Adenosine A_1 Antagonists. 3.[†] Structure–Activity Relationships on Amelioration against Scopolamine- or N^6-((*R*)-Phenylisopropyl)adenosine-Induced Cognitive Disturbance

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The effects of a variety of adenosine A_1 and A_2 antagonists on N^6-((*R*)-phenylisopropyl)adenosine (*R*-PIA)- and scopolamine-induced amnesias were investigated in rodents in order to clarify the role of adenosine receptors in learning and memory. Some of the selective adenosine A_1 antagonists exhibited antiamnesic activities at several doses where they did not induce an increase of spontaneous locomotion. These results suggest that the blockade of A_1 receptors is more important than that of A_2 receptors in learning and memory. Detailed studies of structure–activity relationships of adenosine A_1 antagonists in two amnesia models demonstrated that there were three types of adenosine A_1 antagonists: (A) Compounds **3–5** (8-substituted 1,3-dipropylxanthines) ameliorated the shortened latency in both models. (B) Compounds **7–11** (8-substituted 1,3-dialkylxanthines) and **19–21** (imidazo[2,1-*i*]purin-5(4*H*)-one derivatives) ameliorated the shortened latency in the (*R*)-PIA-induced amnesia model but not in the scopolamine-induced amnesia model. (C) Compounds **14–16** ameliorated the shortened latency in the scopolamine model but not in the (*R*)-PIA model. Aminophenethyl-substituted compounds C did not exhibit adenosine A_1 antagonism in vivo presumably due to rapid metabolism. The dramatic change in the activities of A and B could not be explained by their simple pharmacokinetic differences because both types of compounds showed clear blockade of central adenosine A_1 receptors in the (*R*)-PIA model. 8-(3-Dicyclopropylmethyl)-1,3-dipropylxanthine (**5**) (KF15372) was chosen for further studies and is currently under preclinical development as a cognition enhancer.

Introduction

Adenosine and its analogs depress both spontaneous and evoked neuronal firing.[1] Furthermore, adenosine has been shown to modulate neuronal function via receptor-mediated mechanisms. There are two major subtypes of adenosine receptors, designated as A_1 and A_2. A_1 receptors inhibit whereas A_2 receptors stimulate adenylate cyclase.[2,3] The majority of adenosine receptors are localized in the brain. A_2 receptors are found predominantly in the striatum, whereas A_1 receptors predominate in the hippocampus and in the cortex.[4] A_1 receptors in the hippocampus are densely concentrated in the CA1 and CA3 regions.[5,6] In general, the presynaptic A_1 receptors cause an inhibition of the release of neurotransmitters and the postsynaptic A_1 receptors cause a decrease in excitability.[5] Recent work has revealed that A_1 receptors also play a role in the development of long-term potentiation (LTP) particularly in the CA1 region.[7,8] LTP is one of the most striking examples of synaptic plasticity which is postulated to be an underlying event in learning and memory.[9] From these results, A_1 antagonists can be expected to enhance the release of various neuronal transmitters such as acetylcholine to depolarize postsynaptic neurons, to increase LTP, and thus to be useful for treatment of cognitive deficiency in humans.[10]

It is well known that scopolamine (a central muscarinic receptor antagonist) induces a similar cognitive disturbance in humans and animals.[11] Scopolamine-induced impairment of retention was blocked by the cholinomimetic, physostigmine, but not by *d*-amphetamine, leading Drachman to suggest that the amnesic effect of scopolamine was specifically due to its blocking of cholinergic receptors.[11c] Passive avoidance is a behavioral task widely employed to assess amounts of learning and memory. Thus, the scopolamine-induced amnesia model using passive avoidance has been used in evaluating the action of drugs such as cognition enhancers.[12] On the other hand, our group[13] and Barraco's group[14] found that a systematically administered A_1 receptor agonist such as N^6-((*R*)-phenylisopropyl)adenosine ((*R*)-PIA) or N^6-cyclohexyladenosine, but not *N*-ethyladenosin-5′-uronamide (NECA; A_1 and A_2 agonist), impaired dose-dependently memory of passive avoidance behavior. The findings from these studies suggest that selective activation of a central population of A_1 receptors, presumably concentrated densely in the hippocampus, impairs retention of a passive avoidance response, possibly via influence on hippocampal excitability. Recently, we have succeeded in obtaining a series of selective A_1 and A_2 antagonists, respectively.[15] Thus, the present study describes the effects of selective subtype antagonists and nonselective antagonists such as theophylline (**1**) and caffeine (**2**) on scopolamine-induced amnesia in rats and on (*R*)-PIA-induced amnesia in mice for assessing interactions between endogenous adenosine and A_1 receptors in learning and memory.

Chemistry

Syntheses of compounds **3–5** and **8–11** were described previously.[15a,b] As shown in Scheme I, 2-thioxanthine derivatives (**6** and **7**) and 8-styrylxanthine derivatives (**12**, **13**) were synthesized from corresponding 5,6-diamino-

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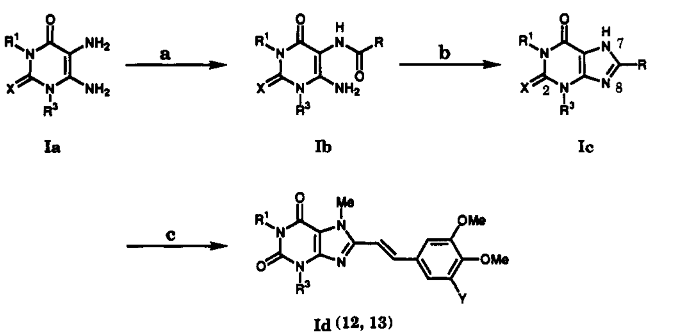
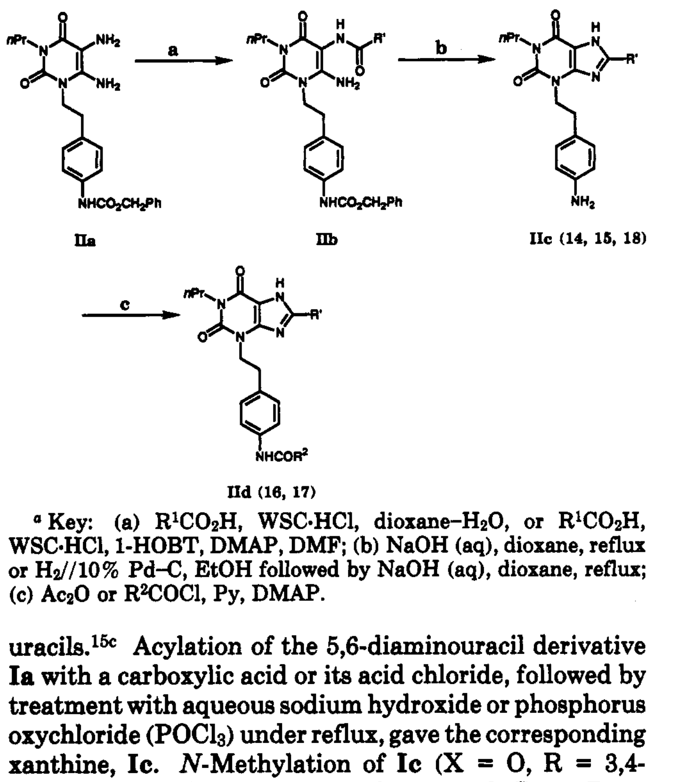
Scheme I[a]



[a] Key: (a) RCOCl, Py, or RCO_2H, 1-ethyl-3-[3-(dimethylamino-)propyl]carbodiimide hydrochloride (WSC·HCl), dioxane–H_2O; (b) NaOH (aq), dioxane, reflux, or $POCl_3$ reflux; (c) MeI, K_2CO_3, DMF, 50 °C.

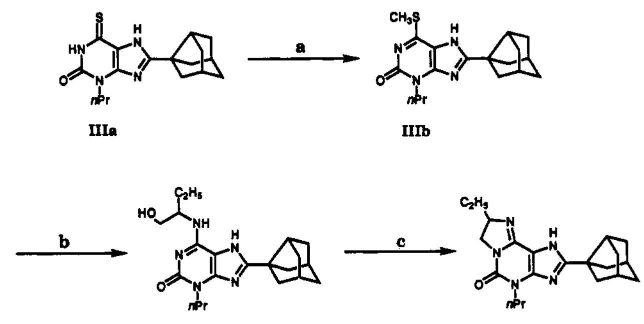
Scheme II[a]



[a] Key: (a) R^1CO_2H, WSC·HCl, dioxane–H_2O, or R^1CO_2H, WSC·HCl, 1-HOBT, DMAP, DMF; (b) NaOH (aq), dioxane, reflux or H_2//10% Pd–C, EtOH followed by NaOH (aq), dioxane, reflux; (c) Ac_2O or R^2COCl, Py, DMAP.

uracils.[15c] Acylation of the 5,6-diaminouracil derivative **Ia** with a carboxylic acid or its acid chloride, followed by treatment with aqueous sodium hydroxide or phosphorus oxychloride ($POCl_3$) under reflux, gave the corresponding xanthine, **Ic**. *N*-Methylation of **Ic** (X = O, R = 3,4-dimethoxystyryl or 3,4,5-trimethoxystyryl, $R_1 = R_3$ = *n*-propyl or methyl) at the 7-position was done under the basic conditions to afford **Id** (**12, 13**). Synthetic methods for **14–18** are outlined in Scheme II. The aminophenethyl-substituted xanthine **IIc** (**14, 15, 18**), which was similarly prepared from **IIa**, was acylated by the appropriate acid chloride or acid anhydride to afford **IId** (**16, 17**). Synthesis of imidazo[2,1-*i*]purine derivatives are shown in Scheme III. 6-Thioxanthine derivative **IIIa** was treated with methyl iodide (1.5 equiv) in aqueous alkaline solution to afford 6-(methylthio)-8-(3-noradamantyl)-3-propyl-7*H*-purin-2(3*H*)-one (**IIIb**) (yield 74%).[16] Reaction of **IIIb** with excess 2-amino-1-butanol (5 equiv) in DMSO at 150 °C gave 6-[(1-ethyl-2-hydroxyethyl)amino]-8-(3-noradamantyl)-3-propyl-7*H*-purin-2(3*H*)-one (**IIIc**) (yield 62%). The amino alcohol was converted to 7,8-dihydro-8-ethyl-2-(3-noradamantyl)-4-propyl-1*H*-imidazo[2,1-*i*]purin-5(4*H*)-one (**19**) which was isolated as a HCl salt.[17] Its *R* and *S* enantiomers (**20** and **21**) were similarly prepared from the corresponding optically active 2-amino-1-butanol. These were isolated as L-tartrate and D-tartrate salts, respectively. Optical purities of **20** and **21** were determined to be >99% and 99%, respectively, by HPLC.

