6-[^{3}H]cyclohexyladenosine using rat forebrain membranes as described before,[8,14a] K_i values of compound 4 and 42 were 0.49 ± 0.06 and 0.19 ± 0.042 nM, respectively. These compounds are about 10-fold more potent at the A_1 receptor in rat brain than in guinea pig brain.

Table IV. Effects of Substituents in the 1- and 3-Positions on the Activity of 8-(3-Noradamantyl)xanthine Derivatives at A_1 and A_2 Adenosine Receptors[a]



no.	R^1	R^3	K_i,[a] nM A_1	K_i,[a] nM A_2	K_i ratio A_2/A_1
46	methyl	methyl	41 ± 3.1	1200 ± 33	29
47	ethyl	ethyl	7.1 ± 0.88	1600 ± 430	230
42	propyl	propyl	1.3 ± 0.12	380 ± 30	290
48	butyl	butyl	10 ± 0.83	1100 ± 77	110
49	methyl	isobutyl	15 ± 0.88	850 ± 130	57
50	H	propyl	370	>100000	>270

[a] See footnote *a* in Table I.

Since 1,3-dipropyl-8-(3-noradamantyl)xanthine (42) was identified to be a selective and the most potent A_1 receptor antagonist reported to date, the effects of other substituent in 1- and 3-positions were examined (Table IV). As expected from earlier studies, propyl substitution at both 1- and 3-positions was optimum to the potent and selective A_1 antagonism (46–50).

N^6-Cycloalkyl or N^6-bicycloalkyladenosines, such as N^6-cyclopentyladenosine (54; CPA)[22] or N^6-2-*endo*-norbornyladenosine (52)[23] are known to be selective A_1 agonists. As described above, the cycloalkyl or bicycloalkyl group also appeared to confer the optimal A_1 selectivity with 8-substituted xanthines. *These results may support the previous hypothesis*[8,16c] *that the 8-substituent of xanthines and the N^6-substituent of adenosine agonists bind to the same region of the A_1 receptor.* Comparative effects of the 8-substituent in antagonists and the N^6-substituent in agonists on A_1 binding were shown in Table VI. Effects of endo and exo stereochemistry on binding were similar in antagonists and agonists (compare 38 and 39 with 52 and 53). Among disubstituted methyl series, the same order in the binding activity was observed (antagonists, 25, 24, 23, 26; agonists, 57, 59, 60, 62, 64). The 3-pentyl group which is an open-chain analogue of the cyclopentyl group, gave the highest potency. Enhancement of affinity to the A_1 receptor by dicyclopropylmethyl substitution was observed both in an antagonist (5) and an agonist (51). On the other hand, effects of a quaternary carbon at 1'-position of the substituent were slightly different between antagonists and agonists. In xanthines, as mentioned above, incorporation of such a quaternary carbon enhanced A_1 selectivity without affecting affinity to the A_1 receptor (34, 44, 28, and 27). In agonists, a

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Table V. Analytical Data for 8-Substituted Xanthines

