H, Im-CH_2), 7.05 (s, 1 H, Im-H), 7.3 (s, 1 H, Im-H). Anal. ($C_9H_{14}N_4O_3$) C, H, N.

1-(2-Nitro-1-imidazolyl)-3,3-dimethyl-3-(1-aziridinyl)-2-propanol (23). 1-Potassio-2-nitroimidazole (3.05 g, 20.2 mmol) in dry CH_3CN (50 mL) was stirred with 4-bromo-2-methylbut-2-ene (4.75 g, 31.8 mmol) and 18-crown-6 (0.26 g, 0.98 mmol) for 24 h. The suspension was evaporated and redissolved in $CHCl_3$ (200 mL) and washed with H_2O (4 × 75 mL) and saturated NaCl (75 mL) and then dried and evaporated to dryness. The residue was purified on silica gel eluting with $CHCl_3$ to afford 0.8 g (22%) of 1-(3-methylbutenyl)-2-nitroimidazole (**21**) as a pale yellow oil: NMR ($CDCl_3$) δ 1.8 (bs, 6 H, CH=C(CH_3)$_2$), 5.1 (bd, 2 H, Im-CH_2), 5.4 (m, 1 H, C*H*=C(CH_3)$_2$), 7.1 (s, 1 H, Im-H), 7.15 (s, 1 H, Im-H).

The above alkene (2.7 g, 14.9 mmol) was dissolved in CH_2Cl_2 (100 mL) and heated under reflux with MCPBA (6.29 g, 20.1 mmol) for 1 h, cooled, diluted with CH_2Cl_2 (100 mL), and washed with 10% Na_2SO_3(aq) (3 × 150 mL), H_2O (2 × 150 mL), and saturated $NaHCO_3$(aq) (2 × 150 mL). The solution was dried (Na_2SO_4) and evaporated, and the residue was purified on silica, eluting with EtOAc, to give 1.8 g (81.7%) of 1-(3,3-dimethyl-2,3-epoxybutyl)-2-nitroimidazole (**22**) as a pale yellow oil: NMR ($CDCl_3$) δ 1.4 (s, 3 H, oxirane 3-CH_3), 1.45 (s, 3 H, oxirane 3-CH_3), 3.2 (dd, 1 H, *J* = 3.6 and 8.4 Hz, oxirane 2-CH), 4.3 (dd, 1 H, *J* = 8.4 and 13.5 Hz), and 5.1 (dd, 1 H, *J* = 3.6 and 14.4 Hz), Im-CH_2, 7.15 (s, 1 H, Im-H), 7.3 (s, 1 H, Im-H).

The oxiranyl synthon **22** (1.09 g, 5.5 mmol) was dissolved in EtOH (1% Et_3N) (30 mL) and heated under reflux with 1*H*-aziridine (2.0 g, 46.5 mmol) for 10 h. Further aziridine (5 mL, 116 mmol) was then added, and heating was continued for another 4 h. The solution was then evaporated and the residue purified on silica (eluting with $CHCl_3$/MeOH/Et_3N (90:9:1)) to afford, after recrystallization from EtOH (1% Et_3N), 0.32 g (32.8%) of **23** as a pale yellow solid: mp 127–128 °C; NMR ($(CD_3)_2SO$) δ 0.78 (s, 3 H, C(CH_3)), 0.83 (s, 3 H, C(CH_3)), 1.4 (m, 4 H, 2 × aziridine CH_2), 4.25 (dd, 1 H, *J* = 10.7 and 13.5 Hz) and 4.92 (dd, 1 H, *J* = 1.5 and 13.5 Hz), Im-CH_2, 5.07 (d, 1 H, *J* = 6.2 Hz, OH), 7.14 (s, 1 H, Im-H), 7.59 (s, 1 H, Im-H); NMR ($CDCl_3$) δ 0.92 (s, 3 H, C(CH_3)), 0.98 (s, 3 H, C(CH_3)), 1.5 (m, 2 H) and 1.53 (m, 1 H) and 1.61 (m, 1 H), 2 × aziridine CH_2, 3.66 (dd, 1 H, *J* = 1.7 and 10.1 Hz, C*H*OH), 4.10 (dd, 1 H, *J* = 10.2 and 13.5 Hz) and 4.9 (dd, 1 H, *J* = 1.7 and 13.5 Hz), Im-CH_2, 4.2 (br, 1 H, OH), 7.08 (d, 1 H, *J* = 1.1 Hz, Im-H), 7.27 (d, 1 H, *J* = 1.1 Hz, Im-H). Anal. ($C_{10}H_{16}N_4O_3$) C, H, N.