Scheme III[a]



[a] Key: (a) CH_3I (1.5 equiv)/NaOH aq–EtOH, rt; (b) 2-amino-1-butanol (5 equiv), DMSO, 150 °C; (c) $SOCl_2$, reflux.

Results

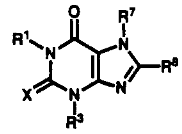
The potency of the xanthine derivatives at the adenosine A_1 and A_2 receptor was determined by standard radioligand binding procedures. A_1 receptor binding was performed with N^6-[^{3}H]cyclohexyladenosine in guinea pig forebrain membranes, and A_2 receptor binding was performed with *N*-[^{3}H]ethyladenosin-5′-uronamide in rat striatal membranes.[20] Results of these compounds are presented in Tables I–III along with comparable data from the literature. The structure–activity relationships of **5** and **8–11** as adenosine A_1 antagonists and those of **12** and **13** as adenosine A_2 antagonists have been discussed previously.[15] 2-Thio derivatives **6**[21] and **7** increased A_1 selectivity compared with that of parent compounds **3** and **5**, respectively. 4-Aminophenethyl substitution at the 3-position retained affinity at the A_1 receptors (compare **14**, **15**, and **18** with **3**, **9**, and **4**). Compound **14** (BW-A844U) has been used as a highly specific ligand (^{125}I-BWA844U) and as a photoaffinity label (^{125}I-azido-BW-A844U).[22] Acylation of a 4-aminophenethyl group decreased affinity for the A_1 receptor (**16, 17**). As in the 1,3-dipropylxanthine analogues, substitution by a 3-oxocyclopentyl group at the 8-position decreased adenosine A_1 antagonism compared with that by a cyclopentyl or a 3-noradamantyl group (compare **18** with **14** and **15**).

As the permeability of the blood–brain barrier (BBB) is affected by the lipophilicity of compounds, the octanol/water partition coefficients[28] of **5**, **9**, and **13** were determined to be 3.67, 4.06, and 3.19, respectively.

Behavioral pharmacological testing was performed with a step-through-type passive avoidance method.[23] None of the adenosine antagonists at doses tested had any significant effect on the step-through latency at the acquisition trial (training). Intraperitoneal administration of scopolamine at a dose of 1.0 mg/kg 30 min prior to the acquisition trial significantly shortened the latency of the step-through response during the test trial in rats. The adenosine antagonists were orally administered 1 h before the acquisition trial in order to evaluate their actions in the acquisition and consolidation phase of the cognitive tasks. On the other hand, intraperitoneal administration of (*R*)-PIA at a dose of 0.3 mg/kg 30 min prior to the acquisition trial similarly shortened the retention latency in mice.[13] The adenosine antagonists were also orally administered 1 h before the acquisition trial. The test trial was performed 24 h later when no stimulatory or depressant effects were observed. Effects of adenosine antagonists on scopolamine- and (*R*)-PIA-induced passive avoidance failures were shown in Table IV.

Theophylline (**1**) and caffeine (**2**), which are known to be CNS stimulants, did not change the shortened latency

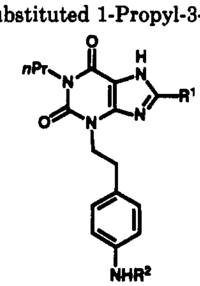
Table I. A_1 and A_2 Adenosine Receptor Binding of 8-Substituted 1,3-Dialkylxanthine Derivatives



compd	R[1]	R[3]	R[7]	R[8]	X	K_i,[a] nM A1	K_i,[a] nM A2	K_i ratio A2/A1
1	Me	Me	H	H	O	23000 ± 330 (8470)[b]	16000 ± 2200	0.7
2	Me	Me	Me	H	O	100000 ± 2000 (29100)[b]	27000 ± 1700	0.27
3	nPr	nPr	H	cyclopentyl	O	6.4 ± 0.35 (0.46)[c]	590 ± 48	92 (1280)[d]
4	nPr	nPr	H	3-oxocyclopentyl	O	15 (10.5 ± 2.8)[e]	2700 (1512)[f]	180
5	nPr	nPr	H	dicyclopropylmethyl	O	3.0 ± 0.21 (0.99 ± 0.04)[c]	430 ± 5.8	140 (430)[d]
6	nPr	nPr	H	cyclopentyl	S	6.6	>10000	>1500
7	nPr	nPr	H	dicyclopropylmethyl	S	6.1 ± 2.4	2000 ± 480	330
8	Me	isobutyl	H	dicyclopropylmethyl	O	12 ± 4.6	410 ± 140	34
9	nPr	nPr	H	noradamantyl	O	1.3 ± 0.12 (0.19 ± 0.04)[c]	380 ± 30	290 (2000)[d]
10	nPr	nPr	H	(1R*,2R*,5R*)-bicyclo[3.3.0]octan-2-yl	O	3.5 ± 0.20 (0.75)[c]	330 ± 4.7	94 (440)[d]
11	nPr	nPr	H	adamantyl	O	13 ± 2.8 (1.5)[c]	5100 ± 1100	390 (3400)[d]
12	nPr	nPr	Me	3,4-dimethoxystyryl	O	1500 ± 7.8 (430 ± 150)[c]	7.8 ± 2.7	0.005 (0.018)[d]
13	Me	Me	Me	3,4,5-trimethoxystyryl	O	>100 000	18 ± 4.2	0.0002

[a] A_1 binding was carried out with N^6-[^{3}H]cyclohexyladenosine in guinea pig forebrain membranes as described,[19] and A_2 binding was carried out with N-[^{3}H]ethyladenosin-5′-uroamide (NECA) in the presence of 50 nM cyclopentyladenosine in rat striatal membranes.[20] 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.[15] 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]cyclohexyladenoisne to rat whole membranes.[8,24] [c] A_1 binding measured as inhibition of N^6-[^{3}H]cyclohexyladenosine to rat forebrain membranes in our laboratory.[15] [d] K_i ratio of rat A_1 (forebrain membraines) and rat A_2 (striatal membranes). [e] A_1 binding measured as inhibition of [^{3}H]DPCPX to rhesus monkey cortex.[25] [f] A_1 binding measured as inhibition of [^{3}H]NECA in the presence of 30 nM (R)-PIA to rhesus monkey striatum.[25]

Table II. A_1 and A_2 Adenosine Receptor Binding of 8-Substituted 1-Propyl-3-(4-aminophenethyl)xanthine Derivatives



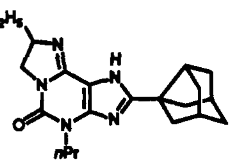
compd	R[1]	R[2]	K_i,[a] nM A1	K_i,[a] nM A2	K_i ratio A2/A1
14	cyclopentyl	H	5.6 (0.23 ± 0.06)[b]	430 (2000 ± 400)[c]	77
15	3-noradamantanyl	H	2.4	>100 000	>40 000
16	cyclopentyl	acetyl	[66][d]	>100 000	
17	cyclopentyl	isobutyryl	16	>100 000	>6000
18	3-oxocyclopentyl	H	23	>100 000	>4000

[a] See footnote a in Table I. [b] A_1 binding measured as inhibition of ^{125}I-N^6-aminobenzyladenosine to bovine brain.[22] [c] A_2 binding measured as inhibition of ^{125}I-N^6-aminobenzyladenosine to human platelets.[22] [d] Percent inhibition at 10^{-5} M.

at the dose range of 0.08 to 20 mg/kg. However, these compounds induced a dose-dependent increase in locomotor activity in mice (Table V). Three selective adenosine A_1 antagonists such as 8-cyclopentyl-1,3-dipropylxanthine (**3**) (DPCPX),[24] 8-(3-oxocyclopentyl)-1,3-dipropylxanthine (**4**) (KFM19),[25] and 8-(dicyclopropylmethyl)-1,3-dipropylxanthine (**5**) (KF15372)[15a] significantly ameliorated the shortened latency induced by scopolamine or (R)-PIA at several doses. On the other hand, other adenosine A_1-selective antagonists were found to have different pharmacological profiles in two models. Compound **6** did not clearly prolong the shortened latency in scopolamine- and (R)-PIA-induced amnesia models. Compounds **7**, **8**, **10**, and **11** did not inhibit scopolamine-induced amnesia but did potently inhibit (R)-PIA-induced amnesia. Compound **9**, which was reported to exhibit potent diuretic and renal protective activities,[26] tended to prolong the shortened latency induced by scopolamine, but this effect was not statistically significant. It is interesting to note that these selective adenosine A_1 antagonists **3–5** did not induce a statistically significant increase in the spontaneous locomotion at a dose of 10 mg/kg (po) (Table V).

Although 4-aminophenethyl-substituted compounds **14–16** potently ameliorated scopolamine-induced amnesia,

Table III. A_1 and A_2 Adenosine Receptor Binding of Imidazo[2,1-*i*]purin-5(4*H*)-one Derivatives



compd		K_i,[a] nM		
		A_1	A_2	K_i ratio A_2/A_1
19	*RS*	5.7 ± 0.51	330	58
20	*R*	2.7 ± 0.09 (0.56)[b]	290	107 (517)[c]
21	*S*	120	250	2.1

[a] See footnote *a* in Table I. [b] See footnote *c* in Table I. [c] K_i ratio of rat A_1 (forebrain membraines) and rat A_2 (striatal membranes).

they had weak effects on (*R*)-PIA-induced amnesia. Compound **17** exhibited potent activity in the (*R*)-PIA-induced amnesia model but did not have any effect on scopolamine-induced amnesia. Compound **18** showed weak activities in both models.

Nonxanthine-type adenosine A_1 antagonists, imidazopurine derivatives **19–21**, were designed and synthesized in order to improve water solubility.[17] These compounds showed much better water solubility (ca. 3 mg/mL) than those (3.3, 220, and 8.5 μg/mL) of **3–5**. Compounds **19–21** significantly antagonized (*R*)-PIA-induced amnesia but showed weak effects on scopolamine-induced amnesia. Compound **19** potently increased spontaneous locomotion at a dose of 5 mg/kg (po).