no.	synthetic method	% yield[a]	mp, °C (recryst solvent)	formula[b]
10	A	68	254–255[c] (2-PrOH/H_2O)	$C_{15}H_{18}N_4O_3$
11	B	44	267–268[d]	$C_{15}H_{17}N_4O_6SK\cdot0.3H_2O$
12	A	26	271–272[e] (2-PrOH)	$C_{15}H_{18}N_4O_2S$
13	C	36	258–260 (EtOH)	$C_{16}H_{21}N_5O_2$
14	C	27	268–269 (EtOH)	$C_{13}H_{16}N_6O_2S\cdot0.5H_2O$
15	C	59	236–238 (EtOH/H_2O)	$C_{13}H_{16}N_6O_2S\cdot0.25H_2O$
16	C	79	227–228 (EtOH)	$C_{15}H_{19}N_5O_2S$
17	C[f]	37	278–280 (EtOH/H_2O)	$C_{12}H_{16}N_8O_2\cdot0.75H_2O$
18	C	64	223–225 (2-PrOH/H_2O)	$C_{20}H_{24}N_4O_2$
19	C	35	202–203 (tol/cyclohex)	$C_{24}H_{24}N_4O_2\cdot0.5C_6H_{12}$
20	C	77	282–284 (EtOH)	$C_{19}H_{20}N_4O_3$
21	A	61	308–309 (EtOH)	$C_{19}H_{20}N_4O_2S$
22	C	41	252–253 (EtOH)	$C_{20}H_{23}N_5O_2\cdot0.2EtOH$
23	A	86	141–142 (EtOH/H_2O)	$C_{14}H_{22}N_4O_2$
24	C	49	90–91 (2-PrOH/H_2O)	$C_{15}H_{24}N_4O_2$
25	C	36	88–90 (2-PrOH/H_2O)	$C_{16}H_{26}N_4O_2$
26	C	27	109–110 (2-PrOH/H_2O)	$C_{18}H_{30}N_4O_2$
27	A	53	148–149 (2-PrOH/H_2O)	$C_{15}H_{24}N_4O_2$
28	A	76	105–106 (2-PrOH/H_2O)	$C_{16}H_{26}N_4O_2$
29	A	61	85–86 (MeOH/H_2O)	$C_{17}H_{28}N_4O_2$
30	A[f]	89	95–96 (hex)	$C_{15}H_{24}N_4O_3$
31	A[f]	46	126–127 (hex)	$C_{16}H_{26}N_4O_3$
32	C	56	170 (EtOH/H_2O)	$C_{15}H_{22}N_4O_2$
33	A	10	141–142 (EtOH/H_2O)	$C_{16}H_{26}N_4O_2$
34	A	32	98–99 (2-PrOH/H_2O)	$C_{18}H_{28}N_4O_2$
35	D	28	199–200 (EtOH/H_2O)	$C_{20}H_{32}N_4O_2$
36	C	47	100–102 (heptane)	$C_{19}H_{28}N_4O_2$
37	C	4	118–120 (heptane)	$C_{19}H_{28}N_4O_2$
38	C	52	122–123 (2-PrOH/H_2O)	$C_{18}H_{24}N_4O_2$
39	C	18	168 (EtOH)	$C_{18}H_{24}N_4O_2$
40	C	f	151–152 (2-PrOH/H_2O)	$C_{18}H_{28}N_4O_2$
41	C	f	140–143 (2-PrOH/H_2O)	$C_{18}H_{28}N_4O_2$
42	A	84	190 (EtOH/H_2O)	$C_{20}H_{28}N_4O_2$
43	C	40	120–121 (2-PrOH/H_2O)	$C_{19}H_{28}N_4O_2$
44	D	13	183–184[g] (2-PrOH/H_2O)	$C_{21}H_{30}N_4O_2$
45	E	49	178–180 (2-PrOH/H_2O)	$C_{22}H_{32}N_4O_2$
46	A	46	>300 (EtOH/H_2O)	$C_{16}H_{20}N_4O_2$
47	A	51	260–263 (EtOH/H_2O)	$C_{18}H_{24}N_4O_2$
48	A	85	160–161 (EtOH/H_2O)	$C_{22}H_{32}N_4O_2$
49	A	56	266–269 (EtOH/H_2O)	$C_{19}H_{26}N_4O_2$
50	A	57	>290 (dioxane/H_2O)	$C_{17}H_{22}N_4O_2$

[a] Overall yield from 5,6-diaminouracil (6). [b] All compounds were analyzed for C, H, N. [c] Lit.[13c] mp 252 °C. [d] Not recrystallized. [e] Lit.[13c] mp 259 °C. [f] See the Experimental Section. [g] Lit.[13b] mp 194–196 °C.

quaternary carbon at 1′-position of N^6-substituents (substitution at the S-4 subregion[23a]) was not well tolerated, resulting in lower affinity to the A_1 receptor (**55**, **56**, **58**, and **61**). Since **55**, **56**, **58**, and **61** were almost inactive toward the A_2 receptor,[23a] bulkiness around the 1′-position of N^6-substituents showed greater effects on the A_2 receptor binding than on the A_1 receptor binding. The sterical requirement of the 2′-position of the substituent also appeared to be different between antagonists and agonists (compare **32** and **33** with **65** and **63**).

