to superpose the three-dimensional structures of teleocidin and TPA using computers.[22,23] We have also superposed them by a new rational method which is designed to superpose molecules in terms of physical and chemical properties related to receptor binding, but not in terms of superficial chemical structures or positions of heteroatoms.[24] In our study, the superpositions of both the twist and the sofa form conformers of teleocidin onto the TPA molecule were examined independently, whereas the other groups examined the superposition only for the twist conformation. The results showed that the TPA molecule and the teleocidin sofa form could interact with the common receptor through three hydrogen bonds, and the sofa form could be superposed onto TPA much better than the twist form. In the superposed structures, the spatial position of the alkyl group at C-12 in teleocidin corresponded to that of the methyl group at C-2 in the TPA molecule.

In this study, the biological activity of the four indolactams can be reasonably interpreted in terms of the existence ratio of the sofa form. This finding is consistent with the results from the superposition of teleocidin and TPA molecules. The coincidence of the results from two independent approaches favors the hypothesis that the sofa form is very close to the active conformation for tumor-promoting activity of teleocidins.

This work has also shown that MD calculations are very useful for searching for the stable conformations in highly strained cyclic compounds. They are especially useful in molecules whose stability is strongly influenced by the conformations of the substituent groups on them.

Conclusion

The importance of the sofa form for the tumor-promoting activity of teleocidins and indolactams was indicated by conformation analyses of four indolactam congeners using high-temperature MD calculations.

Experimental Section

(±)-Indolactam-G (3). The preparation method, combustion elemental analysis, and ^{1}H NMR at room temperature have been published.[14] The 400-MHz ^{1}H NMR spectrum of indolactam-G at −30 °C was measured with a JEOL GX400 spectrometer. The chemical shifts at −30 °C are as follows: The fold conformer, 2.78 (dd, 1 H, J = 15.4, 8.3, 8-CH$_2$), 2.86 (s, 3 H, NCH$_3$), 3.17 (dd, 1 H, J = 15.4, 6.9, 8-CH$_2$), 3.51 (d, 1 H, J = 13.5, 12-CH$_2$), 3.58 (dd, 1 H, J = 11.3, 8.2, 14-CH$_2$), 3.69 (dd, 1 H, J = 11.3, 4.1, 14-CH$_2$), 3.94 (d, 1 H, J = 13.5, 12-CH$_2$), 5.05 (m, 1 H, 9-CH), 6.91 (d, 1 H, J = 7.6, 5-CH), 6.94 (s, 1 H, 2-CH), 7.03 (t, 1 H, J = 7.6, 6-CH), 7.09 (d, 1 H, J = 7.6, 7-CH); The S8 conformer, 2.94 (s, 3 H, NCH$_3$), 3.06 (d, 1 H, J = 13.8, 12-CH$_2$), 4.18 (d, 1 H, J = 13.8, 12-CH$_2$), 6.78 (d, 1 H, J = 7.6, 5-CH); other peaks could not be assigned since they overlapped with the peaks of the fold form. The signal ratio of these two conformers is 1:0.2.

Registry No. 1, 11032-05-6; 2, 90365-57-4; 3, 84590-50-1; 4, 110073-31-9; 5, 110073-28-4.

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Nucleosides and Nucleotides. 107. 2-(Cycloalkylalkynyl)adenosines: Adenosine A$_2$ Receptor Agonists with Potent Antihypertensive Effects[1]

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Adenosine receptor-binding profiles in rat brain tissues and antihypertensive effects in spontaneously hypertensive rats (SHR) of a series of 2-(cycloalkylalkynyl)adenosines (2-CAAs) and their congeners are described. The structure–activity relationship of this series of compounds is discussed, focusing on the length of the alkynyl side chain and bulkiness of the terminal cycloalkyl substituents in terms of binding activity and cardiovascular effects. All the 2-CAAs had a preferential affinity for A$_2$ receptors. Of these derivatives, 2-(3-cyclopentyl-1-propyn-1-yl)adenosine (**10b**) exhibited the most selective affinity for A$_2$ receptors (K_i ratio: A$_1$/A$_2$ = 70) on the basis of receptor binding. In the C-2 binding region of adenosine, compounds often have potent and/or selective A$_2$ activity from introduction of an acetylenic group at the C-2 position followed by one methylene residue further followed by a hydrophobic substituent such as a cycloalkyl ring at the terminal position of the alkynyl side chain. Intravenous injection of **10b** up to 100 μg/kg had a potent hypotensive effect without a marked decrease in heart rate in anesthetized SHR. Compounds **10j–s**, with a hydroxyl group in the C-3″ position of the alkynyl side chain, had a potent affinity for both A$_1$ and A$_2$ receptors, but they were not highly selective for A$_2$ receptors. These compounds caused a marked bradycardia upon intravenous administration in anesthetized SHR. Oral administration of **10b** (0.1–1 mg/kg) had a potent and long-lasting antihypertensive effect in conscious SHR.

Adenosine receptors in cell membranes have been classified into A$_1$ and A$_2$ receptors on the basis of receptor-mediated inhibition (A$_1$ receptors) or stimulation (A$_2$ receptors) of adenylate cyclase.[2] Some adenosine ana-

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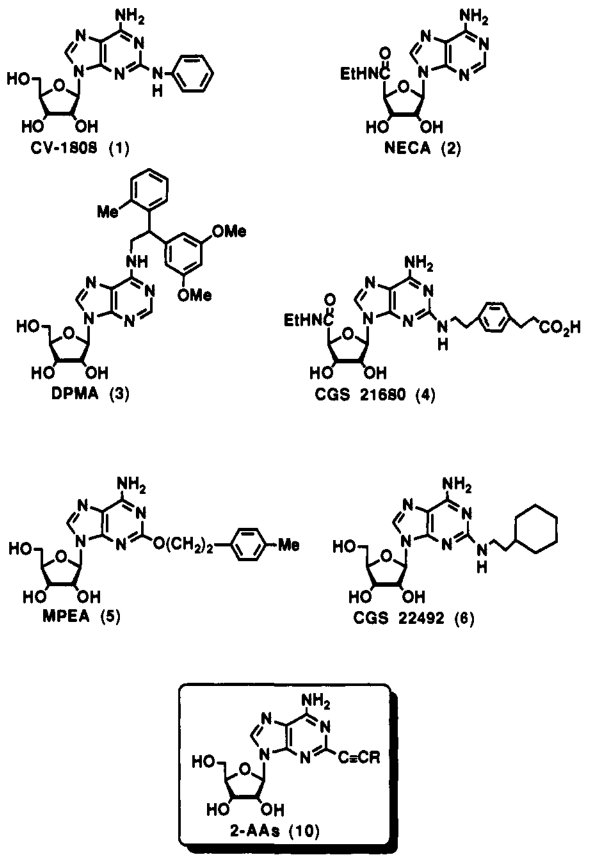
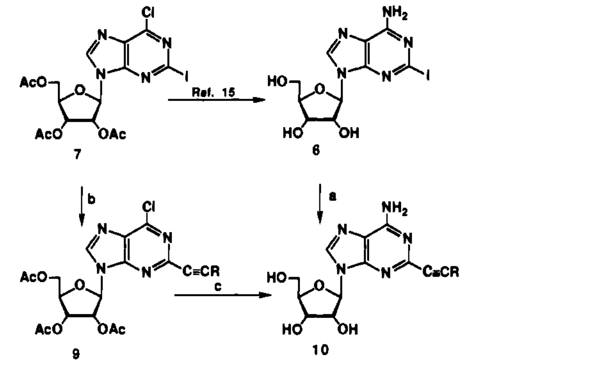
0022-2623/92/1835-2253$03.00/0