A_2 selective antagonists, (*E*)-7-methyl-1,3-dialkyl-8-styrylxanthine derivatives **12** and **13** which were identified previously to show A_2 antagonism in vivo,[15c] did not have any influence on the shortened latency in both models at the dose range of 0.08–20 mg/kg.

Discussion

Evidence has accumulated for distinct tissue and species differences in adenosine receptors.[18] 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 for the adenosine A_1 receptor was basically measured with N^6-[^{3}H]cyclohexyladenosine binding in guinea pig forebrain membranes.[19] However, affinities of selected compounds for the A_1 receptor were measured with N^6-[^{3}H]cyclohexyladenosine binding in rat forebrain membranes for comparison. The K_i values of compounds **3**, **5**, **9**, **10**, **11**, and **20** for the A_1 receptors in rat brain membranes (Table IV) were 0.46, 0.99, 0.19, 0.75, 1.5, and 0.56 nM, respectively, which were 3- to 10-fold smaller than those in guinea pig forebrain membranes. These results are consistent with other literature values that A_1 affinity is higher in the rat brain than in the guinea pig brain.[18] On the other hand, amnesic models were well-established in rats. Thus, we examined pharmacological activities of our compounds in the rat models.

It is well known that the permeability of the BBB is related to the lipophilicity.[27] When the octanol/water partition coefficient is greater than about 0.03, the brain uptake for most compounds is nearly complete in a single passage.[27a] From the coefficients of **5**, **9**, and **13** (3.67, 4.06, and 3.19, respectively), these types of compounds could penetrate the BBB to a considerable degree.[27,28]

In previous studies,[13,14] it was reported that intraperitoneal administration of (*R*)-PIA or N^6-cyclopentyladenosine (CPA) 30 min prior to acquisition training impaired dose-dependently retention of a passive avoidance task in mice. Furthermore, there is good evidence from related in vivo studies that both (*R*)-PIA and **3** (DPCPX) can readily penetrate the BBB following intraperitoneal injections and, accordingly, thereby act selectively and potently on central A_1 receptors concentrated in specific brain regions.[29] However, many xanthines are known to have a short half-life (<1 h) in vivo. Thus, plasma concentrations of selected compounds were measured using HPLC. These values of **5** and **9** were 1.8 and 0.15 μg/mL 1 h after oral administration in rats at a dose of 6.25 mg/kg, respectively. Although plasma concentration of **12** (KF 17837) was 0.054 μg/mL 4 h after oral administration at a dose 30 mg/kg, its brain concentration was 0.076 μg/g brain. These concentrations of adenosine antagonists are sufficient to fully antagonize adenosine receptors in the CNS. In fact, oral administration of **12** and **13** at a dose of 10 mg/kg antagonized CGS-21680 (adenosine A_{2a} agonist, intracerebroventricular injection)-induced locomotor depression. Detailed studies will be published elsewhere.

The retention deficiency elicited by (*R*)-PIA was not reversed by a peripheral adenosine antagonist, 8-(*p*-sulfophenyl)theophylline at doses of 1.25, 5, and 10 mg/kg (ip; data not shown) or by selective A_2 antagonists (**12**, **13** at the dose range of 0.08–20 mg/kg (po) but was blocked by most of the adenosine A_1 antagonists (**3–5**, **7–11**, and **19–21**) at the dose range of 0.02–5 mg/kg (po) as shown in Table IV. Thus, (*R*)-PIA-induced amnesia in mice is mediated via central adenosine A_1 receptors. In another study, administration of (*R*)-PIA similarly retarded the acquisition of a conditioned response in rabbits.[30] The retarding effects of (*R*)-PIA on associative learning were proved to be mediated by A_1 receptors.[30b]

The amnesic effect achieved with scopolamine given 30 min before the acquisition trial is consistent with the demonstrated amnesic properties of scopolamine.[31] Although adenosine A_1 antagonists **3–4** and **5** did not elicit major excitatory behavioral effects when given alone at these doses (Table V), these compounds significantly ameliorated the amnesia induced by scopolamine and (*R*)-PIA. Thus, the excitatory behavioral effect of theophylline (**1**) and caffeine (**2**), which are nonselective adenosine antagonists and weak phosphodiesterase inhibitors, would not be expected to be mediated via the A_1 receptor. Further, this effect may not be an important factor for learning and memory. The antiamnesic effects of **3–5** were weakened when the dose was increased to 20 mg/kg, exhibiting a typical bell-shaped dose–response curve. This type of dose–response was also displayed by indeloxazin, oxiracetam, and tacrine.[32] KFM19 (**4**) was reported to improve learning performance in old-aged and NBM (nucleus basalis magnocellularis)-lesioned rats and to possess enhancing effects on acetylcholine release and synaptic transmission in rat hippocampal slices.[25] Furthermore, compound **5** (KF15372) also improved learning performance in NBM-lesioned rats more potently than **4**. Detailed results will be published elsewhere. These results suggest that adenosine A_1 antagonists can have a therapeutic potential for treatment of cognitive deficits. 8-(3-Dicyclopropylmethyl)-1,3-dipropylxanthine (**5**) (KF15372) was chosen for further studies and is currently under preclinical development as a cognition enhancer.

Other adenosine A_1 antagonists (**7–11** and **19–21**), however, did not have a significant effects on scopolamine-

Table IV. Effects of Adenosine Antagonists on Scopolamine- and (*R*)-PIA-Induced Passive Avoidance Failures

		rat, scoplamine[a] (s)			mouse, (*R*)-PIA[b] (s)		
compd	dose (mg/kg,po)	*n*[c]	acquisition time	retention time	*n*[c]	acquisition time	retention time
1	control[d]	17	10.5 ± 1.8	41.6 ± 15.3	15	27.9 ± 6.7	83.4 ± 22.7
	20	17	10.6 ± 1.5	14.6 ± 3.4			
	5	16	10.8 ± 2.0	29.0 ± 7.5	15	20.3 ± 4.6	103.8 ± 41.8
	1.25	15	11.1 ± 1.1	10.9 ± 2.2	15	16.2 ± 2.7	165.5 ± 46.4
	0.31	15	12.2 ± 1.7	31.2 ± 15.1	15	35.8 ± 7.7	113.3 ± 25.0
	0.08	16	10.6 ± 1.3	45.8 ± 14.2	15	30.8 ± 8.3	85.4 ± 38.9
2	control[d]	9	14.8 ± 2.3	13.7 ± 3.2		NT[e]	
	80	8	29.6 ± 5.0	7.6 ± 1.7			
	20	8	33.8 ± 5.7	9.8 ± 2.2			
	5	8	11.5 ± 1.7	12.5 ± 4.3			
	1.25	8	14.6 ± 2.5	11.9 ± 4.0			
	0.31	8	18.3 ± 8.8	14.9 ± 3.2			
3	control[d]	13	17.8 ± 2.5	23.7 ± 4.8	15	27.9 ± 4.3	60.9 ± 13.4
	5	13	14.6 ± 3.5	68.7 ± 29.2	15	18.4 ± 2.7	433.3 ± 42.2***
	1.25	13	12.4 ± 2.3	143.7 ± 55.4**	15	20.5 ± 2.9	271.5 ± 52.4**
	0.31	13	24.7 ± 4.9	273.3 ± 70.2***	15	19.1 ± 4.0	456.5 ± 49.3***
	0.08	13	21.5 ± 5.3	105.2 ± 36.2**	15	19.4 ± 3.8	190.1 ± 43.9**
	0.02	13	19.8 ± 6.7	32.0 ± 5.9			
4	control[d]	18	10.5 ± 1.7	26.8 ± 7.0	15	24.0 ± 5.0	106.7 ± 20.9
	5	18	9.8 ± 1.9	75.9 ± 33.2*	15	15.1 ± 1.7	318.9 ± 54.0*
	1.25	18	11.4 ± 1.9	85.9 ± 34.7*	15	15.1 ± 1.7	339.0 ± 50.7***
	0.31	18	13.2 ± 2.0	163.1 ± 51.8***	15	22.0 ± 3.5	234.1 ± 32.8**
	0.08	18	12.8 ± 3.6	126.3 ± 40.0*	15	20.8 ± 2.7	322.4 ± 53.6***
	0.02	18	16.4 ± 2.7	168.8 ± 51.9*			
5	control[d]	13	15.6 ± 2.2	38.3 ± 8.7	15	26.6 ± 3.7	80.7 ± 22.4
	5	15	14.7 ± 1.8	120.1 ± 53.0	15	28.1 ± 2.5	248.0 ± 50.0**
	1.25	14	20.4 ± 2.4	202.4 ± 57.1*	15	22.7 ± 3.5	262.4 ± 56.6**
	0.31	14	15.6 ± 3.7	217.7 ± 59.7**	15	21.7 ± 2.3	139.7 ± 38.0*
	0.08	14	19.3 ± 2.5	54.1 ± 16.4	15	46.5 ± 7.9	83.9 ± 28.2
	0.02	14	29.9 ± 3.4	48.8 ± 11.4	15	32.9 ± 5.2	51.3 ± 11.3
6	control[d]	16	8.8 ± 1.9	19.8 ± 3.5	15	28.3 ± 6.0	48.5 ± 14.2
	20	14	6.7 ± 0.9	52.4 ± 26.3			
	5	15	8.5 ± 1.4	21.6 ± 7.7	15	26.9 ± 6.5	103.7 ± 31.9*
	1.25	15	9.9 ± 2.6	56.4 ± 28.1	15	12.3 ± 1.6	52.7 ± 18.6
	0.31	15	8.9 ± 1.7	25.8 ± 15.1	15	32.7 ± 7.2	121.3 ± 50.4
	0.08	14	9.4 ± 1.5	75.3 ± 38.9	15	24.7 ± 7.1	48.1 ± 15.6
	0.02	14	8.9 ± 1.8	19.0 ± 8.1			
7	control[d]	16	9.9 ± 1.9	42.6 ± 17.6	15	16.3 ± 2.5	25.9 ± 7.4
	20	14	11.6 ± 2.7	42.1 ± 16.0			
	5	14	10.2 ± 2.5	28.2 ± 7.3	15	33.6 ± 6.6	281.8 ± 56.4***
	1.25	16	9.8 ± 1.6	64.1 ± 36.1	15	30.5 ± 7.1	149.1 ± 45.8*
	0.31	15	9.3 ± 1.2	59.1 ± 35.9	15	26.3 ± 4.6	70.6 ± 22.7*
	0.08	14	8.1 ± 1.1	28.9 ± 4.8	13	17.8 ± 4.2	97.5 ± 23.9**
	0.02	14	8.1 ± 1.4	115.3 ± 55.7			
8	control[d]	15	9.5 ± 2.7	59.1 ± 16.7	15	16.8 ± 2.0	47.5 ± 15.0
	20	14	9.6 ± 2.3	14.1 ± 2.5			
	5	15	11.5 ± 2.0	9.9 ± 2.3	15	12.5 ± 1.3	358.7 ± 49.8***
	1.25	15	11.8 ± 1.6	22.8 ± 11.5	15	19.9 ± 2.4	349.0 ± 56.0***
	0.31	15	8.3 ± 1.1	50.9 ± 39.3	15	26.4 ± 6.4	370.4 ± 49.8***
	0.08	14	7.1 ± 1.3	17.6 ± 3.7	15	25.7 ± 4.9	170.8 ± 27.4***
	0.02	14	10.1 ± 2.0	17.6 ± 4.0			
9	control[d]	15	16.1 ± 3.4	52.7 ± 16.0	15	16.7 ± 1.7	42.3 ± 8.7
	5	15	24.9 ± 8.6	159.3 ± 44.6	15	17.3 ± 3.0	230.5 ± 47.3***
	1.25	15	30.5 ± 7.9	149.2 51.2	15	18.4 ± 1.7	164.5 ± 47.5***
	0.31	15	22.2 ± 3.1	112.8 ± 43.6	15	20.4 ± 2.1	173.4 ± 35.3**
	0.08	15	32.2 ± 6.6	163.5 ± 60.1	15	19.5 ± 1.7	123.8 ± 27.4**
	0.02	15	23.8 ± 5.2	129.1 ± 51.4	15	17.5 ± 2.8	37.0 ± 8.9
10	control[d]	19	11.6 ± 2.1	44.8 ± 15.1	15	19.9 ± 3.6	144.8 ± 29.4
	20	14	9.9 ± 1.4	35.1 ± 15.3			
	5	15	11.1 ± 1.7	22.6 ± 5.3	15	42.7 ± 8.8	384.1 ± 560.1**
	1.25	18	9.5 ± 1.7	18.0 ± 2.9	15	14.5 ± 2.8	317.3 ± 53.5**
	0.31	17	11.1 ± 1.2	29.6 ± 7.5	15	23.3 ± 3.7	139.7 ± 38.5
	0.08	17	10.8 ± 2.0	30.7 ± 11.3	15	24.0 ± 6.4	83.2 ± 27.4
	0.02	17	13.4 ± 1.5	18.5 ± 2.6			
11	control[d]	18	13.2 ± 2.1	27.4 ± 12.7	15	26.4 ± 3.6	79.1 ± 19.0
	20	14	8.4 ± 1.4	35.0 ± 16.4			
	5	12	11.7 ± 2.0	16.3 ± 2.6	15	13.7 ± 2.8	220.9 ± 50.8**
	1.25	13	12.8 ± 2.0	14.1 ± 2.7	15	19.8 ± 4.3	490.1 ± 41.6***
	0.31	12	16.6 ± 4.2	21.3 ± 6.7	15	19.6 ± 3.7	302.1 ± 48.7***
	0.08	12	11.0 ± 1.4	34.8 ± 26.1	15	19.1 ± 2.4	121.8 ± 32.3
	0.02	14	10.1 ± 2.0	17.6 ± 4.0			
12	control[d]	9	18.3 ± 3.9	24.7 ± 7.9	30	24.1 ± 3.7	27.8 ± 4.7
	20	9	22.2 ± 8.7	15.6 ± 5.4	30	31.2 ± 2.9	92.4 ± 23.5
	5	8	24.4 ± 5.4	4.9 ± 1.6	30	19.8 ± 1.5	37.5 ± 8.4
	1.25	8	10.1 ± 2.2	20.3 ± 6.4	30	25.3 ± 3.8	65.3 ± 15.2
	0.31	8	11.8 ± 1.4	12.9 ± 3.0	30	22.7 ± 2.2	42.4 ± 12.2
	0.08	8	14.9 ± 4.9	31.1 ± 9.1			

