man.[20] As previously reported,[6,8,14b] we also found that the more hydrophilic inhibitors pravastatin (2) and BMY-21950 (4) were more tissue selective than lovastatin in vitro. It might also be concluded from this data that tissue selectivity is not related to a particular structural feature or series of inhibitors, since 2, 4, 8, 9, and 11, which are from four very different chemical series of inhibitors, possess comparable degrees of selectivity. Also of note is the fact that conversion of pyridine 10 to *N*-oxide 11 results in 100- and 35-fold decreases in potency in spleen and testis, respectively, while increasing potency in liver 3-fold. Similar, though less dramatic changes are seen in the pyrazole series (compounds 7–9) on replacement of the *N*-phenyl ring by 2-pyridyl or 2-pyrazinyl.

Of the compounds possessing CLOGP > 2, compound 5 is unusual, in that unlike the other inhibitors, which are more potent in peripheral tissues than in liver, it is equipotent in all tissues. This result suggests that the tissue selectivity reported previously for this compound in cell culture[21] and in vivo[22] is not due to differential tissue potencies, but to some other factor, such as first-pass metabolism.

In summary, with isolated tissue cubes from rat liver, spleen, and testis, it has been shown that the tissue selectivity of a diverse group of potent inhibitors of HMG-CoA reductase was not related to a particular structural feature but was highly dependent on the ability of peripheral tissues to discriminate between compounds on the basis of lipophilicity. This conclusion was supported by a quantitative structure–activity relationship analysis, which not only demonstrated that liver potency was insensitive to changes in lipophilicity at low CLOGP and that a parabolic dependence of potency on lipophilicity (CLOGP) existed in the two peripheral tissues examined but also revealed a linear relationship between lipophilicity and tissue selectivity (tissue IC_{50}/liver IC_{50}). Although the relevance of these observations to the clinical situation is uncertain, these studies suggest that liver selectivity is based on differential membrane sensitivity to lipophilicity, with low CLOGP compounds showing significant selectivity for liver over peripheral tissues. Studies relating the lipophilicity of HMGR inhibitors to tissue selectivity ex vivo and in vivo will be the subject of future reports from these laboratories.

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8-(Dicyclopropylmethyl)-1,3-dipropylxanthine: A Potent and Selective Adenosine A_1 Antagonist with Renal Protective and Diuretic Activities

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. Considerable efforts to search for selective antagonists have been invested in order to elucidate the physiological role of adenosine.[2] Theophylline (1; Figure 1) and caffeine (2) exert pharmacological effects primarily through blockade of adenosine receptors. However, they are virtually nonselective antagonists and have weak affinity for A_1 and A_2 receptors. Studies of structure–activity relationships of xanthines[3–8] revealed that alkyl substitution at the 1- and 3-positions markedly increased affinity at both A_1 and A_2 receptors. On the other hand, 8-aryl or 8-cycloalkyl substitution resulted in selective and potent A_1 antagonists. Further studies suggest that the sp^3 carbons containing cycloalkyl ring has more favorable interactions with a hydrophobic pocket of the A_1 receptor than the sp^2 carbons in an aryl ring.[5,9] Thus 8-cyclopentyl-1,3-dipropylxanthine (4)[5,10] has been known as the most potent A_1 antagonist.

With the aim of characterizing the hydrophobic interactions between the 8-substituent in xanthine and the A_1-receptor site, we designed xanthines with several substituted methyl group (6) on the basis of compound (4) and A_1-selective antagonist 8-(2-methylcyclopropyl)-1,3-dipropylxanthine (5).[11] The present study describes a new xanthine derivative that is a selective and potent A_1 antagonist and exhibits interesting pharmacological activities.