Chart I



Scheme I. (R is defined in Table I)[a]



[a] Reaction conditions: (a) HC≡CR, $(PPh_3)_2PdCl_2$, CuI, Et_3N in DMF, 80° C; (b) HC≡CR, $(PPh_3)_2PdCl_2$, CuI, Et_3N in dioxane, room temperature; (c) concentrated NH_4OH/dioxane, 70 °C.

logues, such as N^6-substituted adenosines, with a preferential affinity for A_1 receptors cause cardiac depression, while analogues with a high affinity for A_2 receptors cause vasodilation.[3] Recently, adenosine has been reported to be clinically useful for the treatment of arrhythmia.[4] However, the therapeutic potential of adenosine agonists as antihypertensives and vasodilators have not been established due to their lack of selectivity for adenosine receptors. Nonselective adenosine agonists produce hypotension and vasodilation accompanied by detrimental effects such as atrio-ventricular block and angina pain.[5] Therefore, selective A_2 receptor agonists have the potential of being useful agents for the treatment of cardiovascular diseases with minimized toxic effects. To improve and separate the adenosine-induced action, a number of adenosine derivatives have been synthesized. Of these analogues, N^6-cyclohexyladenosine (CHA)[6] and N^6-cyclopentyladenosine (CPA)[7] are highly selective A_1 receptor agonists. However, only a few potent and/or selective A_2 receptor agonists have been reported. 2-(Phenylamino)adenosine (CV-1808) (1) was reported as a potent coronary vasodilator and confirmed as a selective A_2 agonist.[8] NECA (N-ethyladenosin-5′-uronamide) (2) was also found to be a coronary vasodilator and a highly potent A_2 agonist but not selective. Recently, more selective A_2 agonists such as DPMA [N^6-[2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl]adenosine] (3),[9] CGS 21680 [2-[[4-(2-carboxyethyl)phenethyl]amino]-N-ethyladenosin-5′-uronamide hydrochloride] (4),[10,11] MPEA [2-[2-(4-methylphenyl)ethoxy]adenosine] (5),[12,13] and CGS 22492 [2-[(2-cyclohexylethyl)amino]adenosine] (6)[14] shown in Chart I have been reported.

Previously, we synthesized a series of 2-alkynyladenosines (2-AAs), some of which were potent inhibitors

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Table I. A_1 and A_2 Receptor Binding Activities of Adenosine Analogues in Rat Brain Tissues and Their Cardiovascular Effects in SHR

no.	R	K_i,[a] nM A_1	A_2	selectivity A_1/A_2	BP ED_{30},[b] μg/kg	HR ED_{10},[c] μg/kg
10a	c-C_5H_9	88 ± 5.2	12 ± 2.5	7	0.29 ± 0.03	>100
10b	c-$C_5H_9CH_2$	162 ± 36	2.3 ± 0.6	70	0.05 ± 0.001	>100
10c	c-$C_5H_9(CH_2)_2$	136 ± 15	3.4 ± 1.1	40	0.16 ± 0.005	>100
10d	c-C_6H_{11}	138 ± 18	10 ± 1.9	14	0.36 ± 0.06	>100
10e	c-$C_6H_{11}CH_2$	208 ± 26	6.5 ± 1.8	32	0.15 ± 0.03	>100
10f	c-$C_6H_{11}(CH_2)_2$	313 ± 45	26 ± 4.2	12	0.48 ± 0.09	>100
10g	c-$C_6H_{11}(CH_2)_3$	>229	46 ± 7.6	>5	1.64 ± 0.56	>100
10h	Ph	701 ± 13	109 ± 28	6	10.1 ± 2.4	>100
10i	$Ph(CH_2)_2$	400 ± 39	37 ± 4.3	11	1.21 ± 0.28	>100
10j	c-$C_5H_8(OH)$	11 ± 1.8	3.3 ± 0.5	3	0.07 ± 0.01	1.6 ± 0.2
10k	c-$C_6H_{10}(OH)$	21 ± 3.3	0.9 ± 0.2	23	0.02 ± 0.004	3.5 ± 1.2
10l	c-$C_7H_{12}(OH)$	27 ± 2.5	1.1 ± 0.3	25	0.02 ± 0.001	5.6 ± 0.9
10m	c-$C_8H_{14}(OH)$	56 ± 6.7	1.9 ± 0.5	29	0.01 ± 0.003	13 ± 2.6
10n	$CH_3(OH)CH$	15 ± 2.1	18 ± 1.9	0.8	0.15 ± 0.01	0.8 ± 0.1
10o	$(CH_3)_2(OH)C$	32 ± 4.2	19 ± 2.1	2	0.14 ± 0.01	1.4 ± 0.3
10p	$CH_3(CH_2)_2(OH)CH$	16 ± 1.9	1.8 ± 0.2	9	0.04 ± 0.01	0.83 ± 0.2
10q	$CH_3(CH_2)_4(OH)CH$	11 ± 1.5	2 ± 0.3	7	0.06 ± 0.004	0.45 ± 0.12
10r	Ph(OH)CH	3.4 ± 0.5	1.9 ± 0.2	2	0.05 ± 0.003	1.3 ± 0.03
10s	$HOCH_2$	8.3 ± 1.0	20 ± 2.2	0.4	0.36 ± 0.14	0.74 ± 0.1
10t	$CH_3(CH_2)_3$	126 ± 8.8	2.8 ± 0.3	45	0.11 ± 0.03	67 ± 6.8
10u	$CH_3(CH_2)_5$	133 ± 20	7.9 ± 1.8	17	0.20 ± 0.02	>100
3		108 ± 10	6.9 ± 2.3	15	12.3 ± 1.6	>100
4		1232 ± 95	8.8 ± 1.2	140	0.97 ± 0.2	>100