In summary, introduction of a quaternary carbon or the conformationary restricted cyclopentyl moiety into the 8-position of 1,3-dipropylxanthines, enhanced the A_1 antagonism dramatically. The 8-substituent of xanthine antagonists and the N^6-substituent of adenosine agonists appears to bind to the same region of the A_1 receptor.

The further detailed hydrophobic interactions of xanthines with the A_1 receptor are under active studies in our laboratories. The pharmacological activities of these A_1 antagonists will be reported in due course.

Experimental Section

Melting points were determined on a Yanagimoto hot plate micro melting point apparatus and are uncorrected. Infrared (IR) spectra were measured on a JASCO IR-810 spectrophotometer. Proton nuclear magnetic resonance (^1H NMR) spectra were measured on a JEOL JNM-PMX60, HITACHI R-90H, or a JEOL JNM GX-270 spectrometer with tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were determined on a JEOL JMS-D300 instrument at an ionization potential of 70 eV. Microanalysis was performed on a Perkin-Elmer 2400CHN and agree within ±0.4% of calculated values unless otherwise noted. For column chromatography, Silica gel 60 (E. Merck, 0.063–0.200 mm) was used.

1,3-Dialkyl-5,6-diaminouracils were synthesized by using the method of Blicke and Godt.[17c] The following carboxylic acids were synthesized by published procedures: 1,2,3-thiadiazole-5-carboxylic acid,[24] 1,2,5-thiadiazole-3-carboxylic acid,[25] 2-methylthiazole-4-carboxylic acid,[26] 2,2,5,5-tetramethylcyclopentanecarboxylic acid,[27] and cyclopropylacetic acid.[28] The other

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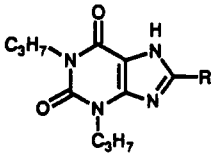
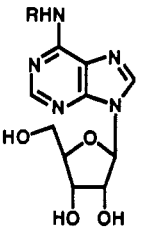
Table VI. Effects of Substituents in Agonists and Antagonists on Binding Affinities for A_1 Receptors





compounds	no.	N^6-[^{3}H]cyclohexyladenosine binding:[a] K_i, nM	no.	N^6-[^{3}H]cyclohexyladenosine binding:[c] K_i, nM
dicyclopropylmethyl	**5**	3.0	**51**	0.75
2-*endo*-norbornyl	**38**	3.8	**52**	0.32 (0.42)[d]
2-*exo*-norbornyl	**39**	4.4	**53**	0.70 (0.91)[d]
cyclopentyl	**4**	6.4 (0.46)[b]	**54**	0.32 (0.59)[d]
1-methylcyclohexyl	**34**	11	**55**	70
1-adamantyl	**44**	13	**56**	73
3-pentyl	**25**	19	**57**	0.75
2-methyl-2-butyl	**28**	23	**58**	16
2-butyl	**24**	(*RS*) 25	**59**	(*R*) 1.3
			60	(*S*) 0.80
tert-butyl	**27**	31	**61**	20
2-propyl	**23**	49	**62**	1.9
2,2-dimethyl-1-propyl	**33**	49	**63**	17
4-heptyl	**26**	78	**64**	3.3
cyclopropylmethyl	**32**	120	**65**	0.75

[a] See footnote *a* in Table I. [b] See footnote *g* in Table I. [c] A_1 binding measured as inhibition of N^6-[^{3}H]cyclohexyladenosine binding to rat brain membranes.[23a] [d] Reference 23c.

carboxylic acids were of analytical grade and were obtained from standard local sources unless otherwise noted.

Method A. 8-(Benzo[*b*]thiophene-2-yl)-1,3-dipropylxanthine (21). 5,6-Diamino-1,3-dipropyluracil[11b] (1.00 g, 4.4 mmol) was dissolved in 5 mL of pyridine, and then benzo[*b*]-thiophene-2-carbonyl chloride (956 mg, 4.9 mmol) was added portionwise with stirring at 0 °C. After 1 h of stirring at room temperature, the reaction mixture was concentrated under reduced pressure. A saturated $NaHCO_3$ solution was added, and the mixture was extracted with $CHCl_3$ three times. The combined organic layer was dried over Na_2SO_4, and the solvent was removed under vacuo to afford 1.54 g (90%) of 6-amino-1,3-dipropyl-5-[[(benzo[*b*]thiophene-2-yl)carbonyl]amino]uracil. The crude uracil was dissolved in 20 mL of 2 N NaOH and 20 mL of dioxane and heated under reflux for 10 min. After cooling to 0 °C, the product was precipitated by adjusting the pH to 4.0 with 4 N HCl. After filtration and washing with water, recrystallization from EtOH yielded 1.01 g (61%) of **21** as colorless needles:mp 308–309 °C. Anal. ($C_{19}H_{20}N_4O_2S$) C, H, N.