1,2-*cis*-2,3-*trans*-3-Aziridin-1-yl-2-hydroxy-1-(2-nitroimidazol-1-yl)cyclohexane (26). 1-Cyclohex-2-enyl-2-nitroimidazole was prepared and epoxidized with MCPBA as described previously.[18] The anti-isomer **24** was isolated as unreacted starting material when a mixture of isomers was used for the following reaction. The syn-isomer **25** reacts with aziridine, but could be obtained in pure form when the above epoxidation was carried out with dried peroxy acid as described previously.[18]

The oxiranyl synthon **25** (0.5 g, 2.4 mmol) was refluxed in 40 mL of EtOH (1% Et_3N) with 1*H*-aziridine (2.0 g, 46.5 mmol) for 1.5 h. The solution was evaporated to dryness and the residue purified on silica, eluting with $CHCl_3$/MeOH/Et_3N (90:9:1), to give 0.15 g (26%) of **26** as a pale yellow solid, recrystallized from acetone: mp 204–206 °C; NMR ($(CD_3)_2SO$) δ 1.12 (dd, 1 H, *J* = 6.0 and 3.3 Hz, aziridine-H syn to N-cycohexane bond), 1.16 (dd, 1 H, *J* = 6.0 and 3.4 Hz, aziridine-H syn to *N*-cyclohexane bond), 1.45–1.90 (m, 7 H, 2 × aziridine-H anti to *N*-cyclohexane bond + 4ax,4eq,5ax,5eq,6eq-H), 2.17 (dq, 1 H, *J* = 11.4 and 3.4 Hz, 6ax-H), 3.34 (m, 1 H, 3-H), 3.91 (m, 1 H, 2-H), 5.11 (d, 1 H, *J* = 5.6 Hz, OH), 5.49 (d ca. t, 1 H, *J* = 11.9 and 3 Hz, 1-H), 7.15 (d, 1 H, *J* = 0.7 Hz, Im-4H), 7.67 (d, 1 H, *J* = 0.7 Hz, Im-5H); EIMS 252.1222 (calcd for $C_{11}H_{15}N_4O_3$ 252.1240).

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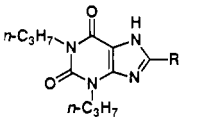
Communications to the Editor

7,8-Dihydro-8-ethyl-2-(3-noradamantyl)-4-propyl-1*H*-imidazo[2,1-*i*]purin-5(4*H*)-one: A Potent and Water-Soluble Adenosine A_1 Antagonist

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. A_1 receptors exhibit relatively high affinity to adenosine in binding studies (nM) and some are coupled to and inhibit adenylate cyclase. In contrast, A_2 receptors exhibit low affinity to adenosine (μM) and some are coupled to, but stimulate adenylate cyclase.[2,3]

Considerable effort to search for selective antagonists has been invested in order to elucidate the physiological role of adenosine and develop therapeutic agents.[4,5] Although many selective adenosine A_1 antagonists such as 1 (DPCPX)[6] and 2 (KF15372)[7] are recently available



compound		R
1	(CPX)	cyclopentyl
2	(KF15372)	dicyclopropylmethyl
3	(KW-3902)	3-noradamantyl
10	(KFM19)	3-oxocyclopentyl

Figure 1. Chemical structure of xanthine derivatives.