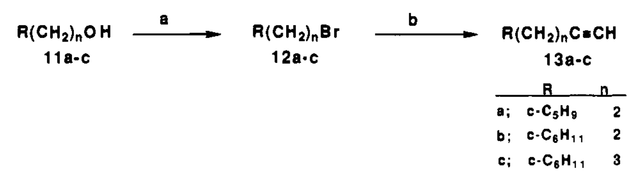
[a] Inhibition constant for A_1 (rat brain membranes, [^{3}H]CHA) or A_2 (rat striatal membranes, [^{3}H]NECA receptor binding activities of agonists. Affinities for A_1 and A_2 receptors are means ± SE of three separate experiments in triplicate. The K_d values for the binding of [^{3}H]CHA and [^{3}H]NECA were 1.24 ± 0.11 and 4.47 ± 0.53 nM, respectively. [b] Dose of compound which produced a 30% decrease in blood pressure of anesthetized SHR. [c] Dose of compound which produced a 10% decrease in heart rate of anesthetized SHR. ED_{30} and ED_{10} values are means ± SE of four animals.

of the passive cutaneous anaphylaxis reaction and had cardiovascular effects in normotensive rats.[15] We also reported that 2-(1-hexyn-1-yl)adenosine (**10t**) and 2-(1-octyn-1-yl)adenosine (YT-146) (**10u**) are A_2 selective agonists that have a potent and long-lasting antihypertensive effect in spontaneous hypertensive rats (SHR).[16] Furthermore, we examined the SAR of a series of 2-AAs and identified the optimal chain length at the C-2 position for selective A_2 binding affinity.[17] Recently, Ueeda et al.[12,13] proposed a model of the A_2 receptor where pharmacological effects of a series of 2-(alkoxy)adenosines were examined. The experiment using Langendorf guinea pig heart preparations showed that **5** was highly selective for A_2 receptors. Francis et al. have reported the SAR of N-alkylated 2-aminoadenosines, in which **6** is extremely A_2 selective compound (530-fold).[14] However, the nature of regions in the A_2 receptors has not been fully understood. This paper expands the mapping of C-2 regions of adenosine receptors by examining the SAR of 2-CAAs with respect to potency and selectivity of adenosine A_1/A_2 receptor binding affinity and cardiovascular effects in SHR and describes an improved method for the synthesis of 2-AAs, especially 2-CAAs and their hydroxyl derivatives.

Results and Discussion

Chemistry. Some of 2-AAs **10h,i,o–q** were synthesized following published procedures.[15,17] Treatment of 2-iodoadenosine (**8**) with terminal alkynes, using catalytic amounts of bis(triphenylphosphine)palladium dichloride and cuprous iodide (CuI) in *N,N*-dimethylformamide (DMF) and triethylamine at 80 °C for 1 h under argon atmosphere gave 2-AAs and their hydroxyl derivatives **10** (method A). However, to obtain the pure products, treatment of the reaction mixture with hydrogen sulfide gas (H_2S) with subsequent purification on silica gel column chromatography was required because of chelation of metals between 6-NH_2 and N^7 of the adenine ring. To avoid such processes, we devised an improved procedure, which is outlined in Scheme I.

Scheme II[a]



[a] Reaction conditions: (a) concentrated H_2SO_4/ 48% HBr, reflux; (b) LiC≡CH · $H_2NCH_2CH_2NH_2$ in DMSO, room temperature.

Palladium-catalyzed cross-coupling reaction of 9-(2,3,5-tri-*O*-acetyl-1-β-D-ribofuranosyl)-6-chloro-2-iodopurine (**7**), which is readily available in three steps from guanosine,[17] with 1-octyne in dioxane at room temperature gave the corresponding 6-chloro-2-octyn-1-ylpurine nucleoside **9u** in high isolated yield. This reaction proceeded smoothly at low temperature with little coloration, which is frequently observed in such reactions in DMF at high temperature. Cuprous iodide was easily removed by washing with aqueous solution of ethylenediaminetetraacetic acid disodium salt without using H_2S. Amination and deacetylation of **9u** using concentrated NH_4OH in dioxane in sealed tube at 70 °C gave **10u** in 86% yield from **7** (method B). The IR, ^{1}H NMR, and UV data of **10u** were identical to those described previously.[17] A number of 2-CAAs was synthesized in two steps by this new route in 75–85% yield (Table II). The synthesis of the cyclo-

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alkylalkynes such as 4-cyclopentyl-1-butyne, 4-cyclohexyl-1-butyne, and 5-cyclohexyl-1-pentyne (**13a–c**) was done by treatment of a lithium acetylide–ethylenediamine complex with proper cycloalkyl bromides (**12a–c**) (Scheme II).

Adenosine Receptor Binding Activity. The A_1 binding assay was done in adenosine deaminase (ADA)-pretreated rat brain membranes (without cerebellum and brainstem) by measuring the ability of test compounds to displace [^{3}H]CHA binding according to a previously described procedure,[18] with modifications.[16] The A_2 binding assay was done in ADA-pretreated rat striatal membranes using [^{3}H]NECA,[18] with modifications.[16] The results are summarized in Table I.

A series of 2-CAAs **10a–g** showed a substantial A_2 selectivity. Of these analogues, 2-(3-cyclopentyl-1-propyn-1-yl)adenosine (**10b**) had the highest selectivity (70-fold) for A_2 receptors with K_i values of 162 and 2.3 nM for A_1 and A_2 receptors, respectively. These values are essentially similar to those of 2-(1-hexyn-1-yl)adenosine (**10t**), which we recently reported.[16] Affinities of these 2-CAAs for receptor subtypes varied according to the number of methylene residues between the terminal cycloalkyl ring and the acetylenic bond in the side chain. Among compounds **10a–c**, which have a cyclopentyl ring at the terminal position of the alkynyl side chain, **10b** had the most potent A_2 activity, while it showed modest activity for A_1 receptors. Similarly, among the cyclohexyl analogues **10d–g**, **10e** had the most A_2 selectivity. In both series the maximum binding activity and selectivity for A_2 receptors was observed when one methylene group separated the cycloalkyl ring from the acetylenic bond. Increases or decreases of this number reduced the activity. Similar effects on activity were observed when a bulky substituent was adjacent to the acetylenic bond as shown by 2-[2-(trimethylsilyl)-1-ethyn-1-yl]adenosine[17] and the phenylethynyl derivative **10h**. Similarly, it was observed in the SAR of 2-alkoxyadenosines[12] and N-alkylated 2-aminoadenosines[14] that decrease or increase in the number of methylene group varied the affinity and selectivity for A_2 receptors. Therefore, a number of methylene groups is essential for potent A_2 activity.