Table IV (Continued)

		rat, scopolamine[a] (s)			mouse, (*R*)-PIA[b] (s)		
compd	dose (mg/kg,po)	n^c	acquisition time	retention time	n^c	acquisition time	retention time
13	control[d]	9	12.0 ± 2.1	45.6 ± 12.4	30	22.2 ± 2.8	43.9 ± 8.9
	20	9	13.2 ± 3.1	26.8 ± 9.7	30	21.0 ± 1.8	74.9 ± 21.4
	5	9	11.3 ± 2.3	31.4 ± 13.5	30	33.8 ± 2.9	49.9 ± 10.5
	1.25	9	26.6 ± 7.4	33.7 ± 12.4	30	24.7 ± 2.7	23.0 ± 4.0
	0.31	9	21.3 ± 4.1	36.3 ± 9.9	30	22.1 ± 3.0	63.8 ± 21.1
	0.08	9	9.9 ± 1.1	28.9 ± 6.2			
14	control[d]	12	13.2 ± 1.9	48.1 ± 8.8	15	20.2 ± 3.0	84.3 ± 16.8
	5	12	12.3 ± 1.4	254.6 ± 70.2*	15	23.5 ± 3.3	317.6 ± 45.9***
	1.25	12	18.3 ± 2.0	383.8 ± 67.6**	15	28.7 ± 7.8	152.3 ± 36.2
	0.31	12	11.1 ± 1.8	255.1 ± 66.6**	15	23.1 ± 3.9	177.3 ± 48.4
	0.08	12	20.8 ± 4.2	160.2 ± 62.0	15	21.2 ± 3.3	112.7 ± 27.4
	0.02	12	25.7 ± 4.1	150.8 ± 68.3			
15	control[d]	15	12.4 ± 2.4	13.5 ± 3.0	15	17.3 ± 3.3	71.9 ± 20.1
	20	9	18.3 ± 4.2	231.9 ± 76.2***	15	14.7 ± 1.3	98.7 ± 38.6
	5	15	11.9 ± 2.1	182.3 ± 57.5**	15	14.7 ± 2.2	92.5 ± 25.5
	1.25	15	15.3 ± 2.3	136.4 ± 41.9***	15	20.3 ± 3.5	167.7 ± 49.5*
	0.31	15	8.3 ± 1.0	95.9 ± 41.1**	15	14.8 ± 3.1	60.3 ± 18.4
	0.08	15	12.0 ± 2.9	20.5 ± 3.5			
	0.02	15	18.1 ± 3.2	22.9 ± 5.5			
16	control[d]	17	10.8 ± 1.6	36.0 ± 8.2	15	31.5 ± 6.3	72.1 ± 17.1
	20	17	13.8 ± 2.1	116.2 ± 43.4	15	20.5 ± 3.0	32.2 ± 7.8
	5	18	15.9 ± 1.8	187.2 ± 50.2***	15	27.8 ± 6.6	47.5 ± 18.4
	1.25	17	12.6 ± 2.7	170.3 ± 50.4*	15	18.8 ± 2.3	20.0 ± 2.7
	0.31	18	15.5 ± 2.9	130.4 ± 38.5**	15	18.9 ± 1.8	38.7 ± 16.2
	0.08	18	15.4 ± 1.8	174.8 ± 56.1*	15	23.9 ± 3.2	75.4 ± 29.1
	0.02	17	12.2 ± 1.6	137.3 ± 44.5			
17	control[d]	8	9.1 ± 3.0	10.4 ± 1.6	15	22.9 ± 6.1	42.5 ± 12.3
	20	7	9.0 ± 3.2	65.4 ± 51.4			
	5	7	11.9 ± 2.0	20.0 ± 6.8	15	34.4 ± 7.3	94.7 ± 22.3*
	1.25	8	6.6 ± 1.6	19.3 ± 5.9	15	33.3 ± 8.8	171.2 ± 55.4*
	0.31	7	10.1 ± 1.2	18.6 ± 4.7	15	29.3 ± 4.2	88.6 ± 27.1*
	0.08	7	10.1 ± 3.0	10.7 ± 3.5	15	16.5 ± 3.0	32.9 ± 12.2
	0.02	7	6.0 ± 1.2	9.4 ± 3.2			
18	control[d]	20	10.6 ± 1.5	42.5 ± 7.7	15	26.9 ± 7.5	24.6 ± 7.1
	20	19	13.6 ± 3.1	117.2 ± 39.4			
	5	20	10.2 ± 1.5	107.7 ± 38.7	15	12.9 ± 2.9	67.7 ± 17.1*
	1.25	20	12.1 ± 2.1	163.1 ± 43.2*	15	14.6 ± 1.5	19.1 ± 7.8
	0.31	20	13.1 ± 1.5	108.8 ± 32.8	15	17.5 ± 3.8	23.4 ± 5.1
	0.08	20	10.5 ± 1.6	118.7 ± 41.6	15	16.4 ± 2.2	18.7 ± 5.4
	0.02	20	14.2 ± 2.1	73.9 ± 29.1			
19	control[d]	30	21.7 ± 3.2	89.8 ± 24.5	15	20.7 ± 3.4	71.2 ± 17.2
	20	10	26.6 ± 5.7	21.0 ± 4.7			
	5	16	22.5 ± 4.9	66.3 ± 25.6	15	24.9 ± 5.5	276.9 ± 51.2***
	1.25	16	14.1 ± 3.2	40.8 ± 10.1	15	21.2 ± 2.9	231.3 ± 46.8**
	0.31	26	17.3 ± 2.1	220.8 ± 48.3	15	22.7 ± 6.1	292.1 ± 59.9***
	0.08	26	21.3 ± 3.0	250.6 ± 44.7***	15	23.5 ± 4.5	196.3 ± 33.3***
	0.02	25	23.0 ± 3.8	168.3 ± 36.7			
20	control[d]	17	14.0 ± 1.2	20.6 ± 4.6	15	17.6 ± 4.5	20.4 ± 4.6
	20	16	17.2 ± 2.4	76.6 ± 43.1			
	5	16	14.4 ± 2.9	42.1 ± 27.7	15	23.7 ± 4.7	185.8 ± 41.1***
	1.25	16	20.1 ± 3.9	80.9 ± 41.6	15	16.5 ± 3.2	326.0 ± 60.0***
	0.31	16	14.1 ± 1.7	74.1 ± 40.5	15	15.9 ± 1.5	191.5 ± 45.6***
	0.08	16	17.3 ± 2.8	27.1 ± 9.1	15	35.1 ± 7.9	156.0 ± 33.4***
	0.02	16	13.6 ± 2.1	16.1 ± 2.2			
21	control[d]	8	10.0 ± 3.2	40.4 ± 7.7	15	15.5 ± 1.8	80.9 ± 20.4
	20	7	7.0 ± 1.0	19.6 ± 5.8			
	5	7	14.0 ± 3.6	13.3 ± 4.9	15	12.9 ± 2.8	431.4 ± 53.6***
	1.25	8	15.1 ± 2.2	20.3 ± 5.9	15	14.3 ± 2.3	351.4 ± 58.1**
	0.31	8	10.9 ± 3.4	81.3 ± 43.5	15	22.9 ± 6.4	489.0 ± 40.5***
	0.08	7	8.0 ± 1.6	40.7 ± 12.2	15	13.4 ± 1.9	463.8 ± 48.0***
	0.02	7	14.3 ± 3.4	108.6 ± 82.0			