(1) Jacobson, K. A.; van Galen, P. J. M.; Williams, M. Adenosine Receptors: Pharmacology, Structure-Activity Relationships, and Therapeutic Potential. *J. Med. Chem.* **1992**, *35*, 407–422.
(2) Londos, C.; Wolff, J. Two Distinct Adenosine-Sensitive Sites on Adenylate Cyclase. *Proc. Natl. Acad. U.S.A.* **1977**, *74*, 5482–5486.
(3) (a) Van Calker, D.; Müler, M.; Hamprecht, B. Adenosine Regulates via Two Different Types of Receptors, the Accumulation of Cyclic AMP in Cultured Brain Cells. *J. Neurochem.* **1979**, *33*, 999–1005. (b) Linden, J. Structure and Function of A_1 Adenosine Receptors. *FASEB J.* **1991**, *5*, 2668–2676.
(4) Williams, M. Adenosine antagonists. *Med. Res. Rev.* **1989**, *9*, 219–243.
(5) Bruns, R. F. Structure Activity Relationships for Adenosine Antagonists. In *Purines in Cellular Signaling: Targets for New Drugs*. Jacobson, K. A., Daly, J. W., Manganiello, V., Eds.; Springer: New York, 1990; pp 126–135.
(6) Bruns, R. F.; Fergus, J. H.; Badger, E. W.; Bristol, J. A.; Stantay, L. A.; Hartman, J. D.; Hays, S. J.; Huang, C. C. Binding of the A_1-Selective Adenosine Antagonist 8-Cyclopentyl-1,3-dipropylxanthine to Rat Brain Membranes. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1987**, *335*, 59–63.

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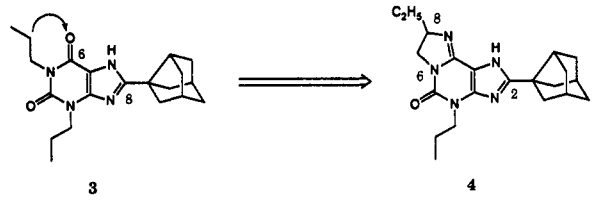
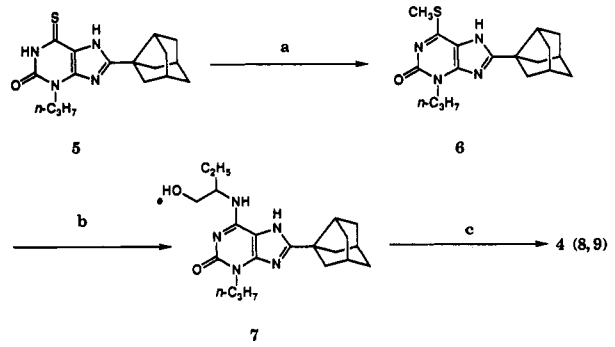
Scheme I



Scheme II[a]



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

(Figure 1), their pharmacological studies have been hampered by low water solubility. Thus we have screened for a water-soluble and potent adenosine A_1 antagonist.

As an initial structural approach, we considered the xanthines as a reasonable starting point for the development of such a compound. We recently reported that introduction of the conformationally restricted cyclopentyl moiety into the 8-position of 1,3-dipropylxanthines enhanced the A_1 antagonism and the 8-(3-noradamantyl)-substituted xanthine **3** (KW-3902) was identified to be a selective and the most potent A_1 receptor antagonist reported to date.[8] Like many other xanthines, however, **3** shows low water solubility, which precludes the development of a parenteral dosage form. Therefore, basic non-xanthine compounds, with similar structural and functional features, became the initial targets. The design of these compounds involved "constraining" the 1-propyl group present in **3** onto the pyrimidine ring to form a tricyclic ring system as shown in Scheme I. The oxygen at the 6-position was replaced by nitrogen. Formation of an acid salt of such a basic dihydroimidazole should increase the water solubility. Critical to the early success of this approach would be demonstration of adenosine A_1 antagonism and improved water solubility.

As shown in Scheme II, 6-thioxanthine derivative **5** 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 (**6**; yield 74%).[9] Reaction of **6** 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 (**7**; 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-

Table I. A_1 and A_2 Receptor Binding and Water Solubility of Adenosine Antagonists

compd	K_i,[a] nM A_1	K_i,[a] nM A_2	K_i ratio A_2/A_1	solubility,[b] μg/mL water	solubility,[b] μg/mL saline
1	6.4 ± 0.35	590 ± 48	92	3.3	NT
2	3.0 ± 0.21	430 ± 5.8	140	8.5	5.8
3	1.3 ± 0.12	430 ± 30	290	0.5	0.6
10	15	2700	180	220	200
4	5.7 ± 0.51	330	58	3200	990
8(*R*)	2.7 ± 0.09	290	107	3000	NT
9(*S*)	120	250	2.1	2900	NT

[a] A_1 binding was carried out with N^6-[^{3}H]cyclohexyladenosine in guinea pig forebrain membranes as described,[8] 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.[16] When the assays were carried out three or more times, standard errors (SEM) are given in the table. [b] Compounds (10 mg) were agitated in water (2.5 mL) at 20 °C for 1 h. After filtration, content of compounds in water (solubility) was assessed by HPLC analysis [YMC AM-312 (ODS) column (Yamamura Kagaku); eluent, CH_3CN–0.05 M phosphate buffer solution (pH 3.0); detector (UV), 295 nm; column temperature 40 °C].