Recently, Ueeda et al.[12,13] reported models of C-2 binding regions of adenosine A_1 and A_2 receptors in SAR studies of 2-(alkoxy)adenosines. They proposed at least three subregions near the C-2 position for A_2 receptors: (a) an X subregion that accommodates the oxygen atom that links the alkyl substituent to the adenine C-2, (b) an alkyl subregion, which follows the X subregion and is of very limited bulk tolerance, and (c) a hydrophobic subregion, which is a prominent feature only for A_2 receptors, that accommodates cycloalkyl, bicycloalkyl, or phenyl rings. From our results together with previous observations, it is clear that there is the X subregion that accommodates –O–, –NH–, and –C≡C– groups at the C-2 position. The nature of the region together with the N^1 and N^3 positions of the adenine ring has polar characteristics including hydrogen-bonding. The alkyl region can be tolerant of a linear alkyl substituent with one or two methylene groups. Two methylene groups are required for maximum affinity to the A_2 receptor for the C-2 alkoxy[12] and alkylamino[11,14] derivatives but only one methylene for 2-CAAs. Therefore the total number of atoms or distance between the C-2 position and the terminal substituent is most important. Although the presence of a hydrophobic subregion was proposed, adjacent to the alkyl subregion, it was not clear from our previous studies of a series of 2-AAs having linear alkyl substituents. However, it is now obvious that a region that accommodates the cyclopentyl or cyclohexyl rings is related to the hydrophobic subregion proposed. The cyclopentyl derivative **10b** had higher affinities to A_2 receptors than the cyclohexyl derivative **10e**, and these relations are inverse to the potencies of 2-(cyclopentylethoxy)adenosine and 2-(cyclohexylethoxy)adenosine as seen in the report by Ueeda et al.[12,13] This inverse relations were also observed in the SAR of N-alkylated 2-aminoadenosines.[14] These differences can be explained as a consequence of the differences between the position of the distal groups at the C-2 position, since the side chain attached to the oxygen atom or nitrogen atoms is bent at the heteroatom in the 2-alkoxyadenosines and N-alkylated 2-aminoadenosines, respectively, while the acetylenic bond in the 2-AAs is linear. The lower affinities of the phenyl derivatives **10h** and **10i** than those of the phenylalkoxy derivatives could be explained in a similar way. We previously proposed that the shape of the C-2 substituent of 2-alkynyladenosines may be linear,[17] but this study implies that the shape of the alkyl substituent could be like cycloalkanes when they bind to A_2 receptors, because cyclopentyl derivatives **10b** have more potent A_2 binding activity than **10u**, with *n*-octynyl side chain, although they have a C-2 side chain with the same number of carbon atoms. This is supported by the SAR study of N-alkylated 2-aminoadenosines in which a lipophilic side chain alone is not sufficient to produce strong binding affinity and the ring attached to the side chain plays an important role in the binding.[14] Essentially, our results of 2-AAs and 2-CAAs on A_2 affinity support the receptor models proposed.

We next investigated propargyl alcohol derivatives **10j–s** for further structural requirements for the affinity and the subtype selectivity. Previously, we disclosed that the propargyl alcohol derivative **10s** and its ethers could be inversely important in binding to the A_1 receptors.[17] As can be seen from Table I, introduction of a hydroxyl group at the C-3″ position potentiates both A_1 and A_2 binding affinities compared to the corresponding 2-CAAs **10a** and **10d**. Although we described above how the alkyl subregion is of limited bulk tolerance, a series of 2-AAs and 2-CAAs having a hydroxyl group at the C-3″ position instead favors steric bulk for binding to both receptors. Especially, **10r** showed about 200- and 60-fold more potent affinities to A_1 and A_2 receptors than those of **10h**, respectively. From the viewpoint of increase in the selectivity to the receptor subtypes, introduction of the hydroxyl group is not adequate, but **10k** is one of the most potent agonists so far known. These suggest that in addition to the three subregions described above there is another polar subregion adjacent to the alkyl subregions in both receptors.

Antihypertensive Activity. The potency of test compounds to decrease blood pressure (BP) and heart rate (HR) were compared in SHR. The relative potency to decrease BP was estimated on the basis of the ED_{30} value, the mean dose that produced a 30% decrease in BP. Similarly, the relative potency to decrease HR was estimated on the basis of the ED_{10} value, the mean dose that produced a 10% decrease in HR. Some compounds were examined for antihypertensive effects by oral administration in conscious SHR.

A series of 2-CAAs **10a–g** showed a potent hypotensive effect without showing a marked HR decrease in doses lower than 100 μg/kg in intravenous (iv) administration (Figures 1 and 2). These compounds produced a weak tachycardia at the doses lower than 10 μg/kg. However,

(18) Bruns, R. F.; Lu, G. H.; Pugsley, T. A. Characterization of the A_2 adenosine receptor labeled by [^{3}H]NECA in rat striatal membranes. *Mol. Pharmacol.* 1986, *29*, 331–346.

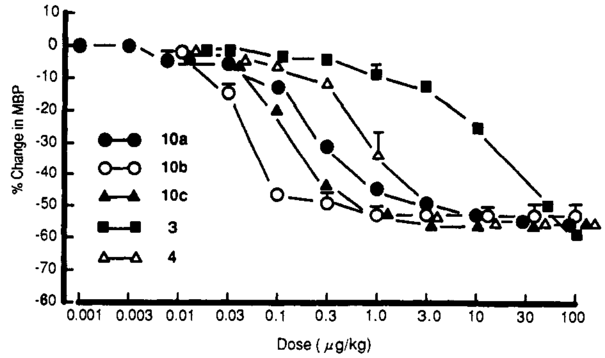

Figure 1. Effects of 2-(cyclopentylalkynyl)adenosines and other 2-substituted adenosines on mean blood pressure (MBP) in anesthetized male SHR. Each compound was administered iv in a cumulative manner at 5-min intervals. Values are means ± SE of four animals.