Synthetic methods are outlined in Scheme I. Acylation of the appropriate 5,6-diaminouracil (7)[12] with a carboxylic acid or its acid chloride, followed by treatment with aqueous sodium hydroxide or phosphorus oxychloride under reflux, gave the corresponding xanthines (6).[13]

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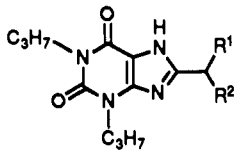
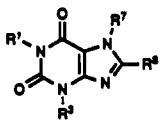
Table I. Affinities of A_1 and A_2 Adenosine Receptor Binding of 8-Substituted-1,3-dipropylxanthines



no.	R^1	R^2	K_i,[a] nM A_1	K_i,[a] nM A_2	K_i ratio A_2/A_1
9	methyl	methyl	49 ± 9.4	1500 ± 150	31
10	methyl	ethyl	25 ± 0.58	1200 U 73	48
11	methyl	amino	3000 ± 250	>100000	>33
12	methyl	benzyl	260 ± 33	480 ± 59	1.8
13	methyl	(4-methoxyphenyl)methyl	220 ± 8.8	580 ± 150	2.6
14	ethyl	ethyl	19 ± 1.0	570 ± 44	30
15	ethyl	phenyl	100 ± 9.8	1100 ± 120	11
16	ethyl	phenoxy	900 ± 46	3300 ± 580	3.7
17	propyl	propyl	78 ± 4.1	590 ± 49	7.6
18	cyclopropyl	cyclopropyl	3.0 ± 0.21	430 ± 5.8	140
19	cyclopropyl	phenyl	150 ± 28	1800 ± 33	12
20	cyclopropyl	4-methoxyphenyl	250 ± 32	2200 ± 650	8.8
21	cyclopropyl	4-fluorophenyl	250 ± 22	1400 ± 130	5.6
22[b]	2-methylcyclopropyl	2-methylcyclopropyl	9.7 ± 3.7	1000 ± 130	100
23	cyclopentyl	phenyl	400 ± 80	4000 ± 1500	10
24	cyclohexyl	cyclohexyl	>100000	>100000	
25	phenyl	phenyl	2100 ± 200	>100000	>48
1	(theophylline)		23000 ± 330	16000 ± 2200	0.70
2	(caffeine)		>100000	27000 ± 1700	
3	(1,3-dipropylxanthine)		1200 ± 120	2400 ± 420	1.7
4	(8-cyclopentyl-1,3-dipropylxanthine)		6.4 ± 0.35	590 ± 48	92

[a] A_1 binding was carried out with [^{3}H]cyclohexyladenosine in guinea pig forebrain membranes as described,[14] and A_2 binding was carried out with [^{3}H]-5'-(*N*-ethylcarbamoyl)adenosine in the presence of 50 nM cyclopentyladenosine in rat striatal membranes.[4] Concentration-inhibition curves were carried out in duplicate with five or more concentrations of test agent, and IC_{50} values were calculated using nonlinear least-squares curve fitting.[4] IC_{50} values were converted to K_i values as described.[4] All values are means ± SEM for three separate determinations. [b] Mixture of possible stereoisomers.

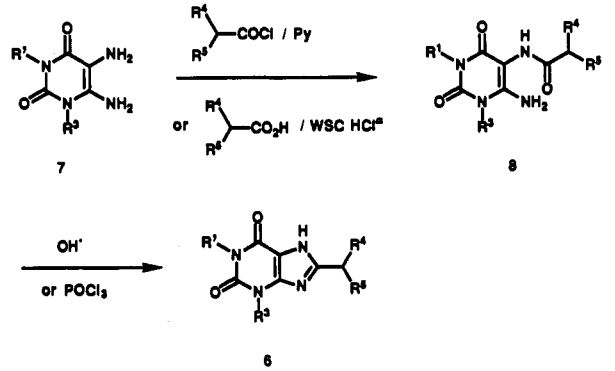


	R^1	R^3	R^7	R^8
1	methyl	methyl	H	H
2	methyl	methyl	methyl	H
3	propyl	propyl	H	H
4	propyl	propyl	H	cyclopentyl
5	propyl	propyl	H	2-methylcycloproryl

Figure 1. Xanthine derivatives.