1,3-Dipropyl-8-(2-hydroxy-2-butyl)xanthine (30). To a solution of 2-hydroxy-2-methylbutyric acid (5.00 g, 42.3 mmol) and 4-(dimethylamino)pyridine (520 mg, 4.2 mmol) in pyridine (110 mL) was dropwise added acetic anhydride (4.8 mL, 50.8 mmol) at 0 °C with stirring. After 1 h of stirring at 0 °C, the reaction mixture was concentrated under reduced pressure. After dilution with 1% MeOH/$CHCl_3$ and filtration (silica gel), 2-acetoxy-2-methylbutyric acid (6.76 g, quantitative) was obtained as an oil. To a solution of this acid (2.84 g, 17.7 mmol) in pyridine (40 mL) was dropwise added thionyl chloride (0.97 mL, 13.3 mmol) at 0 °C with stirring. The reaction mixture was heated at 60 °C for 10 min, and 5,6-diamino-1,3-dipropyluracil (2.0 g, 8.85 mmol) was added portionwise. Then compound **30** was obtained in the same manner as **21** in 89% yield after recrystallization from hexane, mp 95–96 °C. The acetyl group was removed under the cyclization condition. Anal. ($C_{15}H_{24}N_4O_3$) C, H, N.

1,3-Dipropyl-8-(3-hydroxy-3-pentyl)xanthine (31). From 2-ethyl-2-hydroxybutyric acid, **31** was obtained as above in 46% yield after recrystallization from hexane, mp 126–127 °C. Anal. ($C_{16}H_{26}N_4O_3$) C, H, N.

(1′*R,2′*R**,5′*R**)-8-Bicyclo[3.3.0]octan-2-yl-1,3-dipropylxanthine (36) and (1′*R**,2′*S**,5′*R**) Isomer 37.** From *cis*-bicyclo[3.3.0]octane-2-carboxylic acid (Aldrich Chemical Co., Inc.), **36** and **37** were obtained in the same manner as **30** in 47 and 4% yields, respectively, after separation on silica gel column chromatography (eluent: 25% ethyl acetate/hexane) and recrystallization. **36**: mp 100–102 °C; ^{1}H NMR (DMSO-d_6) δ 13.12 (brs, 1 H), 3.94 (t, 2 H), 3.83 (t, 2 H), 2.75–2.50 (m, 3 H), 2.10–1.45 (m, 12 H), 1.42–1.35 (m, 1 H), 1.30–1.15 (m, 1 H), 0.95–0.85 (m, 6 H). Anal. ($C_{19}H_{28}N_4O_2$), C, H, N. **37**: mp 118–120 °C; ^{1}H NMR ($CDCl_3$) δ 12.30 (brs, 1 H), 4.11 (t, 2 H), 4.02 (t, 2 H), 3.30 (ddd, *J* = 6, 8, 14 Hz, 1 H), 3.00–2.85 (m, 1 H), 2.70–2.53 (m, 1 H), 2.25–0.90 (m, 20 H). Anal. ($C_{19}H_{28}N_4O_2$) C, H, N.