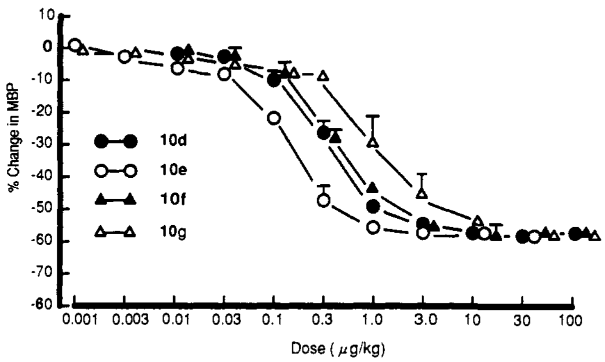

Figure 2. Effects of 2-(cyclohexylalkynyl)adenosines on MBP in anesthetized male SHR. Each compound was administered iv in a cumulative manner at 5-min intervals. Values are means ± SE of four animals.

the increase and decrease in HR caused by these compounds were within 6% (data not shown). The ED_{30} value for BP and ED_{10} value for HR of each compound are shown in Table I. Compound **10b**, which was the most A_2 selective in the series, had the most potent hypotensive effect and was 17- and 240-fold more potent than those of **4** and **3**, respectively, which are currently the gold standards as A_2 agonists. Compound **6** has been reported to be an extremely A_2 selective agent and showed a hypotensive effect accompanied by a marked tachycardia, which may result from its extremely low A_1 affinity.[14] On the other hand, the tachycardia caused by 2-CAAs were weaker than that of **6**, since A_1 affinities of 2-CAAs were much higher than that of **6**. Generally, hypotensive effects of these nucleosides paralleled affinities for the A_2 receptors.

Although 2-CAAs with a hydroxyl group at the C-3″ position **10j–s** showed a highly potent hypotensive effect in iv administration, a marked HR decrease was also observed at doses more than 1 μg/kg as shown in Figure 3. Dose–response curves of these compounds for decreases in BP showed two phases; i.e., the first phase reached a plateau at a dose as high as 0.3 μg/kg with a 50–60% decrease in BP and the second phase showed further decreases in BP, up to 70–80% at doses more than 3 μg/kg. The decrease in BP observed in the second phase is thought to be caused by the depression of the heart via the A_1 receptor activation, since **10j–m** had potent affinities for A_1 receptors. It has been known that the adenosine-induced decrease in BP and HR are mediated via A_2 and A_1 receptors, respectively. In this study, there was a positive correlation between the A_2 activity and decreases in the BP of tested compounds ($r = 0.79$, $p < 0.001$) and

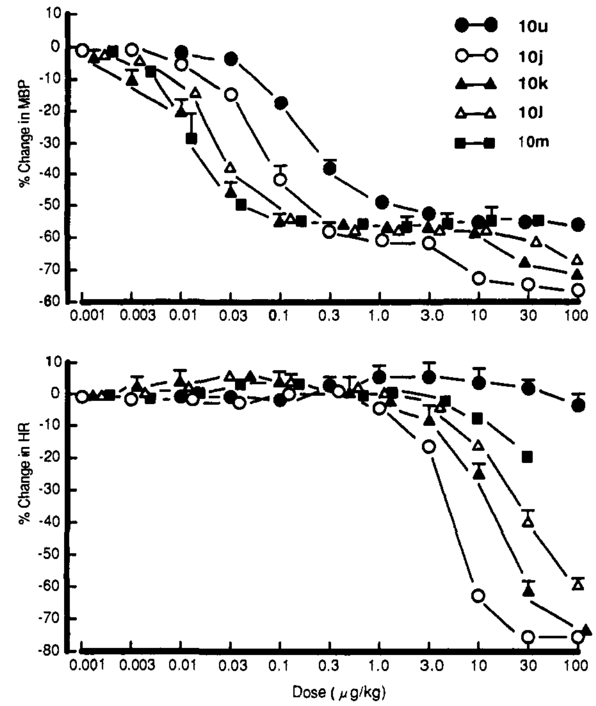

Figure 3. Effects of 2-[2-(1-hydroxycycloalkyl)-1-ethyn-1-yl]-adenosines and **10u** on MBP and HR in anesthetized male SHR. Each compound was administered iv in a cumulative manner at 5-min intervals. Values are means ± SE of four animals.

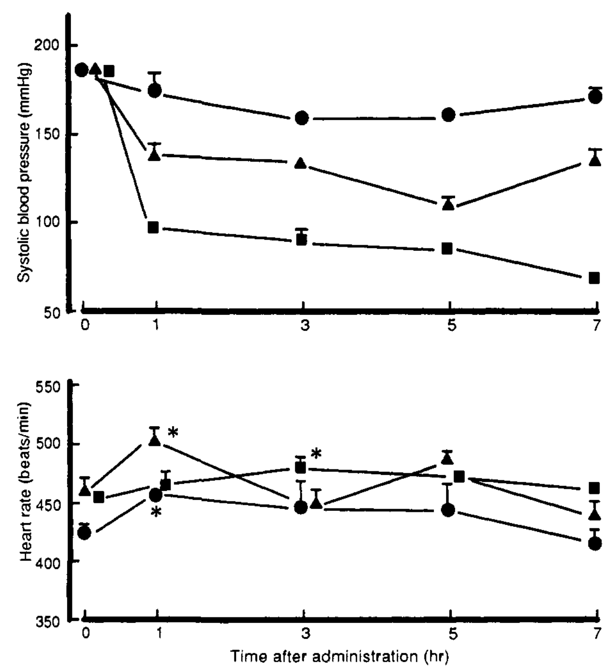

Figure 4. Antihypertensive effects of a single oral administration of **10b** (0.1 mg/kg, ●; 0.3 mg/kg, ▲; 1 mg/kg, ■) on systolic blood pressure and heart rate in conscious male SHR. Values are means ± SE of five animals. Significantly different from corresponding values of predose at $p < 0.05$ (*).

between the A_1 activity and decreases in the HR ($r = 0.62$, $p < 0.05$) among compounds of which the ED_{10} is lower than 100 μg/kg. The potencies of **3** and **4** for the hypotensive effects were weaker than those of 2-CAAs, even though they had similar degrees of A_2 affinities to those nucleosides **10a**, **10d**, and **10i**. Hence, it is possible that hypotensive effects induced by 2-CAAs may involve some other mechanism than direct A_2 receptor activation.