Table I shows a series of 1,3-dipropylxanthine derivatives containing substituted methyl group at 8-position with K_i values. 8-Alkyl substitution enhanced affinity to A_1 and A_2 receptors (compare **9**, **10**, **14**, **17**, and **18** with **3**). 1,3-Dipropyl-8-(3-pentyl)xanthine (**14**), a open-chain analogue of **4**, had about 63-fold higher affinity to the A_1 receptor than a parent compound (**3**) and moderate A_1 selectivity. But **14** was a less potent A_1 antagonist than **4**. A further increase or decrease in the size of alkyl substitutent (R^1 or R^2) caused a loss of affinity at the A_1 receptor (compare **9**, **10**, and **17** with **14**). An amino or a phenoxy group reduced affinity to A_1 and A_2 receptors (**11** and **16**). Benzyl (**12** and **13**) or phenyl (**15**) substitution in R^2 caused a reduction of affinity for the A_1 receptor as compared with the corresponding alkyl analogues (**9**, **10**, **14**). Furthermore in the phenyl-substituted series, the bulkiness of another substituent (ethyl **15**, cyclopropyl **19–21**, cyclopentyl **23**) had little effect on affinity to A_1 receptor. Thus the electrostatic effect of phenyl groups appeared to be unfavorable for receptor interactions.

Scheme I[a]



[a] Water-soluble carbodiimide hydrochloride [1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride].

Dicyclopropyl substitution (**18**) caused a remarkable enhancement of affinity at the A_1 receptor (K_i = 3.0 nM), resulting in an antagonist with higher potency and selectivity (140-fold) than those of **4**.[4,10] Incorporation of methyl group to dicyclopropyl substitution (**22**) slightly reduced affinity to both A_1 and A_2 receptors. Dicyclohexyl (**24**) or diphenyl (**25**) substitution was inactive at both A_1 and A_2 receptors.

Since 8-(dicyclopropylmethyl)-1,3-dipropylxanthine (**18**) was a potent and selective antagonist at the A_1 receptor, the effects of other substituents in the 1-, 3-, and 7-positions were examined (Table II). As expected from earlier studies,[3,5] propyl substitution at both 1- and 3-positions,

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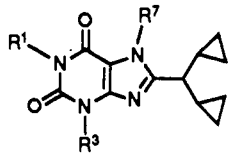
Table II. EFfects of Substituents in the 1-, 3-, and 7-Positions on the Activity of 8-(Dicyclopropylmethyl)xanthine Derivatives at A_1 and A_2 Adenosine Receptors[a]



no.	R^1	R^3	R^7	K_i,[a] nM A_1	K_i,[a] nM A_2	K_i ratio A_2/A_1
26	methyl	methyl	H	81 ± 3.7	2700 ± 270	33
27	ethyl	ethyl	H	13 ± 1.5	690 ± 66	53
18	propyl	propyl	H	3.0 ± 0.21	430 ± 5.8	140
28	butyl	butyl	H	5.5 ± 0.52	440 ± 69	80
29	methyl	isobutyl	H	12 ± 4.6	410 ± 140	34
30	H	propyl	H	1300 ± 58	>100000	>77
31	propyl	propyl	methyl	7400 ± 1000	29000 ± 3500	3.9
32	propyl	propyl	ethyl	1600 ± 150	14000 ± 670	8.8
33	propyl	propyl	propyl	13000 ± 1600	6300 ± 660	0.48
34	propyl	propyl	carboxymethyl	6900 ± 1400	>100000	>14

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

Table III. Effects on Urine Volume and Na^+ and K^+ Excretion after Oral Administration in Rats[a]

compound	UV[g]	Na^+	K^+	Na^+/K^+[h]
18[b]	2.39	2.69	1.10	2.11
4[c]	1.87	1.98	1.26	1.57
theophylline (1)[d]	1.42	1.52	1.16	1.31
caffeine (2)[e]	0.92	1.10	0.99	1.10
furosemide[f]	1.59	1.62	1.32	1.22