8-(2-*endo*-Norbornen-5-yl)-1,3-dipropylxanthine (38) and Exo Isomer 39. From bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (Lancaster Synthesis Ltd.), **38** and **39** was obtained as above in 52 and 18% yields, respectively, after separation on silica gel column chromatography (eluent: 25% ethyl acetate/hexane) and recrystallization. **38**: mp 122–123 °C; ^{1}H NMR (DMSO-d_6) δ 12.84 (brs, 1 H), 6.17 (dd, *J* = 3.2, 5.6 Hz, 1 H), 5.72 (dd, *J* = 2.7, 5.6 Hz, 1 H), 3.91 (t, 2 H), 3.82 (t, 2 H), 3.43 (ddd, *J* = 4.2, 4.2, 9.3 Hz, 1 H), 3.28 (brs, 1 H), 2.92 (brs, 1 H), 2.08 (ddd, *J* = 3.7, 9.3, 13.0 Hz, 1 H), 1.75–1.50 (m, 5 H), 1.45–1.35 (m, 2 H), 0.90–0.80 (m, 6 H). Anal. ($C_{18}H_{24}N_4O_2$) C, H, N. **39**: mp 168 °C; ^{1}H NMR (DMSO-d_6) δ 13.11 (brs, 1 H), 6.21 (d, *J* = 1.4 Hz, 2 H), 3.95 (t, 2 H), 3.84 (t, 2 H), 2.96 (brs, 2 H), 2.63 (ddd, *J* = 0.7, 4.2, 8.2 Hz, 1 H), 2.10 (ddd, *J* = 4.2, 4.2, 11.5 Hz, 1 H), 1.72–1.45 (m, 5 H), 1.35–1.22 (m, 2 H), 0.92–0.80 (m, 6 H). Anal. ($C_{18}H_{24}N_4O_2$) C, H, N.

8-(2-*endo*-Norbornyl)-1,3-dipropylxanthine (40) and Exo Isomer 41. From bicyclo[2.2.1]heptane-2-carboxylic acid (Lancaster Synthesis Ltd.), 8-(2-norbornyl)-1,3-dipropylxanthine (ca. 7:3 mixture of **40** and **41**) was obtained in 39% yield after recrystallization from heptane, mp 118–120 °C. The product was further purified by reverse-phase HPLC (YMC-Pack ODS R-354 column (300 × 50 mm, Yamamura Kagaku Co.) and eluting with 85% MeOH/H_2O) to pure **40** and **41**. **40**: mp 151–152 °C; ^{1}H NMR (DMSO-d_6) δ 13.00 (brs, 1 H), 3.97 (t, 2 H), 3.84 (t, 2 H), 3.21 (ddd, *J* = 4.2, 4.2, 11.6 Hz, 1 H), 2.55 (brs, 1 H), 2.28 (brs, 1 H), 1.90–1.22 (m, 11 H), 1.15–1.03 (m, 1 H), 0.95–0.82 (m, 6 H). Anal. ($C_{18}H_{26}N_4O_2$) C, H, N. **41**: mp 140–143 °C; ^{1}H NMR (DMSO-d_6) δ 12.99 (brs, 1 H), 3.94 (t, 2 H), 3.83 (t, 2 H), 2.79 (dd, *J* = 4.9, 8.5 Hz, 1 H), 2.39 (brs, 1 H), 2.31 (brs, 1 H), 2.08–1.96 (m, 1 H), 1.80–1.45 (m, 8 H), 1.38–1.12 (m, 3 H), 0.95–0.80 (m, 6 H). Anal. ($C_{18}H_{26}N_4O_2$) C, H, N.

Method B. 1,3-Dipropyl-8-(4-sulfo-2-furyl)xanthine Potassium Salt (11). To a solution of 2.50 g (11 mmol) of 5,6-diamino-1,3-dipropyluracil in 130 mL of MeOH and 6.5 mL of AcOH was slowly added portionwise 5-formyl-2-furansulfonic acid

sodium salt (2.19 g, 11 mmol) with stirring. After 2 h of stirring at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was suspended in 200 mL of EtOH, and $FeCl_3$ (1.80 g, 11 mmol) in 25 mL of EtOH was added with stirring. The mixture was refluxed for 4 h, then concentrated. After adjusting the pH to 8.0 with 1 N KOH, the residue was purified by DIAION HP-40 (Mitubishi Chemical Industries Co. Ltd.; eluent: 50% MeOH/H_2O) to afford 11 (2.08 g, 44%) as a colorless powder, mp 267–268 °C. Anal. ($C_{15}H_{17}N_4O_6SK \cdot 0.3H_2O$) C, H, N.