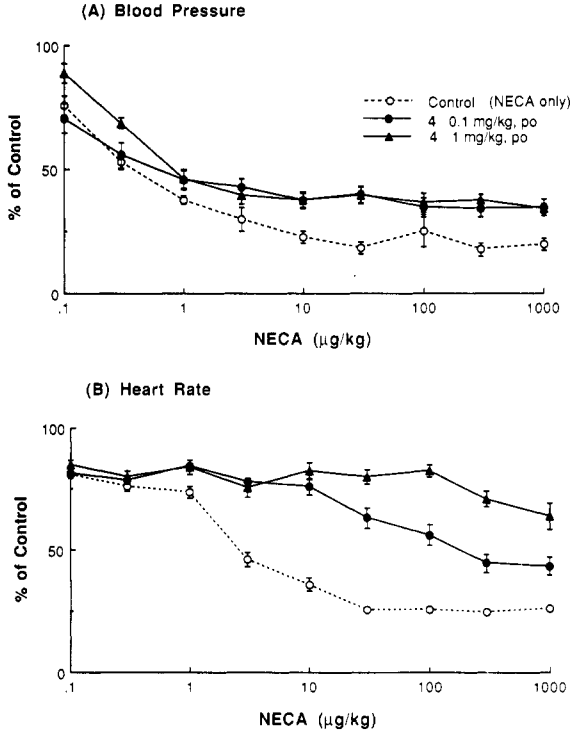


Figure 2. Effect of compound **4** on NECA-induced (A) hypotensive and (b) bradycardic responses in anesthetized rats. The dotted line shows the effects of NECA. Compound **4** was dissolved with saline and administered orally at the doses of 0.1 and 1 mg/kg, respectively. One hour later, increasing doses of NECA were given intravenously and the changes in diastolic blood pressure and heart rate were recorded. Data are expressed as the mean ± SEM (n = 6–10).

(7) Shimada, J.; Suzuki, F.; Nonaka, H.; Karasawa, A.; Mizumoto, H.; Ohno, T.; Kubo, K.; Ishii, A. 8-(Dicyclopropylmethyl)-1,3-dipropylxanthine: a Potent and Selective Adenosine A_1 Antagonist with Renal Protective and Diuretic Activities. *J. Med. Chem.* **1991**, *34*, 466–469.

(8) (a) Shimada, J.; Suzuki, F.; Nonaka, H.; Ishii, A. Polycycloalkyl-1,3-dipropylxanthines as Potent and Selective Antagonists for A_1-Adenosine Receptors. *J. Med. Chem.* **1992**, *35*, 924–930. (b) Suzuki, F.; Shimada, J.; Mizumoto, H.; Karasawa, A.; Kubo, K.; Nonaka, H.; Ishii, A.; Kawakita, T. Adenosine A_1 Antagonists 2. Structure–Activity Relationships on Diuretic Activities and Protective Effects Against Acute Renal Failure. *J. Med. Chem.* **1992**, *35*, 3066–3075.

(9) Shimada, J.; Suzuki, F. Facile Synthesis of 9*H*-*s*-Triazolo[3,4-*i*]purin-5(6*H*)-ones. *Tetrahedron Lett.* **1992**, *33*, 3151–3154.