[a] After deprivation of food for 18 h, compounds were suspended with saline and administered at a dose of 6.25 mg/25 mL per kg to three groups of three male Wistar rats (SLC, ca. 2000 g), and urine was collected for 6 h. Values are ratios of urinary excretion value in treated rats to urinary excretion value in control rats. [b] Mean urine volume, Na^+ and K^+ excretion values in control rats were 1.00 ± 0.12 (SEM) mL/100 g per 6 h, 0.138 ± 0.011 mequiv/100 g per 6 h, and 0.103 ± 0.009 mequiv/100 g per 6 h, respectively. [c] Mean urine volume, Na^+ and K^+ excretion values in control rats were 1.26 ± 0.21 mL/100 g per 6 h, 0.191 ± 0.029 mequiv/100 g per 6 h, and 0.123 ± 0.007 mequiv/100 g per 6 h, respectively. [d] Mean urine volume, Na^+ and K^+ excretion values in control rats were 0.83 ± 0.08 mL/100 g per 6 h, 0.132 ± 0.010 mequiv/100 g per 6 h, and 0.097 ± 0.006 mequiv/100 g per 6 h, respectively. [e] Mean urine volume, Na^+ and K^+ excretion values in control rats were 0.87 ± 0.04 mL/100 g per 6 h, 0.145 ± 0.011 mequiv/100 g per 6 h, and 0.094 ± 0.005 mequiv/100 g per 6 h, respectively. [f] Mean urine volume, Na^+ and K^+ excretion values in control rats were 0.69 ± 0.03 mL/100 g per 6 h, 0.079 ± 0.006 mequiv/100 per 6 h, and 0.105 ± 0.004 mequiv/100 g per 6 h, respectively. [g] Urine volume. [h] Values are ratios of Na^+/K^+ in treated rats to Na^+/K^+ in control rats.

Table IV. Serum Creatinine (Cr) and Urea Nitrogen (UN) Concentrations in Glycerol-Injected Rats Treated by Vehicle or Compounds[a]

compound	dose, mg/kg, ip	Cr, mg/dL	UN, mg/dL
vehicle		5.43 ± 0.11	182.5 ± 3.4
18	1	2.99 ± 0.28***	107.6 ± 10.2***
4	1	3.75 ± 0.38**	131.7 ± 9.3***
aminophylline	10	5.32 ± 0.19	174.0 ± 10.4
furosemide	10	4.17 ± 0.41[b]	150.3 ± 13.7*[b]

[a] Bowmer's method[20] was modified to induce acute renal failure. Fifty percent v/v glycerol in sterile saline (0.8 mL/100 g) was injected subcutaneously to male Wistar rats (SLC, 250–300 g) 30 min after vehicle or compounds treated. At 24 h after glycerol injection, serum creatinine and urea nitrogen concentrations were determined. All values are the means ± SEM; *, **, ***: significant difference from vehicle-treated group (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$). [b] Serum creatinine and urea nitrogen concentrations of vehicle-treated groups were 3.22 ± 0.35 and 110.7 ± 9.4 mg/dL, respectively.

was optimum to potent and selective A_1 antagonism (**26–29**). Alkyl substitution at 1-position was important for potency, since compound (**30**) was 430-fold less active than compound **18** to the A_1 receptor. Substitution at the 7-position reduced affinity to both A_1 and A_2 receptors (**31–34**).[15] Thus **18** was the optimum A_1 antagonist among the 8-dicyclopropylmethyl-substituted xanthines. Although water solubility[16] (8.5 μg/mL) of **18** is poor, it is a little better than that (3.4 μg/mL) of **4**.

Recently, the mechanism for the diuretic action of xanthines such as theophylline was proposed to be adenosine antagonism.[17] And furthermore, adenosine has been proven to be an important factor in the development of acute renal failure.[18] During our studies, the diuretic effect[17c] and the protective effect of glycerol-induced acute renal failure of theophylline[18b] and 8-cyclopentyl-1,3-dipropylxanthine (**4**)[18c] was reported. We found independently from their studies that the potent and selective A_1 antagonist, compound **18** exhibited not only more potent diuretic and natriuretic activities but also more potent protective effect on glycerol-induced acute renal failure than theophylline (see Tables III and IV).[19] This result supports that A_1 adenosine receptors mediate diuretic activity and the protective effect against acute renal failure.