[a] Behavioral testing was performed with a step-through-type passive avoidance method.[23] Intraperitoneal administration of scopolamine at a dose of 1.0 mg/kg 30 min prior to the acquisition trial (training) significantly shortened the latency of the step-through response in male Wistar rats. Test compound was orally administered 1 h before the acquisition trial. The test trial was performed 24 h later. *$P < 0.05$, **$P < 0.01$, ***$P < 0.005$: significant difference from the vehicle-treated control (Mann–Whitney *U* test). [b] Intraperitoneal administration of (*R*)-PIA at a dose of 0.3 mg/kg 30 min prior to the acquisition trial significantly shortened the latency of the step-through response in male ddY mice. Test compounds were orally administered 1 h before the acquisition trial. The test trial was performed 24 h later. *$P < 0.05$, **$P < 0.01$, ***$P < 0.005$: significance difference from the vehicle-treated control (Mann–Whitney *U* test). [c] Number of animals. [d] The vehicle without test compounds was treated. [e] Not tested.

induced amnesia. This very interesting change could not be explained by their differences in pharmacokinetics because both types of adenosine antagonists clearly provided adenosine A_1 receptor blockade in the CNS ((*R*)-PIA induced amnesia). Further, compound **19** has also been proved to exhibit adenosine A_1 antagonism at a dose of 0.1 mg/kg (po) in the cardiovascular system.[17] Therefore, this difference might be explained by different sites of action between these two amnesia models. It is interesting to note that **19** stimulates spontaneous locomotion at a dose of 5 mg/kg. This increase might not be based on blockade of the adenosine A_1 receptors which

Table V. Locomotor Effects of Adenosine Antagonists

compd	dose (mg/kg, po)	n^a	locomotor activity^b (counts)
1	control	4	3921 ± 1026
	2.5	4	5914 ± 420
	5	4	7682 ± 1072*
	10	4	11031 ± 301**
2	control	4	4524 ± 809
	2.5	4	6413 ± 504
	10	4	9386 ± 689**
	40	4	9693 ± 722**
3	control	4	3976 ± 635
	0.625	4	3826 ± 432
	2.5	4	4679 ± 636
	10	4	5257 ± 1072
4	control	4	6489 ± 1564
	2.5	4	6134 ± 425
	10	4	8204 ± 1202
5	control	8	3927 ± 710
	2.5	8	4365 ± 489
	5	8	5631 ± 503
	10	8	5371 ± 438
14	control	4	4971 ± 686
	2.5	4	6224 ± 918
	10	4	6693 ± 810
	40	4	5867 ± 753
19	control	4	3303 ± 370
	1.25	4	5761 ± 232
	5	4	6907 ± 1189**

^{a} Number of experiments. ^{b} Male dd Y mice (19–21 g) were monitored in the horizontal activity in Automex-II (Columbus Instruments) for 120 min after the oral administration of test compounds. *$P < 0.05$, **$P < 0.01$: significant difference from the vehicle-treated control (Dunnett's multiple range test).

Table VI. Analytical Data for Adenosine Antagonists

no.	% yield	mp, °C (recryst solvent)		formula^a
4	59	171–172^b	(Tol/cyclohexane)	$C_{16}H_{22}N_4O_3$
6	52	228–230^c	($EtOH/H_2O$)	$C_{16}H_{24}N_2OS$
7	46	154–156	($EtOH/H_2O$)	$C_{18}H_{26}N_4OS$
12	71	165–166	($2\text{-}PrOH/H_2O$)	$C_{22}H_{28}N_4O_4$
13	64	250–251^d	($DMSO/H_2O$)	$C_{19}H_{22}N_4O_5$
14	59	248–250^e	(dioxane)	$C_{21}H_{27}N_5O_2$
15	23	284–285	(THF)	$C_{25}H_{31}N_5O_2$
16	63	>270	(EtOH)	$C_{23}H_{29}N_5O_3$
17	56	>270	(EtOH)	$C_{25}H_{33}N_5O_3$
18	16	186–190 (dec)	(dioxane)	$C_{21}H_{25}N_5O_3\cdot 1/2C_4H_8O_2$^{f}
19	67	196–201	(AcOEt)	$C_{21}H_{29}N_5O\cdot HCl$
20	26	209	(2-PrOH)	$C_{21}H_{29}N_5O\cdot C_4H_6O_6$
21	22	209–211	(2-PrOH)	$C_{21}H_{29}N_5O\cdot C_4H_6O_6$

^{a} All compounds were analyzed for C, H, N. ^{b} Lit. 164–168 °C. ^{c} Lit. 217 °C.[21] ^{d} Lit. 245–247 °C.[35] ^{e} Lit. 240–243 °C.[22] ^{f} N: calcd, 15.93; found, 15.39.

are recognized by *R*-PIA in the CNS. Receptor ligand binding of dopamine (D_1, D_2), histamine (H_1, H_2), acetylcholine (M_1), serotonin ($5HT_{1A}$, $5HT_2$), or adrenaline (α_1, α_2, β) was not significantly antagonized by **3**, **5**, **9**, and **19** at 100 μM. These compounds did not inhibit phosphodiesterase subtypes (I–V) isolated from canine tracheal smooth muscle[31] at 10 μM (percent inhibition; below 30%). Thus, these compounds could be specific adenosine A_1 antagonists. Our results might be explained by subtypes in adenosine A_1 receptors. Further division of adenosine A_1 receptors into subclasses has been proposed based on a variety of pharmacological criteria,[34] and although these are not universally accepted, the recent cloning of the adenosine receptor[35] will probably clarify the existence of subtypes of A_1 receptors and their physiological roles.

Aminophenethyl substitution at the 3-position dramatically decreased adenosine antagonism in the CNS (Table IV). Thus, we examined adenosine antagonism of **14** in the cardiovascular system. NECA caused a dose-dependent decrease in heart rate and in blood pressure in anesthetized rats.[36] Compound **14** was orally administered at doses of 1 and 5 mg/kg and did not produce any significant shift to the right in the NECA dose–response curve for heart rate and for blood pressure (data not shown). Adenosine is supposed to reduce heart rate via an effect on the A_1 receptor and blood pressure via the A_2 receptor. Thus, **14** (BW-A844U) did not exhibit adenosine antagonism in vivo (heart). In fact, **14** did not induce diuresis or exhibit renal protective activities at the dose range of 0.2 to 10 mg/kg (po). This unexpected result might be explained by rapid metabolism of **14** after oral administration. Presumably, one of postulated metabolites which is not a potent adenosine antagonist might ameliorate the amnesia induced by scopolamine (Table IV). Compounds **15** and **16** behaved similarly to **14**. However, compound **17** might not be metabolized after its absorption. Therefore, before in vivo experiments are performed using any compounds, their in vivo agonism or antagonism has to be examined.

The present results and previous pharmacological findings suggest that some of selective adenosine A_1 antagonists may be useful for treatment of cognitive deficits but a relationship between adenosine A_1 antagonism and antiamnesic activity is not clear. More detailed pharmacological and biochemical studies of our adenosine A_1 antagonists and studies for A_1 receptor subtypes are actively under way in our laboratories.

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, a HITACHI R-90H, or a JEOL JNM GX-270 spectrometer with tetramethylsilane (TMS) as an internal standard. Optical rotation data were obtained on a JASCO DIP-370 digital polarimeter. Mass spectra (MS) were measured on a JEOL JMS-D300 instrument at an ionization potential of 70 eV. Microanalyses were performed on a Perkin-Elmer 2400CHN and agree within ±0.4% of calculated values unless otherwise noted. For silica gel column chromatography, silica gel 60 (E. Merck, 0.063–0.200 mm) was used. Standard workup refers to $CHCl_3$ extraction washed successively with water and brine, dried over anhydrous Na_2SO_4, and concentrated by a rotary evaporator.