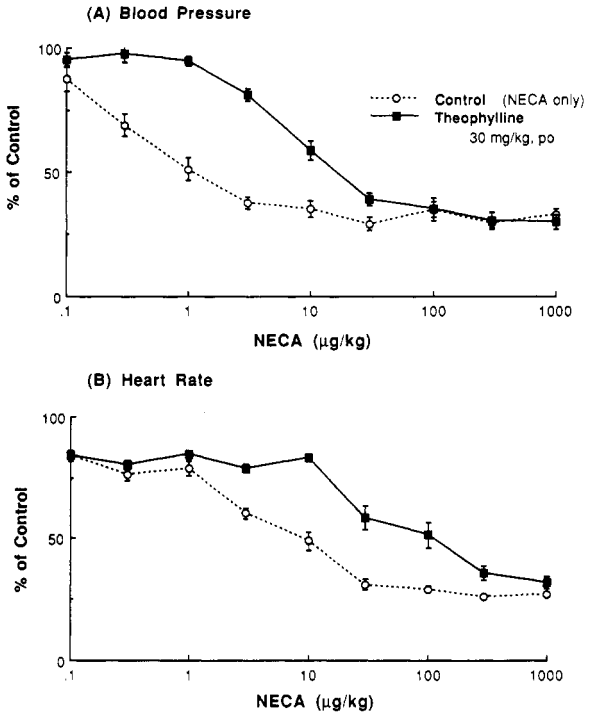


Figure 3. Effect of theophylline on NECA-induced (A) hypotensive and (B) bradycardic response in anesthetized rats. Theophylline was suspended with 0.3% Tween 80 and administered orally at the dose of 30 mg/kg. Data are expressed as the mean ± SEM (n = 6–10).

(4*H*)-one (**4**) on reaction with thionyl chloride under reflux in quantitative yield.[10] Compound **4** was isolated as a HCl salt. Its *R* and *S* enantiomers (**8** and **9**) were similarly prepared from the corresponding optically active 2-amino-1-butanol. These were isolated as L-tartrate and D-tartrate salts, respectively. Optical purity of **8** and **9** were shown to be >99% and 99%, respectively, by HPLC using a CHIRALCEL OD column.

The data of A_1 and A_2 adenosine receptor binding and water solubility of **1**, **2**, **3**, **4**, **8**, and **9** are displayed in Table I. A nonxanthine type heterocycle **4** exhibited high affinity for adenosine A_1 receptors (K_i = 5.7 nM). As expected, this compound **4** showed much better water solubility (3.2 mg/mL) than those (3.3, 8.5, and 220 μg/mL) of **1**, **2**, and recently reported water-soluble A_1 antagonist **10** (KFM 19).[11] We then examined the biological activity of **4** in vivo. As shown in Figure 2, NECA caused a dose-dependent decrease in heart rate and in blood pressure in anesthetized rats.[12] Compound **4** was orally administered at doses of 0.1 and 1 mg/kg and produced a much larger shift to the right in the NECA dose–response curve for heart rate than for blood pressure. By contrast, theophylline (30 mg/kg, po), a nonselective antagonist, produced equivalent shifts to the right in the dose–response curves (Figure 3). Adenosine is supposed to reduce heart rate via an effect on the A_1 receptor and blood pressure via the A_2 receptor. Thus **4** was identified to be a selective and potent adenosine A_1 antagonist in vivo (in heart). We recently reported that intraperitoneal administration of A_1 receptor agonist such as *N*-[(*R*)-1-methyl-2-phenylethyl]adenosine ((*R*)-PIA) prior to training impaired memory of passive avoidance behavior.[13] Compound **4** was also evaluated using this (*R*)-PIA-induced amnesia model. As shown in Figure 4, oral administration of **4** 1 h before training ameliorated the shortened latency in (*R*)-PIA-treated rats at doses of 0.08–5 mg/kg. Thus **4** showed potent adenosine A_1 antagonism also in CNS.