Method C. 1,3-Dipropyl-8-(*N*-methylpyrrol-2-yl)xanthine (13). To a solution of 5,6-diamino-1,3-dipropyluracil (3.00 g, 13 mmol) and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (3.31 g, 17 mmol) in 120 mL of dioxane/H_2O (1:1) was slowly added portionwise *N*-methyl-2-pyrrolecarboxylic acid (2.16 g, 17 mmol) with stirring, and the pH was maintained at 5.0 ± 0.5 by the dropwise addition of 2 N HCl. After 4 h of stirring at room temperature, the reaction mixture was treated with 2 N NaOH (60 mL) and heated under reflux for 10 min. After cooling to 0 °C, the product was precipitated by adjusting the pH to 4.0 with 4 N HCl. After filtration and washing with water, recrystallization from EtOH yielded 1.50 g (36%) of **13** as colorless needles, mp 258–260 °C. Anal. ($C_{16}H_{21}N_5O_2$) C, H, N.

1,3-Dipropyl-8-(5-tetrazolyl)xanthine (17). To a solution of ethyl 5-tetrazolecarboxylate[29] (2.18 g, 15.3 mmol) and triethylamine (4.26 mL, 30.6 mmol) in methylene chloride (60 mL) was portionwise added trityl chloride (3.84 g, 13.8 mmol) at 0 °C. After 16 h of stirring at room temperature, a saturated $NaHCO_3$ solution was added, and the mixture was extracted with $CHCl_3$ three times. The combined organic layer was dried over Na_2SO_4, and the solvent was removed under vacuo to yield the crude tritylated ester (5.32 g). To a solution of this ester (5.77 g) in THF (20 mL) and dioxane (50 mL) was added 1 N KOH (16 mL) with stirring. After 1.5 h of stirring at room temperature, the pH was adjusted to 6 with 4 N HCl. 5,6-Diamino-1,3-dipropyluracil (2.26 g, 10 mmol) followed by 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (2.30 g 12 mmol) was portionwise added, then **17** was obtained in the same manner as **13** in 37% yield after recrystallization from EtOH/H_2O, mp 278–280 °C. The trityl group was removed under the cyclization condition. Anal. ($C_{12}H_{16}N_8O_2 \cdot 0.75H_2O$) C, H, N.

Method D. 1,3-Dipropyl-8-(2,2,5,5-tetramethylcyclopentyl)xanthine (35). To a solution of 2,2,5,5-tetramethylcyclopentanecarboxylic acid[26] (2.54 g, 15 mmol) in pyridine (40 mL) was dropwise added thionyl chloride (1.20 mL, 16.5 mmol) at 0 °C with stirring. The reaction mixture was heated at 60 °C for 10 min, and then 5,6-diamino-1,3-dipropyluracil (3.39 g, 15 mmol) in pyridine (10 mL) was slowly added with stirring at 0 °C. After 1 h of stirring at 0 °C, the reaction mixture was concentrated under reduced pressure. A saturated $NaHCO_3$ solution was added, and the mixture was extracted with $CHCl_3$ three times. The combined organic layer was dried over Na_2SO_4, and the solvent was removed under vacuo. Purification on silica gel column chromatography (eluent:25% ethyl acetate/hexane) afforded 6-amino-1,3-dipropyl-5-[[(2,2,5,5-tetramethylcyclopentyl)carbonyl]amino]uracil (2.69 g, 47%). A solution of 3.10 g (8.20 mmol) of this uracil in 20 mL of $POCl_3$ was refluxed for 1.5 h. The excess $POCl_3$ was removed in vacuo, and the residue was neutralized with 50% NH_4OH. Usual workup as above and purification on silica gel column chromatography (eluent:25% ethyl acetate/hexane), followed by recrystallization from EtOH/H_2O afforded 1.75 g (28% overall) of **35** as colorless needles, mp 199–200 °C. Anal. ($C_{20}H_{32}N_4O_2$) C, H, N.