In the next experiment, the antihypertensive effect of **10b**, which had a potent hypotensive effect in iv admin-

Table II. 2-CAAs and Their Congeners

no.	R	synthetic method	yield,[a] %	mp, °C	crystn solvent	IR (KBr) ($\nu_{C\equiv C}$), cm^{-1}	formula[b]
10a	c-C_5H_9	B	77	127–133	EtOH/H_2O	2230	$C_{17}H_{21}N_5O_4 \cdot H_2O$
10b	c-$C_5H_9CH_2$	B	80	125–127	EtOH/H_2O	2230	$C_{18}H_{23}N_5O_4 \cdot {}^2/_3H_2O$
10c	c-$C_5H_9(CH_2)_2$	B	75	108–114	EtOH/H_2O	2235	$C_{18}H_{25}N_5O_4 \cdot {}^2/_3H_2O$
10d	c-C_6H_{11}	B	77	135–141	EtOH/H_2O	2220	$C_{18}H_{23}N_5O_4 \cdot H_2O$
10e	c-$C_6H_{11}CH_2$	B	75	97–103	EtOH/H_2O	2235	$C_{18}H_{25}N_5O_4 \cdot {}^1/_2H_2O$
10f	c-$C_6H_{11}(CH_2)_2$	B	77	104–111	EtOH/H_2O	2240	$C_{20}H_{27}N_5O_4 \cdot {}^2/_3H_2O$
10g	c-$C_6H_{11}(CH_2)_3$	B	77	117–127	EtOH/H_2O	2230	$C_{21}H_{29}N_5O_4 \cdot H_2O$
10h	Ph	A	87	146–147	$CHCl_3$	2210	$C_{18}H_{17}N_5O_4 \cdot H_2O$
10i	Ph$(CH_2)_2$	A	55	115–120	EtOH/H_2O	2230	$C_{20}H_{21}N_5O_4 \cdot {}^1/_2H_2O$
10j	c-C_5H_8(OH)	B	80	138–144	EtOH/H_2O	2230	$C_{17}H_{21}N_5O_5 \cdot H_2O$
10k	c-C_6H_{10}(OH)	B	79	142–147	EtOH/H_2O	2230	$C_{18}H_{23}N_5O_5 \cdot H_2O$
10l	c-C_7H_{12}(OH)	B	79	foam		2230	$C_{19}H_{25}N_5O_5 \cdot H_2O$
10m	c-C_8H_{14}(OH)	B	79	foam		2230	$C_{20}H_{27}N_5O_5 \cdot {}^3/_2H_2O$
10o	$(CH_3)_2$(OH)C	A	50	142–147	MeOH	2250	$C_{15}H_{19}N_5O_5 \cdot H_2O$
10p	$CH_3(CH_2)_2$(OH)CH	A	58	167–169	MeOH	2230	$C_{18}H_{21}N_5O_5$
10q	$CH_3(CH_2)_4$(OH)CH	A	60	177–179	EtOAc	2230	$C_{18}H_{25}N_5O_5$
10u	$CH_3(CH_2)_5$	B	86	101–103	EtOH/H_2O	2230	$C_{18}H_{25}N_5O_4 \cdot {}^1/_5H_2O$

[a] Overall yields from 7. [b] All compounds had satisfactory C, H, and N microanalytical data within ±0.4% of the theoretical value.

istration, was investigated in oral administration in conscious SHR. Oral administration of **10b** at a dose of 0.1, 0.3, or 1 mg/kg decreased systolic blood pressure of SHR dose-dependently as shown in Figure 4. The duration of the antihypertensive effect of this compound was maintained for at least 7 h after administration. Compound **10b** caused a significant tachycardia at 1 or 3 h after the oral administration, but it recovered thereafter. Thus, 2-CAAs are promising as antihypertensive agents that should be considered for further detailed preclinical evaluation.

In conclusion, 2-CAAs were A_2 selective adenosine agonists. In the C-2 binding region of adenosine, compounds often have potent and/or selective A_2 activity from introduction of an acetylenic group at the C-2 position followed by one methylene residue further followed by a hydrophobic substituent such as a cycloalkyl ring at the terminal position of the alkynyl side chain. Above all, 2-(3-cyclopentyl-1-propyn-1-yl)adenosine (**10b**) showed 70-fold A_2 selectivity and potent antihypertensive activity in both iv and oral administration. Introduction of a hydroxyl group into the C-3″ position of the alkynyl side chain increased the affinity for both receptor subtypes, while it also produced a potent HR decreasing effect by the increase in the A_1 affinity.

Experimental Section

Melting points were measured on a Yamato MP-21 melting point apparatus and are uncorrected. Elemental analyses were done at Yanaco MT-5. The ^1H NMR spectra were recorded on a JEOL GSX-400 (400 MHz) spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were detected by addition of D_2O. UV absorption spectra were recorded with a Shimadzu UV-160A spectrophotometer. IR spectra was recorded with Hitachi 260-50 spectrometer with KBr pellets. TLC was done on Merck Kieselgel F254 precoated plates. The silica gel used for column chromatography was Merck Kieselgel 60 (70–230 mesh). All acetylene compounds except for 4-cyclopentyl-1-butyne (**13a**), 4-cyclohexyl-1-butyne (**13b**), and 5-cyclohexyl-1-pentyne (**13c**) were purchased from Hydrus Chemical Co. Physical and analytical data for the compounds **10a–u** were shown in Table II.

General Method for the Preparation of 2-AAs (10h,i,o–q). Compound **8** (393 mg, 1 mmol), CuI (9.5 mg, 0.05 mmol), bis(triphenylphosphine)palladium dichloride (36 mg, 10 mol %), triethylamine (0.16 mL, 1.2 mmol), and terminal alkyne (1.2 equiv of phenylacetylene, 4-phenyl-1-butyne, 2-methyl-3-butyn-2-ol, 1-hexyn-3-ol, or 1-octyn-3-ol) in DMF (7 mL) was heated at 80 °C for several hours under an argon atmosphere. After the starting material was completely consumed, judged by TLC ($CHCl_3$/EtOH = 10:1, v/v), the reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in $CHCl_3$, and H_2S gas was introduced to the solution (~30 s) followed by N_2 gas. The suspension was filtered through a Celite pad and washed with $CHCl_3$. The combined filtrate and washings were concentrated to dryness in vacuo, and the residue was purified by a silica gel column using an appropriately mixed MeOH–$CHCl_3$ solvent system.