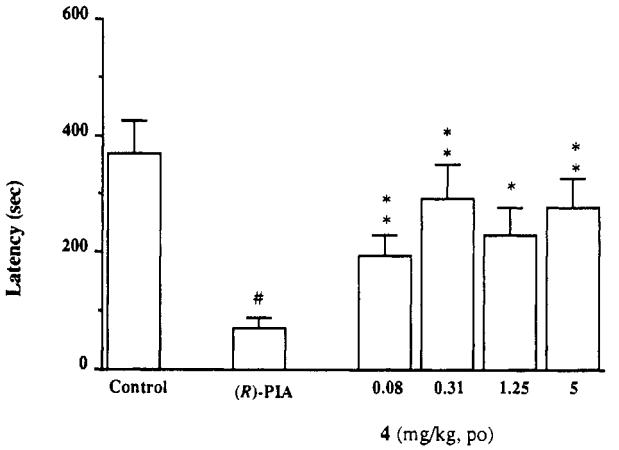


Figure 4. Effects of **4** on (*R*)-PIA-induced passive avoidance failure in mice. Behavioral testing was performed with a step-through type passive avoidance method as described before.[13,17] As experimental apparatus, two compartments (bright and dark) were used. The dark compartment had a grid floor of stainless rods used to give a foot shock delivered by shock generator (2 mA for 2 s). In the test trial, given 24 h after the acquisition trial, mouse (ddY, male, 22–27 g) was again placed in the bright compartment and the response latency to enter the dark compartment was measured. The latency of animals which did not move into the dark compartment during the observation period was calculated to be 600 s. 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 rats. Compound **4** was orally administered 1 h before training (acquisition trial). Vertical bars represent the mean ± SEM. (#) $p < 0.001$: significant difference from the normal-control (n = 15). (*) $p < 0.01$, (**) $p < 0.001$: significant difference from the (*R*)-PIA-treated control (Mann-Whitney U test).

It is clear from Table I that the *R* and *S* enantiomers **8** and **9** have significantly different affinities for A_1 receptors with the *R* enantiomer (**8**) being more potent. In adenosine agonists, (*R*)-PIA possesses higher affinity for the A_1 receptors than N^6-[(*S*)-1-methyl-2-phenylethyl]-adenosine ((*S*)-PIA).[14] In xanthines, 1,3-dipropyl-8-[(*R*)-1-methyl-2-phenylethyl]xanthine is more potent than its *S* isomer at A_1 receptors.[15] This marked stereochemical

(10) Suzuki, F.; Shimada, J.; Kuroda, T.; Kubo, K.; Karasawa, A.; Ohno, T.; Ohmori, K. Eur. Patent 423805, 1991; *Chem. Abstr.* **1991**, *115*, 136115s.
(11) Schingnitz, G.; Küfner-Mühl, U.; Ensinger, H.; Lehr, E.; Kuhn, F. J. Selective A_1-Antagonists for Treatment of Cognitive Deficits. *Nucleosides Nucleotides* **1991**, *10*, 1067–1076.
(12) Fredholm, B. B.; Jacobson, K. A.; Jonzon, B.; Kirk, K. L.; Li, Y. O.; Daly, J. W. Evidence that a Novel 8-Phenyl-Substituted Xanthine Derivative is a Cardioselective Adenosine Receptor Antagonist In Vivo. *J. Cardiovasc. Pharmacol.* **1987**, *9*, 396–400.
(13) Shiozaki, S.; Ishii, A.; Shuto, K.; Suzuki, F. Effects of N^6-(L-Phenylisopropyl) adenosine of the Passive Avoidance in Mice. *Jpn. J. Pharmacol.* **1990**, *52* (Suppl. II), 107P.
(14) Daly, J. W.; Padgett, W.; Thompson, R. D.; Kusachi, S.; Bugni, W. J.; Olsson, R. A. Structure–Activity Relationships for N^6-Substituted Adenosines at Brain A_1-Adenosine Receptor with a Comparison to an A_2-Adenosine Receptor Regulating Coronary Blood Flow. *Biochem. Pharmacol.* **1986**, *35*, 2467–2481.
(15) Peet, N. P.; Lentz, N. L.; Meng, E. C.; Dudley, M. W.; Ogden, A. M. L.; Demeter, D. A.; Weintraub, H. J. R.; Bey, P. A Novel Synthesis of Xanthines: Support for a New Binding Mode for Xanthines with Respect to Adenosine at Adenosine Receptors. *J. Med. Chem.* **1990**, *33*, 3130–3132.
(16) Cheng, Y. C.; Prusoff, W. H. Relationship between the Inhibition Constant (K_i) and the Concentration of Inhibitor which Causes 50% Inhibition (I_{50}) of an Enzymatic Reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099–3108.

requirement for receptor affinity suggests the hypothesis that the C^8 substituent of a xanthine antagonist is binding in the same region as is the N^6 substituent of an adenosine agonist. In our dihydroimidazopurine, the *R* enantiomer (C-8) preferred A_1 receptor binding. If a C-8 substituent in the dihydroimidazopurine of **4**, **8**, and **9** recognizes the same space as does the N^6 substituent of an adenosine agonist or the C-8 substituent of an xanthine antagonist, a new receptor binding mode for this ligand has to be suggested. On the other hand, Quinn's hypothesis[18] suggests that the dihydroimidazole moieties of enantiomers (**8** and **9**) might recognize a ribose binding domain and produce different activities in adenosine binding. More detailed analysis of the binding mode for this new class of A_1 antagonists will be the subject of a future report.