Method E. 8-(1-Adamantyl)methyl-1,3-dipropylxanthine (45). To a solution of 5,6-diamino-1,3-dipropyluracil (2.00 g, 8.85 mmol) and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (2.04 g, 10.6 mmol) in 60 mL of dioxane/H_2O (2:1) was added portionwise 1-adamantaneacetic acid (2.06 g, 10.6 mmol) with stirring, and the pH was maintained at 5.0 ± 0.5 by the dropwise addition of 2 N HCl. After 2 h of stirring at room temperature, water was added and the mixture was extracted with $CHCl_3$ three times. The combined organic layer was dried over Na_2SO_4, and the solvent was removed under vacuo to afford 4.02 g (quantitative) of 6-amino-1,3-dipropyl-5-[[(1-adamantyl)-acetyl]amino]uracil. The crude uracil was treated with $POCl_3$ (40 mL) as described above, and the mixture was heated under reflux for 2 h. Usual workup and purification on silica gel column chromatography (eluent:25% ethyl acetate/hexane), followed by recrystallization from 2-propanol/H_2O afforded 1.69 g (49%) of **45** as colorless needles, mp 178–180 °C. Anal. ($C_{22}H_{32}N_4O_2$) C, H, N.

Biochemistry. N^6-[^{3}H]Cyclohexyladenosine A_1 Binding.[20] Guinea pig forebrain was homogenized in ice-cold 50 mM Tris (tris(hydroxymethyl)aminomethane)-HCl pH 7.7 buffer with a Polytron homogenizer. The homogenate was centrifuged at 50000*g* for 10 min (0–5 °C), and the pellet was washed in fresh buffer. The pellet was resuspended in 10 vol (w/v) of buffer containing adenosine deaminase (ADA; 2.0 units/mL; Sigma Chemical Co.). Following a 30-min incubation at 37 °C, the suspension was cooled on ice and recentrifuged as before, and the final pellet was resuspended in fresh buffer (10 mg tissue/mL) for use in the binding assay.

The homogenate was dispensed (1.0 mL aliquots) into glass tubes containing 1.1 nM N^6-[^{3}H]cyclohexyladenosine (sp act = 27 Ci/mmol; NEN Du Pont), 10 mg of tissue, 50 mM Tris-HCl buffer, and xanthine solution in aqueous dimethyl sulfoxide (the final concentration of dimethyl sulfoxide was less than 0.9%). Nonspecific binding was defined by the addition of 10 μM (*R*)-N^6-(2-phenyl-1-methylethyl)adenosine. Following a 90-min incubation at 25 °C, binding was terminated by filtering samples over Whatman GF/C glass filters using a Brandel cell harvester apparatus. The filters were washed three times with 5 mL of ice-cold buffer, and the radio activities were counted (Ex-H; Wako Pure Chemical Industries, Ltd.) using a liquid scintillation counter (Packard Instrument Co.). Concentration–inhibition curves were carried out in duplicate with five or more concentrations of each test agent, and IC_{50} values were calculated from computerization of logit log curve. The inhibition constants (K_i) were calculated according to the Cheng and Prusoff equation.[30] When the assays were carried out three or more times, standard errors (SEM) are given in the table.

N^6-[^{3}H]Cyclohexyladenosine A_1 binding assay using rat forebrain membranes was performed according to the same protocol as above.

***N*-[^{3}H]Ethyladenosin-5′-uronamide A_2 Binding.**[8] Rat striatal tissue was homogenized in ice-cold 50 mM Tris-HCl pH 7.7 buffer, the homogenate was centrifuged as above, and the pellet was washed in fresh buffer and recentrifuged. The final pellet was resuspended in fresh buffer (5 mg tissue/mL).

The homogenate was dispensed (1.0-mL aliquots) into glass tubes containing 3.8 nM *N*-[^{3}H]ethyladenosin-5′-uronamide (26 Ci/mmol; Amersham Corp.), 5 mg of tissue, 50 mM Tris-HCl pH 7.7 buffer containing 10 mM $MgCl_2$, 0.1 unit/mL ADA, 50 nM N^6-cyclopentyladenosine, and xanthine solution (aqueous dimethyl sulfoxide). Nonspecific binding was determined by the addition of 100 μM N^6-cyclopentyladenosine. Following a 2-h incubation at 25 °C, the reaction was stopped by vacuum filtration, and samples were quantified as above.

For the assays, IC_{50} values or inhibition constants (K_i) were calculated as above. When the assays were carried out three or more times, standard errors (SEM) are given in the table.

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