Theophylline (**1**) and caffeine (**2**) were purchased from Nacalai Tesque Co., Japan. DPCPX (**3**),[24] KFM19 (**4**),[25] **6**,[21a] and **13**[37] were prepared by published procedures. The synthesis of 8-polycycloalkyl-substituted xanthines **5** and **8–11** has been described elsewhere.[15] 1,3-Dialkyl-5,6-diaminouracils were synthesized by published procedures.[21a,38]

8-(Dicyclopropylmethyl)-1,3-dipropyl-2-thioxanthine (7). To a stirred solution of dicyclopropylacetic acid[39] (1.27 g, 9.1 mmol) in pyridine (25 mL) was added thionyl chloride (0.65 mL, 9.1 mmol) at 0 °C. The reaction mixture was heated at 60 °C for 10 min, and then 5,6-diamino-1,3-dipropyl-2-thiouracil[21a] (2.00 g, 8.3 mmol) in pyridine (10 mL) was slowly added at 0 °C. The mixture was stirred for an additional 30 min and concentrated. Water was added, and standard workup followed by purification on silica gel chromatography (eluent: 1% $MeOH/CHCl_3$) gave 6-amino-5-[(dicyclopropylacetyl)amino]uracil (2.42 g, 81%). A solution of 2.00 g (5.5 mmol) of this uracil in 20 mL of $POCl_3$ was refluxed for 3 h. The excess $POCl_3$ was removed in vacuo, and the residue was neutralized with 50% NH_4OH. Standard workup followed by purification on silica gel column chromatography (eluent: 15% AcOEt/hexane), followed by recrystallization from $EtOH/H_2O$, gave 1.09 g (46% overall) of **7** as colorless needles: mp 154–156 °C; IR (KBr) 1674, 1493, 1408 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 12.79 (br s, 1 H), 4.69 (t, 2 H, J = 7.3 Hz), 4.57 (t, 2 H, J = 7.3 Hz), 2.00–1.70 (m, 5 H), 1.50–1.34 (m, 2 H), 1.10–0.95 (m, 6 H), 0.80–0.60 (m, 2 H), 0.50–0.20 (m, 6 H). Anal. ($C_{18}H_{26}N_4OS$) C, H, N.

(E)-1,3-Dipropyl-8-(3,4-dimethoxystyryl)-7-methylxanthine (12). To a solution of 5,6-diamino-1,3-dipropyluracil[38c] (2.00 g, 8.9 mmol) and 1-ethyl-2-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (2.54 g, 13 mmol) in 100 mL of dioxane/H_2O (1:1) was added portionwise (E)-3,4-dimethoxycinnamic acid (2.03 g, 9.7 mmol) with stirring, and the pH was adjusted at 5.0 ± 0.5 by the dropwise addition of 2 N HCl. The mixture was stirred for an additional 2 h and neutralized. After standard workup, the residue was treated with 100 mL of 1 N NaOH/dioxane (1:1) and heated under reflux for 10 min. After being cooled 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 DMSO/H_2O yielded 2.56 g (72%) of (E)-1,3-dipropyl-8-(3,4-dimethoxystyryl)xanthine: mp 260–264 °C; IR (KBr) 1701, 1640 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.39 (br s, 1 H), 7.59 (d, 1 H, J = 16.7 Hz), 7.26 (d, 1 H, J = 1.8 Hz), 7.13 (dd, 1 H, J = 1.8, 8.6, Hz), 6.98 (d, 1 H, J = 8.6 Hzd), 6.95 (d, 1 H, J = 16.7 Hz), 4.00–3.85 (m, 4 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 1.80–1.55 (m, 4 H), 1.00–0.85 (m, 6 H). Anal. ($C_{21}H_{26}N_4O_4$) C, H, N.

To a stirred suspension of this compound (1.20 g, 3.0 mmol) and potassium carbonate (1.04 g, 7.6 mmol) in DMF (20 mL) was added methyl iodide (0.38 mL, 6.0 mmol). After the mixture was stirred for 30 min at 50 °C, insoluble materials were filtered off. Water and added, and then standard workup followed by purification on column chromatography and recrystallization from EtOH/H_2O gave 1.22 g (71% overall from uracil) of **12** as colorless needles: mp 164–166 °C; IR (KBr) 1692, 1652 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.60 (d, 1 H, J = 15.8 Hz), 7.40 (d, 1 H, J = 2.0 Hz), 7.28 (dd, 1 H, J = 2.0, 8.4 Hz), 7.18 (d, 1 H, J = 15.8 Hz), 6.99 (d, 1 H, J = 8.4 Hz), 4.02 (s, 3 H), 3.99 (t, 2 H, J = 7.2 Hz), 3.90–3.80 (m, 2 H), 3.85 (s, 3 H), 3.80 (s, 3 H), 1.80–1.55 (m, 4 H), 1.00–0.85 (m, 6 H). Anal. ($C_{22}H_{28}N_4O_4$) C, H, N.

1-[[4-(Benzyloxycarbonyl)amino]phenethyl]-5,6-diamino-3-propyluracil (IIa). To a stirred solution of 4-nitrophenethylamine (127 g, 0.77 mol) in 2.5 L of toluene was added propyl isocyanate (72 mL, 0.76 mol) at room temperature. After stirring for 2 h, the crystals formed were collected and dried to give 172 g (90%) of 1-(4-nitrophenethyl)-3-propylurea as a white powder: mp 140–143 °C; IR (KBr) 3322, 1620, 1578, 1516 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 8.10 (d, 2 H, J = 8.8 Hz), 7.35 (d, 2 H, J = 8.8 Hz), 4.95–4.50 (m, 2 H), 3.70–3.30 (m, 2 H), 3.25–2.75 (m, 6 H), 1.70–1.30 (m, 2 H), 0.90 (t, 3 H, J = 7.0 Hz); MS (EI) m/e 251 (M^+).

A mixture of this urea (170 g, 0.68 mol) and cyanoacetic acid (63.3 g, 0.74 mol) in acetic anhydride (200 mL) was heated at 75 °C for 2 h. The reaction mixture was concentrated, water (200 mL) was added, and the mixture was concentrated again. The resulting crude crystals were recrystallized twice from ethyl acetate to give 42.9 g (20%) of 1-(cyanoacetyl)-3-(4-nitrophenethyl)-1-propylurea as a white powder: mp 97–98 °C; IR (KBr) 3386, 1693, 1678, 1518 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 8.55 (br s, 1 H), 8.16 (d, 2 H, J = 8.7 Hz), 7.38 (d, 2 H, J = 8.7 Hz), 3.78 (s, 2 H), 3.80–3.45 (m, 4 H), 3.01 (t, 2 H, J = 7.0 Hz), 1.80–1.40 (m, 2 H), 0.99 (t, 3 H, J = 7.0 Hz); MS (EI) m/e 318 (M^+).

This urea (57.5 g, 0.81 mol) was treated with 680 mL of 2 N NaOH and heated at 75 °C for 30 min. After cooling, the crystals were collected, washed with water, and dried under reduced pressure to afford 51.7 g (90%) of 6-amino-1-(4-nitrophenethyl)-3-propyluracil as a pale yellow powder: mp 194–198 °C; IR (KBr) 1658, 1639, 1611, 1518 cm^{-1}; ^1H NMR (DMSO-d_6, 90 MHz) δ 8.10 (d, 2 H, J = 8.5 Hz), 7.47 (d, 2 H, J = 8.5 Hz), 6.82 (br s, 2 H), 4.78 (s, 1 H), 4.08 (t, 2 H, J = 7.2 Hz), 1.65–1.15 (m, 2 H), 0.77 (t, 3 H, J = 7 Hz); MS (EI) m/e 318 (M^+).

A mixture of 20.0 g (63 mmol) of this uracil and 1 g of 10% Pd/C was stirred for 8 h under hydrogen. The catalyst was filtered off, and the filtrate was concentrated and made alkaline by the addition of 1 N NaOH. The precipitated crystals were collected by filtration, washed with water, and dried under reduced pressure to afford 15.6 g (87%) of 6-amino-1-(4-aminophenethyl)-3-propyluracil as a white powder: mp 177–183 °C; IR (KBr) 1658, 1613, 1517 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.00 (d, 2 H, J = 8.0 Hz), 6.67 (d, 2 H, J = 8.0 Hz), 4.82 (s, 1 H), 4.20–3.70 (m, 6 H), 2.90 (t, 2 H, J = 7.5 Hz), 1.80–1.50 (m, 4 H), 0.95 (t, 3 H, J = 7.2 Hz); MS (EI) m/e 288 (M^+).

To a solution of 7.00 g (24 mmol) of this uracil and $NaHCO_3$ (4.13 g, 49 mmol) in 180 mL of THF and 120 mL of water was added dropwise a 30% solution (11.9 g, 21 mmol) of benzyl chloroformate in toluene at 5–10 °C, and the pH was adjusted at 8.5 ± 0.5 by the dropwise addition of 2 N NaOH. The mixture was stirred for an additional 30 min and concentrated. Water was added, and the mixture was extracted with EtOAc three times. The organic extracts were washed with brine, dried, and concentrated to give 10.0 g (98%) of 6-amino-1-[4-[(benzyloxycarbonyl)amino]phenethyl]-3-propyluracil as a white powder: mp 118–125 °C; IR (KBr) 1706, 1660, 1606, 1527, 1511 cm^{-1}; ^1H NMR (DMSO-d_6, 90 MHz) δ 8.63 (br s, 1 H), 7.65–7.20 (m, 7 H), 7.11 (d, 2 H, J = 8.5 Hz), 5.15 (s, 2 H), 4.67 (s, 1 H), 3.99 (t, 2 H, J = 7.0 Hz), 3.62 (t, 2 H, J = 7.5 Hz), 2.73 (t, 2 H, J = 7.0 Hz), 1.55–1.25 (m, 2 H), 0.78 (t, 3 H, J = 7.5 Hz); MS (EI) m/e 422 (M^+).

To a solution of 9.85 g (22 mmol) of this aminouracil in 120 mL of EtOH and 40 mL of water was added 2.87 mL of concd HCl followed by 1.82 g (26 mmol) of $NaNO_2$ at 30 °C. After additional stirring for 30 min, the precipitated purplish red crystals were collected, washed with water, and dried to give 8.66 g (82%) of 6-amino-1-[4-[(benzyloxycarbonyl)amino]-phenethyl]-5-nitroso-3-propyluracil: mp 193–195 °C; IR (KBr) 1730, 1670, 1642, 1527, 1515 cm^{-1}; ^1H NMR (DMSO-d_6, 90 MHz) δ 9.62 (br s, 1 H), 7.45–7.20 (m, 7 H), 7.08 (d, 2 H, J = 8.8 Hz), 5.12 (s, 2 H), 4.06 (t, 2 H, J = 7.5 Hz), 3.79 (t, 2 H J = 7.0 Hz), 2.75 (t, 2 H, J = 7.5 Hz), 1.70–1.25 (m, 2 H), 0.84 (t, 3 H, J = 7.0 Hz); MS (EI) m/e 451 (M^+).

To a stirred suspension of 6.30 g (14.0 mmol) of this nitrosouracil in 280 mL of EtOH/water (1:1) was added portionwise 9.70 g (56 mmol) of $Na_2S_2O_4$ over 30 min. After insoluble materials were filtered off, the filtrate was concentrated. The resulting crystals were collected, washed with water, and dried to give 5.23 g (86%) of **IIb**.