Water-soluble A_1 antagonists will be widely applicable in biochemical and pharmacological studies.

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Supplementary Material Available: Detailed experimental procedures for the preparation of **4**–**9**, the binding assay, and the pharmacological assays (7 pages). Ordering information is given on any current masthead page.

(17) Shiozaki, S.; Ishii, A.; Shuto, K. Effects of KW-6055, A Novel Benzylpyridine Derivative on Various Experimental Amnesia Models. In *Basic, Chemical, and Therapeutic Aspects of Alzheimer's and Parkinson's Diseases*; Nagatsu, T., Ed.; Plenum, New York, 1990; Vol. 2, pp 449–452.

(18) Dooley, M. J.; Quinn, R. J. The Three Binding Domain Model of Adenosine Receptors: Molecular Modelling Aspects. *J. Med. Chem.* **1992**, *35*, 211–216.

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N-(1-Oxododecyl)-4α,10-dimethyl-8-aza-*trans*-decal-3β-ol: A Potent Competitive Inhibitor of 2,3-Oxidosqualene Cyclase

Inhibition of the enzyme HMG-CoA reductase is an effective approach for the inhibition of de novo cholesterol biosynthesis and the treatment of hypercholesterolemia.[1] HMG-CoA reductase catalyzes the rate-limiting step in cholesterol biosynthesis; however, its inhibition can lead to an increase in enzyme synthesis.[1b] The enzymes squalene synthase,[2,3] squalene epoxidase,[4] and 2,3-oxidosqualene cyclase (OSC)[5] are attractive targets for drug development since they are positioned in the biosynthetic pathway at a point where sterol synthesis is committed. Therefore, selective inhibition should not interfere with essential non-sterol pathways or result in the accumulation of steroidal precursors.[2,6] Recently, it has been demonstrated that inhibitors of OSC can regulate HMG-CoA reductase via a putative feedback mechanism involving the formation of C25-oxysterols.[7] Our approach to the design of inhibitors of OSC was initially based on the use of amines as mimics (e.g. **2b–d**) of high-energy intermediate carbocations involved in the cyclization of 2,3-oxidosqualene (Scheme I) as previously described.[8-11] However, we have determined that the amine functionality is not necessary for potent OSC inhibition. Furthermore, in HepG2 cells, the 8-azadecalins are more potent inhibitors of other enzymes in the cholesterol biosynthesis pathway than OSC. In this communication, we report the synthesis and activity of an amide derivative of **2c**, *N*-(1-oxododecyl)-4α,10-dimethyl-8-aza-*trans*-decal-3β-ol (**1a**), which

(1) (a) Alberts, A. W. Lovastatin and Simvastatin-Inhibitors of HMG CoA Reductase and Cholesterol Biosynthesis. *Cardiology* **1990**, *77*, 14–21. (b) Endo, A. Compactin (ML-236B) and Related Compounds as Potential Cholesterol-Lowering Agents that Inhibit HMG-CoA Reductase. *J. Med. Chem.* **1985**, *28*, 401–405.

(2) (a) Biller, S. A.; Forster, C.; Gordon, E. M.; Harrity, T.; Scott, W. A.; Ciosek, C. P. Isoprenoid (Phosphinylmethyl)-phosphonates as Inhibitors of Squalene Synthetase. *J. Med. Chem.* **1988**, *31*, 1869–1871. (b) Biller, S. A.; Forster, C.; Gordon, E. M.; Harrity, T.; Rich, L. C.; Marretta, J.; Ciosek, C. P. Isoprenyl Phosphinylformates: New Inhibitors of Squalene Synthetase. *J. Med. Chem.* **1991**, *34*, 1912–1914. (c) Biller, S. A.; Sofia, M. J.; DeLange, B.; Forster, C.; Gordon, E. M.; Harrity, T.; Rich, L. C.; Ciosek, C. P. The First Potent Inhibitor of Squalene Synthase: A Profound Contribution of an Ether Oxygen to Inhibitor–Enzyme Interaction. *J. Am. Chem. Soc.* **1991**, *113*, 8522–8524.