2-(Phenylethyn-1-yl)adenosine (10h). Compound **10h** (373 mg, 97%) was obtained from **8** with phenylacetylene: UV (H_2O) λ_{max} 261 nm (23000), 285 (20800), 304 (19000), λ_{min} 239 (17100), 275 (19400), 293 (18800); UV (0.05 N HCl) λ_{max} 274 nm (16600), 320 (21300), λ_{min} (10800), 291 (12400); NMR (DMSO-d_6) δ 3.67 (2 H, m, H-5′a,b), 4.03 (1 H, m, H-4′), 4.19 (1 H, dd, H-3′), 4.58 (1 H, t, H-2′), 5.93 (1 H, d, H-1′), 7.42 (2 H, br s, NH_2), 7.45–7.67 (5 H, m, Ph), 8.49 (1 H, s, H-8).

2-(4-Phenyl-1-butyn-1-yl)adenosine (10i). Compound **10i** (240 mg, 61%) was obtained from **8** with 4-phenyl-1-butyne: UV (H_2O) λ_{max} 270 nm (14500), 287 sh (9900), λ_{min} 247 nm (7300); UV (0.05 N HCl) λ_{max} 271 nm (16000), 295 (11700), λ_{min} 247 (7300), 284 (10700); NMR (DMSO-d_6) δ 2.71 (2 H, t, C≡CCH_2), 2.87 (2 H, t, PhCH_2), 3.54–3.69 (2 H, m, H-5′a,b), 3.95 (1 H, m, H-4′), 4.13 (1 H, dd, H-3′), 4.54 (1 H, t, H-2′), 5.85 (1 H, d, H-1′), 7.20–7.33 (5 H, m, Ph), 7.42 (2 H, br s, NH_2), 8.40 (1 H, s, H-8).

2-(3-Hydroxy-3-methyl-1-butyn-1-yl)adenosine (10o). Compound **10o** (190 mg, 55%) was obtained from **8** with 2-methyl-3-butyn-2-ol: UV (H_2O) λ_{max} 270 nm (14300), 289 (9800), λ_{min} 245 (6200), 281 (9500); UV (0.05 N HCl) λ_{max} 271 nm (15500), 294 (10700), λ_{min} 246 (6600), 283 (9800); NMR (DMSO-d_6) δ 1.46 (6 H, s, Me), 3.40–3.69 (2 H, m, H-5′a,b), 3.94 (1 H, m, H-4′), 4.12 (1 H, dd, H-3′), 4.48 (1 H, t, H-2′), 5.13–5.17 (2 H, m, OH × 2), 5.45 (1 H, d, OH), 5.55 (1 H, s, C≡CCOH), 5.87 (1 H, d, H-1′), 7.44 (2 H, br s, NH_2), 8.41 (1 H, s, H-8).

2-(3-Hydroxy-1-hexyn-1-yl)adenosine (10p). Compound **10p** (235 mg, 64%) was obtained from **8** with 1-hexyn-3-ol: UV (H_2O) λ_{max} 265 sh nm (14100), 270 (14500), 289 (9900), λ_{min} 246 (7600), 282 (9700); UV (0.05 N HCl) λ_{max} 265 sh nm (12500), 272 (14000), 297 (9900), λ_{min} 247 (5700), 283 (8800); NMR (DMSO-d_6) δ 0.92 (3 H, t, Me), 1.33–1.76 (4 H, m, CH_2), 3.58 2 H, m, H-5′a,b), 3.95 (1 H, m, H-4′), 4.12 (1 H, dd, H-3′), 4.48 (1 H, t, H-2′), 5.86 (1 H, d, H-1′), 7.44 (2 H, br s, NH_2), 8.41 (1 H, s, H-8).

2-(3-Hydroxy-1-octyn-1-yl)adenosine (10q). Compound **10q** (260 mg, 67%) was obtained from **8** with 1-octyn-3-ol: UV (H_2O) λ_{max} 270 nm (13800), 289 (9500), λ_{min} 245 (6500), 281 (9400); UV (0.05 N HCl) λ_{max} 271 nm (15000), 294 (10900), λ_{min} 246 (6700), 282 (9900); NMR (DMSO-d_6) δ 0.88 (3 H, t, Me), 1.24–1.67 (8 H, m, CH_2), 3.53–3.69 (2 H, m, H-5′a,b), 3.95 (1 H, m, H-4′), 4.12 (1 H, dd, H-3′), 4.51 (1 H, dd, H-2′), 5.15–5.17 (2 H, m, OH × 2), 5.45 (1 H, d, OH), 5.50 (1 H, d, OH), 5.86 (1 H, d H-1′), 7.44 (2 H, br s, NH_2), 8.41 (1 H, s, H-8).

Synthesis of Bromoalkylcycloalkanes. A mixture of 2-cyclopentylethanol (**11a**) (5.0 g, 44 mmol), concentrated H_2SO_4 (1.9 mL), and HBr (48%, 11.2 g) was heated under reflux for 6

h. The cooled mixture was diluted with $CHCl_3$, and the whole was washed several times with H_2O. The separated organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo. The resulting oil was distilled under vacuum to give **12a** (5.6 g, 72%): bp 77 °C (16 mmHg); NMR (DMSO-d_6) δ 1.67–1.91 (11 H, m, cyclopentyl-CH_2), 3.51 (2 H, t, CH_2Br). In the case of 2-cyclohexaneethanol (**11b**) (10 g, 78 mmol) or 1-cyclohexyl-3-propanol (**11c**) (10 g, 70.3 mmol), a mixture with concentrated H_2SO_4 (3.8 mL) and HBr (48%, 22.3 g) was heated under reflux for 7 h. A similar workup and distillation gave **12b** (10.4 g, 70%) [bp 78–79 °C (3 mmHg); NMR (DMSO-d_6) δ 0.87–1.72 (13 H, m, cyclohexyl-CH_2), 3.54 (2 H, t, CH_2Br)] or **12c** (10.8 g, 75%) [bp 114–124 °C (3 mmHg); NMR (DMSO-d_6) δ 0.85–1.83 (15 H, m, cyclohexyl-CH_2CH_2), 3.50 (2 H, t, CH_2Br)], respectively.