Recrystallization from MeCN/H_2O (1/3) gave analytically pure sample as a colorless powder: mp 187–188 °C dec; IR (KBr) 3410, 1674, 1582, 1521, 1491 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.68 (br s, 1 H), 7.45–7.30 (m, 7 H), 7.15 (d, 2 H, J = 6.7 Hz), 6.18 (br s, 2 H), 5.14 (s, 2 H), 4.03 (t, 2 H, J = 7.4 Hz), 3.69 (t, 2 H, J = 7.0 Hz), 2.76 (t, 2 H, J = 7.4 Hz), 1.60–1.35 (m, 2 H), 0.79 (t, 3 H, J = 7.2 Hz). Anal. ($C_{23}H_{27}N_5O_4 \cdot 1/2H_2O$) C, H, N.

3-(4-Aminophenethyl)-8-cyclopentyl-1-propylxanthine (14). To a solution of **IIb** (13.4 g, 31 mmol) and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (6.41 g, 33 mmol) in 300 mL of dioxane/H_2O (2:1) was added dropwise cyclopentanecarboxylic acid (3.86 g, 34 mmol). The reaction mixture was stirred for an additional 18 h and concentrated. Standard workup gave 15.7 g (98%) of crude 6-amino-1-[4-[(benzyloxycarbonyl)amino]phenethyl]-5-[(cyclopentanecarbonyl)amino]-3-propyluracil.

A solution of 15.7 g (29 mmol) of this uracil in dioxane (70 mL) and 2 N NaOH (170 mL) was heated under reflux for 1 h. The product was precipitated by neutralization. Recrystallization from dioxane gave 6.80 g (59% overall) of **14** as a colorless powder: mp 248–250 °C; IR (KBr) 1694, 1645, 1500 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.05 (br s, 1 H), 6.84 (d, 2 H, J = 8.0 Hz), 6.47 (d, 2 H, J = 8.0 Hz), 4.87 (br s, 2 H), 4.09 (t, 2 H, J = 7.4 Hz), 3.82 (t, 2 H, J = 6.9 Hz), 3.20–3.05 (m, 1 H), 2.77 (t, 2 H, J = 7.4 Hz), 2.10–1.50 (m, 10 H), 0.85 (t, 3 H, J = 7.4 Hz). Anal. ($C_{21}H_{27}N_5O_2$) C, H, N.

3-(4-Aminophenethyl)-8-(3-noradamantyl)-3-propylxanthine (15). To a solution of 2.79 g (17 mmol) of 3-noradamantanecarboxylic acid in THF (50 mL) and CH_2Cl_2 (50 mL) were added 1-hydroxybenztriazole (2.57 g, 17 mmol) followed by 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (3.22 g, 17 mmol) at 0 °C. The reaction mixture was stirred for an additional 4 h at room temperature. To the mixture were added 4-(dimethylamino)pyridine (170 mg, 1.4 mmol) followed by a solution of **IIb** (6.12 g, 14 mmol) in DMF (20 mL) and THF (20 mL) over 10 min. After 1 h with stirring at room temperature, the reaction mixture was concentrated to about 1/2 volume. Usual workup followed by purification on silica gel column chromatography (eluent: 2% MeOH/$CHCl_3$) gave 6.95 (85%) of 6-amino-1-[4-[(benzyloxycarbonyl)amino]phenethyl]-5-[(3-noradamantylcarbonyl)amino]-3-propyluracil as an amorphous solid: IR (KBr) 1685, 1652 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.99 (br s, 1 H), 7.50–7.25 (m, 7 H), 7.12 (d, 2 H, J = 7.8 Hz), 6.89 (br s, 1 H), 5.20 (s, 2 H), 4.25–3.65 (m, 6 H), 3.05–2.75 (m, 3 H), 2.45–1.45 (m, 14), 0.90 (t, 3 H, J = 7.0 Hz).

A mixture of 6.81 g (12 mmol) of this uracil and 600 mg of 10% Pd/C in 200 mL of EtOH was stirred for 15 h under hydrogen. Usual workup and purification on silica gel column chromatography (eluent: 5% MeOH/$CHCl_3$) followed by trituration with 25% hexane/Et_2O gave 3.65 g (69%) of 6-amino-1-(4-aminophenethyl)-5-[(3-noradamantylcarbonyl)amino]-3-propyluracil as a pale yellow powder: mp 117–120 °C; IR (KBr) 1696, 1641, 1519 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.32 (brs, 1 H), 6.97 (d, 2 H, J = 8.5 Hz), 6.60 (d, 2 H, J = 8.5 Hz), 5.28 (br s, 2 H), 4.20–3.75 (m, 4 H), 3.27 (br s, 2 H), 3.00–2.75 (m, 3 H), 2.45–1.45 (m, 14 H), 0.96 (t, 3 H, J = 7.0 Hz).

A solution of 3.50 g (7.8 mmol) of this uracil in dioxane (80 mL) and 1 N NaOH (240 mL) was heated under reflux for 1 h. Usual workup followed by recrystallization from THF gave 1.33 g (23% overall from **IIb**) of **15** as a pale yellow powder: mp 284–285 °C; IR (KBr) 1694, 1644, 1554, 1519, 1494 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.0 (br s, 1 H), 6.83 (d, 2 H, J = 8.4 Hz), 6.46 (d, 2 H, J = 8.4 Hz), 4.86 (br s, 2 H), 4.10 (t, 2 H, J = 7.4 Hz), 3.83 (t, 2 H, J = 7.4 Hz), 2.78 (t, 2 H, J = 7.4 Hz), 2.61 (t, 1 H, J = 6.5 Hz), 2.35–2.25 (m, 2 H), 2.20–2.10 (m, 2 H), 2.00–1.85 (m, 4 H), 1.70–1.50 (m, 6 H), 0.86 (t, 3 H, J = 8.0 Hz). Anal. ($C_{25}H_{31}N_5O_2$) C, H, N.

3-[4-(Acetylamino)phenethyl]-8-cyclopentyl-1-propylxanthine (16). To a stirred solution of 14 (1.00 g, 2.6 mmol), triethylamine (0.97 mL, 7.9 mmol), and 4-(dimethylamino)pyridine (64 mg, 0.52 mmol) was added dropwise 0.52 mL (5.5 mmol) of acetic anhydride, and the reaction mixture was stirred for additional 2 h. After water (100 mL) was added, standard workup and purification on silica gel column chromatography (eluent: 3% MeOH/$CHCl_3$) followed by recrystallization from EtOH yielded **16** (695 mg, 63%) as a colorless powder: mp > 270 °C; IR (KBr) 1699, 1661, 1647, 1533, 1504 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.04 (br s, 1 H), 9.84 (br s, 1 H), 7.45 (d, 2 H, J = 8.4 Hz), 7.07 (d, 2 H, J = 8.4 Hz), 4.16 (t, 2 H, J = 7.4 Hz), 3.81 (t, 2 H, J = 6.9 Hz), 3.35–3.05 (m, 1 H), 2.91 (t, 2 H, J = 7.4 Hz), 2.05–1.50 (m, 10 H), 2.00 (s, 3 H), 0.83 (t, 3 H, J = 7.4 Hz). Anal. ($C_{23}H_{29}N_5O_3$) C, H, N.

8-Cyclopentyl-3-[4-(isobutyrylamino)phenethyl]-1-propylxanthine (17). From compound 14 and isobutyryl chloride was obtained **17** as above in 56% yield after recrystallization from EtOH: mp > 270 °C; IR (KBr) 1701, 1655, 1516, 1498 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.04 (br s, 1 H), 9.73 (br s, 1 H), 7.47 (d, 2 H, J = 8.4 Hz), 7.06 (d, 2 H, J = 8.4 Hz), 4.16 (t, 2 H, J = 7.4 Hz), 3.81 (t, 2 H, J = 6.9 Hz), 3.20–3.05 (m, 1 H), 2.90 (t, 2 H, J = 7.4 Hz), 2.65–2.45 (m, 1 H), 2.05–1.50 (m, 10 H), 1.07 (d, 6 H, J = 6.9 Hz), 0.83 (t, 3 H, J = 7.4 Hz). Anal. ($C_{25}H_{33}N_5O_3$) C, H, N.

3-(4-Aminophenethyl)-8-(3-oxocyclopentyl)-1-propylxanthine (18). From 3-oxocyclopentanecarboxylic acid[40] was obtained **18** in the same manner as **15** in 16% overall yield from **IIb** after recrystallization from dioxane: mp 186–190 °C dec; IR (KBr) 1746, 1705, 1651, 1520 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.20 (br s, 1 H), 6.82 (d, 2 H, J = 8.4 Hz), 6.45 (d, 2 H, J = 8.4 Hz), 4.87 (br s, 2 H), 4.08 (t, 2 H, J = 7.5 Hz), 3.82 (t, 2 H, J = 7.4 Hz), 3.70–3.50 (m, 1 H), 2.76 (t, 2 H, J = 7.5 Hz), 2.70–2.05 (m, 6 H), 1.65–1.45 (m, 2 H), 0.85 (t, 3 H, J = 7.4 Hz). Anal. ($C_{21}H_{25}N_5O_3\cdot 1/2C_4H_8O_2$) C, H, N.

8-(3-Noradamantyl)-3-propyl-6-thioxanthine (IIIa). A mixture of 20.0 g (63.7 mmol) of 8-(3-noradamantyl)-3-propylxanthine[15b] and 23.1 g (104 mmol) of phosphorus pentasulfide in pyridine (370 mL) was refluxed for 4 h. The mixture was poured into ice–water (800 mL), and the resulting mixture was concentrated to about 1/3 volume. The solid from the cooled mixture was dissolved in 2 N NaOH and the solution filtered and acidified with concd HCl. The precipitate was filtered and recrystallized from EtOH–H_2O to afford 11.7 g (56%) of **IIIa** as pale yellow needles: mp 214–216 °C; IR (KBr) 1668, 1595 cm^{-1}; ^1H NMR ($CDCl_3$; 90 MHz) δ 10.14 (br s, 1 H), 9.43 (br s, 1 H), 4.05 (t, 2 H, J = 7 Hz), 2.73 (t, 1 H, J = 6 Hz), 2.68–1.40 (m, 14 H), 0.98 (t, 3 H, J = 7 Hz); MS, m/e (relative intensity) 330 (M^+, 100), 288 (18), 250 (17). Anal. ($C_{17}H_{22}N_4OS\cdot 1/5H_2O$) C, H, N.