(3) Poulter, C. D.; Capson, T. L.; Thompson, M. D.; Bard, R. S. Squalene Synthetase. Inhibition by Ammonium Analogues of Carbocationic Intermediates in the Conversion of Presqualene Diphosphate to Squalene. *J. Am. Chem. Soc.* **1989**, *111*, 3734–3739.

(4) (a) Moore, W. R.; Schatzman, G. L.; Jarvi, E. T.; Gross, R. S.; McCarthy, J. R. Terminal Difluoro Olefin Analogues of Squalene Are Time-Dependent Inhibitors of Squalene Epoxidase. *J. Am. Chem. Soc.* **1992**, *114*, 360–361. (b) Van Sickle, W. A.; Angelasto, M. R.; Wilson, P.; Cooper, J. R.; Marquart, A.; Flanagan, M. A. Inhibition of Cholesterol Biosynthesis by Cyclopropylamine Derivatives of Squalene in Human Hepatoblastoma Cells in Culture. *Lipids* **1992**, *27*, 157–160. (c) Mann, J.; Smith, G. P. Synthesis of Potential Inhibitors of Squalene Epoxidase. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2884–2885. (d) Sen, S. E.; Wawrzeńczyk, C.; Prestwich, G. D. Inhibition of Vertebrate Squalene Epoxidase by Extended and Truncated Analogues of Trisnorsqualene Alcohol. *J. Med. Chem.* **1990**, *33*, 1698–1701. (e) Sen, S. E.; Prestwich, G. D. Trisnorsqualene Cyclopropylamine: A Reversible Tight-Binding Inhibitor of Squalene Epoxidase. *J. Am. Chem. Soc.* **1989**, *111*, 8761–8762. (f) Sen, S. E.; Prestwich, G. D. Squalene Analogues Containing Isopropylidene Mimics as Potential Inhibitors of Pig Liver Squalene Epoxidase and Oxidosqualene Cyclase. *J. Med. Chem.* **1989**, *32*, 2152–2158. (g) Sen, S. E.; Prestwich, G. D. Trisnorsqualene Alcohol, a Potent Inhibitor of Vertebrate Squalene Epoxidase. *J. Am. Chem. Soc.* **1989**, *111*, 1508–1510. (h) Horie, M.; Tsuchiya, Y.; Hayashi, M.; Iida, Y.; Iwasawa, Y.; Nagata, Y.; Sawasaki, Y.; Fukuzumi, H.; Kitani, K.; Kamei, T. NB-598: A Potent Competitive Inhibitor of Squalene Epoxidase. *J. Biol. Chem.* **1990**, *265*, 18075–18078.

(5) (a) Xiao, X.; Prestwich, G. D. 29-Methylidene-2,3-oxidosqualene: A Potent Mechanism-Based Inactivator of Oxidosqualene Cyclase. *J. Am. Chem. Soc.* **1991**, *113*, 9673–9674. (b) Viola, F.; Ceruti, M.; Balliano, G.; Caputo, O.; Cattel, L. 22,23-Epoxy-2-aza-2,3-dihydrosqualene Derivatives: Potent New Inhibitors of Squalene 2,3-Oxide-Lanosterol Cyclase. *Farmaco* **1990**, *45*, 965–978. (c) Raveendranath, P. C.; Newcomb, L. F.; Ray, N. C.; Clark, D. S.; Spencer, T. 7,7-Disubstituted Derivatives of 4,4,10β-Trimethyl-*trans*-decal-3β-ol (TMD). *Synth. Commun.* **1990**, *20*, 2723–2731. (d) Ruhl, K. K.; Anzalone, L.; Arguropoulos, E. D.; Gayen, A. K.; Spencer, T. Azadecalin Analogues of 4,4,10β-Trimethyl-*trans*-decal-3β-ol: Synthesis and Assay as Inhibitors of Oxidosqualene Cyclase. *Bioorg. Chem.* **1989**, *17*, 108–120. (e) Corey, E. J.; Oritz de Montellano, P. R.; Lin, K.; Dean, P. D. G. 2,3-Iminosqualene, A Potent Inhibitor of the Enzymic Cyclization of 2,3-Oxidosqualene to Sterols. *J. Am. Chem. Soc.* **1967**, *89*, 2797–2798.

0022-2623/92/1835-3581$03.00/0