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It was notable that furosemide, a high-celing diuretic, showed weaker diuretic activy and lower urinary ratio (Na^+/K^+) than compound 18, and increased the severity of glycerol-induced acute renal failure. They are unsuitable characters for a diuretic. In conclusion, we identified that 8-(dicyclopropylmethyl)-1,3-dipropylxanthine (18, KF-15372) is the most potent and selective adenosine A_1 receptor antagonist reported to date. The physiological role of adenosine A_1 receptors in the kidney and detailed pharmacological activities of 18 are under active study in our laboratories and will be reported in due course.

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Design of a Well-Absorbed Renin Inhibitor

Renin is the first and rate-limiting enzyme in the well-known renin–angiotensin cascade that produces the pressor hormone angiotensin II, thus inhibition of this enzyme could lead to the introduction of a new class of antihypertensive agents.[1] Orally active inhibitors of angiotensin converting enzyme (ACE), the second enzyme in the cascade, have been demonstrated clinically efficacious for controlling hypertension,[2] however an orally active, and hence therapeutically useful, renin inhibitor has yet to be developed. In order to become a viable drug, an orally active renin inhibitor must possess two attributes. It must be absorbed from the gastrointestinal tract into the systemic circulation and it must elicit a dose-related lowering of blood pressure when given orally in a pharmacologic model. Although a number of claims of oral activity for renin inhibitors have appeared in the literature,[3-5] the majority of these claims are based solely upon blood pressure effects observed following oral administration, and absorption is not addressed.[3] In one case an inhibitor was described as orally active only upon the basis of measurement of changes in plasma renin activity.[4] Bioavailability was determined in rats for one renin inhibitor and found to be low.[5]

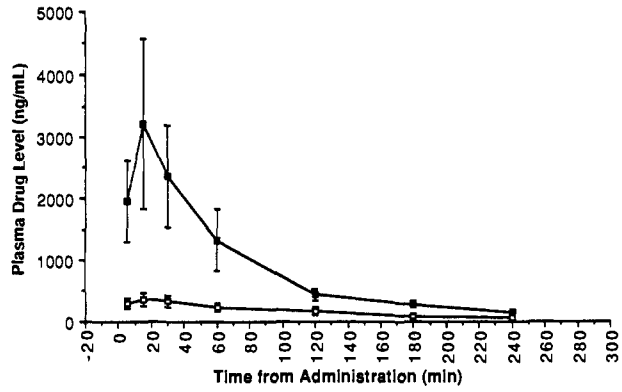

Figure 1. Plasma drug levels from a 10 mg/kg i.d. dose of inhibitor 4 in anesthetized, salt-depleted cynomolgus monkeys ($n = 4$). Points are designated as follows: arterial samples (□) and portal vein samples (■).

We have previously described a series of renin inhibitors that incorporated a C-terminal oxazolidinone. These compounds possessed both high hydrophilicity and excellent intravenous efficacy, but exhibited low bioavailability in monkey and rat models when dosed via the intraduodenal route.[6] The low systemic drug levels were attributed to extensive first pass hepatic uptake followed by biliary excretion.[7] These inhibitors contained histidine at the P_2 site.[8] Since it is known that the presence of polar or potentially ionizable groups can augment biliary excretion,[9] we reasoned that it was the presence of the basic imidazole of the histidine residue that was responsible for the low bioavailability. This report describes the results from a study in which substitution of other groups in place of the imidazole was shown to have profound effects upon intestinal absorption.

The structures of the compounds described are shown in Table I. We have previously shown in another series of renin inhibitors that other heterocycles could replace the histidine imidazole without loss in potency against purified human renal renin at pH 6.0.[10] This was largely the case in the current series with the exception of compound 3, incorporating 1-methylhistidine, which was 7-fold less potent than the parent histidine-containing inhibitor 1[6] in the purified renin assay. In the more physiologically relevant plasma renin assay conducted at pH 7.4, only inhibitor 4, containing (4-thiazolyl)Ala, showed good activity (6-fold loss in potency compared to 1) while the other compounds were 16-fold to 45-fold less potent than 1.

Inhibitors 1–5 were administered intraduodenally to anesthetized rats.[11] Plasma drug levels were determined by a renin inhibition assay[12] from samples taken from both

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