6-(Methylthio)-8-(3-noradamantyl)-3-propyl-7*H*-purin-2-(3*H*)-one (IIIb). To a solution of **IIIa** (10 g, 30.3 mmol) in 120 mL of 0.5 N NaOH and 60 mL of EtOH was added 2.83 mL (45.5 mmol) of MeI at 0 °C. After being stirred for 1 h at room temperature, the mixture was neutralized with 1 N HCl and extracted with $CHCl_3$ three times. The organic extracts were dried over anhydrous sodium sulfate and concentrated. Purification on silica gel column chromatography (eluent: 2% MeOH/$CHCl_3$) followed by recrystallization from cyclohexane gave 7.71 g (74%) of **IIIb** as a white powder: mp 268–271 °C; IR (KBr) 1608, 1560, 1512 cm^{-1}; ^1H NMR ($CDCl_3$; 90 MHz) δ 13.3 (br s, 1 H), 4.23 (t, 2 H, J = 7 Hz), 2.80 (t, 1 H, J = 6 Hz), 2.50–1.45 (m, 14 H), 1.95 (s, 3 H), 0.96 (t, 3 H, J = 7 Hz). Anal. ($C_{18}H_{24}N_4OS$) C, H, N.

6-[(1-Ethyl-2-hydroxyethyl)amino]-8-(3-noradamantyl)-3-propyl-7*H*-purin-2(3*H*)-one (IIIc). A mixture of **IIIb** (3.20 g, 9.30 mmol) and 4.41 mL (46.5 mmol) of 2-amino-1-butanol in 6 mL of DMSO was heated at 150 °C for 3 h. After cooling, water (100 mL) was added, and the mixture was extracted with $CHCl_3$. Usual workup followed by purification on silica gel column chromatography (eluent: 7% MeOH/$CHCl_3$) gave 2.22 g (62%) of **IIIc** as a white powder. An analytical sample was recrystallized from EtOH/toluene: mp > 270 °C; IR (KBr) 1621 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.95 (br s, 1 H), 6.90 (d, 1 H, J = 8.9 Hz), 4.90 (br s, 1 H), 4.10–4.00 (m, 1 H), 3.85 (t, 2 H, J = 7.4 Hz), 3.50–3.35 (m, 2 H), 2.57 t, (1 H, J = 6.3 Hz), 2.40–2.30 (m, 2 H), 2.20–2.05 (m, 2 H), 2.00–1.45 (m, 12 H), 0.91 (t, 3 H, J = 7.3 Hz), 0.84 (t, 3 H, J = 7.4 Hz). Anal. ($C_{21}H_{31}N_5O_2$) C, H, N.

7,8-Dihydro-8-ethyl-2-(3-noradamantyl)-4-propyl-1*H*-imidazo[2,1-*i*]purin-5(4*H*)-one Hydrochloride (19). To a stirred solution of $SOCl_2$ (38 mL) was portionwise added 2.00 g (5.19 mmol) of **IIIc** at 0 °C. The reaction mixture was heated under reflux for 30 min and concentrated. To the residue was added aqueous saturated sodium bicarbonate solution. Extraction with $CHCl_3$, standard workup, followed by purification on silica gel chromatography (eluent: 2% MeOH/$CHCl_3$) gave 2.05 g (quantitative) of **19** as a free base. Treatment of a free base **19** with AcOEt solution saturated by hydrogen chloride gave precipitate which was recrystallized from AcOEt to afford an analytical sample (1.40 g, 67% from **19**) as pale yellow needles: mp 196–201 °C; IR (KBr) 1714, 1681, 1594 cm^{-1}; ^1H NMR (DMSO-d_6) δ 14.0–13.5 (br s, 1 H), 11.0–10.5 (br s, 1), 4.45–4.30 (m, 2 H), 4.10–3.80 (m, 3 H), 2.60 (t, 1 H, J = 6.0 Hz), 2.40–2.30 (m, 2 H), 2.20–2.05 (m, 2 H), 2.03–1.65 (m, 12 H), 0.97 (t, 3 H, J = 7.3 Hz), 0.89 (t, 3 H, J = 7.6 Hz). Anal. ($C_{21}H_{29}N_5O\cdot HCl$) C, H, N.

(*R*)-7,8-Dihydro-8-ethyl-2-(3-noradamantyl)-4-propyl-1*H*-imidazo[2,1-*i*]purin-5(4*H*)-one L-Tartrate (20). Compound **20** was prepared from **IIIb** and (*R*)-2-amino-1-butanol (Tokyo Chem. Ind. Co., Japan) following the same procedure as above. To a solution of the obtained free base (1.36 g, 3.73 mmol) in 40 mL of 2-PrOH was added a solution of 560 mg (3.73 mmol) of L-tartaric acid with stirring. The precipitate was collected and recrystallized twice from 2-PrOH to give 510 mg (26%) of optically pure **20**: mp 209 °C; $[\alpha]^{20}_D$ = +3.58° (c = 1.00, MeOH); optical purity, >99%, determined by HPLC [CHIRALCEL OD column (4.6 × 250 mm, Daicel Chem. Ind.) and eluting with hexane/EtOH/diethylamine = 95/5/0.05]. Anal. ($C_{21}H_{29}N_5O\cdot C_4H_6O_6$) C, H, N.

(*S*)-7,8-Dihydro-8-ethyl-2-(3-noradamantyl)-4-propyl-1*H*-imidazo[2,1-*i*]purin-5(4*H*)-one D-Tartrate (21). Compound **21** was prepared from **IIIb** and (*S*)-2-amino-1-butanol (Tokyo Chem. Ind. Co., Japan) following the same procedure as above. An optically pure sample was obtained by recrystallization twice from 2-PrOH: mp 209–211 °C; $[\alpha]^{20}_D$ = −3.71° (c = 1.00, MeOH); optical purity, 99%, determined by HPLC as above. Anal. ($C_{21}H_{29}N_5O\cdot C_4H_6O_6$) C, H, N.

Biochemistry. N^6-[^{3}H]Cyclohexyladenosine A_1 Binding.[19] 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[R] Dupont), 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-phenylisopropyl)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.). When concentration–inhibition curves were carried out in duplicate with five or more concentrations of each test agent, 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.[15] 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.[20] Rat striatal tissue was homogenized in ice-cold 50 mM Tris–HCl pH 7.7 buffer, and 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 dimethylsulfoxide). 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.

Pharmacology. All compounds were suspended in 0.3% CMC (sodium carboxymethylcellulose) or 0.3% tween 80.

(R)-PIA-Induced Passive Avoidance Failure in Mice.[13,17] These tests were performed with a step-through-type passive avoidance apparatus. As experimental apparatus, two compartments (bright and dark) with automatic management system were used. The automatic management system consisted of bright compartment (15 × 9 × 11 cm) with a 4-W white fluorescent light and dark compartment (15 × 14 × 18 cm). The compartments were separated by a guillotine door (3 × 3 cm). In the acquisition trial, a mouse (ddY, 20–25 g) placed in the bright compartment could enter, through the door, into the dark compartment that had a grid on the floor. As soon as the mouse entered the dark compartment, a scrambled foot-shock (0.3 mA) was delivered to the floor grid for 2 s. Maximum measurement time was for 600 s, and the latency of animals which did not move into the dark compartment during the observation period was calculated to be 600 s. Amnesia was induced by (R)-PIA. Test compounds were orally administered 1 h before the acquisition trial (training), and 30 min prior to the acquisition trial, (R)-PIA (0.3 mg/kg) was intraperitoneally administered in mice. The test trial was performed 24 h later. The latency times of naive mice (without treatment of R-PIA and test compounds) for acquisition and test trials were 18.9 ± 2.4 and 413.3 ± 54.2 s, respectively.

Scopolamine-Induced Passive Avoidance Failure in Rats.[23] As experimental apparatus, two compartments (bright and dark) were similarly used. The experimental box consisted of bright compartment (25 × 25 × 25 cm) with a 100-W bulb light and dark compartment (25 × 25 × 25 cm). The compartments were separated by a guillotine donor (9 × 9 cm). In the acquisition trial, a rat (male, Wistar 220–280 g, Charles River) placed in the bright compartment could enter, through the door, into the dark compartment that had a grid on the floor. As soon as the rat entered the dark compartment, a foot shock (2 mA) was delivered to the floor grid for 2 s. In the test trial, given 24 h after acquisition trial, the animal was again placed in the bright compartment and the response latency into the dark compartment was measured. Maximum measurement time was 600 s, and the latency of animals that did not move into the dark compartment during the observation period was calculated to be 600 s.[32a] Amnesia was induced by scopolamine. Test compounds were orally administered 1 h before the acquisition trial (training), and 30 min prior to the acquisition trial, scopolamine (1.0 mg/kg) was intraperitoneally administered in rat. The test trial was performed 24 h later. The latency times of naive rats (without treatment of scopolamine and test compounds) for acquisition and test trial were 10.6 ± 2.6 and 557.4 ± 21.6 s, respectively.

Locomotor Activity of Mice. Male ddY mice (19–21 g) were monitored in the horizontal activity in Automex-II (Columbus Instruments) for 120 min after the oral administration of test compounds. Data were collected between 4:00 pm and 6:00 pm. Statistical analysis was performed using Dunnet's multiple range test. The results are represented as mean ± SEM for each point (n = 4–8). The number of mice in each experimental group was five.

Cardiovascular Effects in Anesthetized Rats.[15c,36] The experiments were conducted on male Wistar rats (SLC) weighing 250–300 g. Forty-five min after oral administration of the xanthine derivative or the vehicle, anesthesia was induced with urethane (1.25 g/kg, ip). The rats were tracheotomized, and polyethylene catheters were inserted into the common artery for continuous blood pressure and heart rate recording. Another polyethylene catheter was inserted into the external jugular vein for NECA administration. Sixty min after the administration of the xanthine derivative, increasing doses of NECA were given intravenously and the changes in blood pressure and heart rate were recorded. Immediately after injection there was a marked drop in blood pressure and there was also a transient fall in heart rate. The effect of vehicles (saline or 0.3% tween 80) on this blood pressure reduction is negligible or nonexistent. Full dose–response curves were constructed in at least six animals at each dose of the xanthine.

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