Synthesis of Cycloalkylalkylacetylenes. Compound **12a** (5.2 g, 29.4 mmol) was added to a solution of lithium acetylide–ethylenediamine complex (1.1 equiv) in DMSO (10 mL) at 0 °C under argon. After the mixture was stirred for 5 h at room temperature, H_2O was added. The mixture was extracted with $CHCl_3$, washed with H_2O, and dried (Na_2SO_4). The solvent was removed in vacuo and the oil was distilled under vacuum to give **13a** (2.1 g, 59%): bp 56–59 °C (20 mmHg); IR (KBr) 2115 cm^{-1}; NMR (DMSO-d_6) δ 1.02–2.16 (13 H, m, cyclopentyl-CH_2CH_2), 2.71 (1 H, t, C≡CH). 4-Cyclohexyl-1-butyne (**13b**) and 5-cyclohexyl-1-pentyne (**13c**) were obtained similarly from **12b** and **12c**, respectively. **13b** (4.3 g, 60%): bp 30 °C (3 mmHg); IR (KBr) 2115 cm^{-1}; NMR (DMSO-d_6) δ 0.83–2.17 (15 H, m, cyclohexyl-CH_2CH_2), 2.69 (1 H, t, C≡CH). **13c** (4.3 g, 59%): bp 50 °C (3 mmHg); IR (KBr) 2115 cm^{-1}; NMR (DMSO-d_6) δ 0.83–2.14 (17 H, m, cyclohexyl-$CH_2CH_2CH_2$), 2.71 (1 H, t, C≡CH).

General Method for the Preparation of 9a–g,j–m,u. A mixture of **7** (540 mg, 1 mmol), CuI (9.5 mg, 0.05 mmol), bis(triphenylphosphine)palladium dichloride (18 mg, 5 mol %), triethylamine (0.16 mL, 1.2 mmol), and 1-octyne (0.18 mL, 1.2 mmol) in 1,4-dioxane (10 mL) was stirred for 2 h at room temperature under argon (judged by TLC; $CHCl_3$/EtOAc = 4:1, v/v). The solvent was removed in vacuo and the residue dissolved in $CHCl_3$ (50 mL) and triethylamine (0.1 mL), which was washed with saturated aqueous ethylenediaminetetraacetic acid disodium salt (2 × 10 mL) and brine (20 mL). The separated organic phase was dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by a silica gel column with $CHCl_3$/EtOAc (4:1) to give **9u** (490 mg, 95%) as an oil: IR (KBr) 2235 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (3 H, t, Me), 1.30–1.71 (8 H, m, CH_2), 2.08 (3 H, s, Ac), 2.17 (3 H, s, Ac), 2.18 (3 H, s, Ac), 2.49 (2 H, t, C≡CCH_2), 4.41 (2 H, m, H-5'a,b), 4.47 (1 H, dd, H-4'), 5.57 (1 H, dd, H-3'), 5.80 (1 H, t, H-2'), 6.33 (1 H, d, H-1'), 8.31 (1 H, s, H-8). Compounds **9a–g,j–m** were prepared similarly.

9-(2,3,5-Tri-*O*-acetyl-1-β-D-ribofuranosyl)-6-chloro-2-(2-cyclopentyl-1-ethyn-1-yl)purine (9a). From **7** with cyclopentylacetylene (0.14 mL, 1.2 mmol) for 1 h, 430 mg of **9a** (85% as an oil) was obtained: IR (KBr) 2240 cm^{-1}; NMR ($CDCl_3$) δ 1.61–2.14 (8 H, m, c-C_5H_9), 2.08 (3 H, s, Ac), 2.16 (3 H, s, Ac), 2.17 (3 H, s, Ac), 2.90 (1 H, t, C≡CCH), 4.40–4.42 (2 H, m, H-5'a,b), 4.46 (1 H, dd, H-4'), 5.58 (1 H, dd, H-3'), 5.80 (1 H, t, H-2'), 6.32 (1 H, d, H-1'), 8.30 (1 H, s, H-8).

9-(2,3,5-Tri-*O*-acetyl-1-β-D-ribofuranosyl)-6-chloro-2-(3-cyclopentyl-1-propyn-1-yl)purine (9b). From **7** with 3-cyclopentyl-1-propyne (0.16 mL, 1.2 mmol) for 1 h, 480 mg of **9b** (92% as an oil) was obtained: IR (KBr) 2240 cm^{-1}; NMR ($CDCl_3$) δ 1.33–2.23 (11 H, m, c-C_5H_9), 2.08 (3 H, s, Ac), 2.16 (3 H, s, Ac), 2.17 (3 H, s, Ac), 2.49 (2 H, t, C≡CCH_2), 4.41 (2 H, m, H-5'a,b), 4.47 (1 H, dd, H-4'), 5.58 (1 H, dd, H-3'), 5.81 (1 H, t, H-2'), 6.31 (1 H, d, H-1'), 8.30 (1 H, s, H-8).

9-(2,3,5-Tri-*O*-acetyl-1-β-D-ribofuranosyl)-6-chloro-2-(4-cyclopentyl-1-butyn-1-yl)purine (9c). From **7** with 4-cyclopentyl-1-butyne (**13a**) (0.15 mL, 1.2 mmol) for 1 h, 460 mg of **9c** (86% as an oil) was obtained: IR (KBr) 2240 cm^{-1}; NMR ($CDCl_3$) δ 1.10–1.97 (11 H, m, c-C_5H_9), 2.08 (3 H, s, Ac), 2.16 (3 H, s, Ac), 2.17 (3 H, s, Ac), 2.50 (2 H, t, C≡CCH_2), 4.41 (2 H, m, H-5'a,b), 4.47 (1 H, dd, H-4'), 5.57 (1 H, dd, H-3'), 5.81 (1 H, t, H-2'), 6.32 (1 H, d, H-1'), 8.31 (1 H, s, H-8).

9-(2,3,5-Tri-*O*-acetyl-1-β-D-ribofuranosyl)-6-chloro-2-(2-cyclohexyl-1-ethyn-1-yl)purine (9d). From **7** with cyclohexylacetylene (0.15 mL, 1.2 mmol) for 1 h, 480 mg of **9d** (92% as an oil) was obtained: IR (KBr) 2240 cm^{-1}; NMR ($CDCl_3$) δ 1.36–1.97 (10 H, m, c-C_6H_{11}), 2.09 (3 H, s, Ac), 2.16 (3 H, s, Ac), 2.17 (3 H, s, Ac), 2.66 (1 H, t, C≡CCH), 4.41 (2 H, m, H-5'a,b), 4.46 (1 H, dd, H-4'), 5.59 (1 H, dd, H-3'), 5.81 (1 H, t, H-2'), 6.31 (1 H, d, H-1'), 8.30 (1 H, s, H-8).

9-(2,3,5-Tri-*O*-acetyl-1-β-D-ribofuranosyl)-6-chloro-2-(3-cyclohexyl-1-propyn-1-yl)purine (9e). From **7** with 3-cyclohexyl-1-propyne (0.17 mL, 1.2 mmol) for 1 h, 450 mg of **9e** (84% as an oil) was obtained: IR (KBr) 2240 cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.0 (11 H, m, c-C_6H_{11}), 2.08 (3 H, s, Ac), 2.16 (3 H, s, Ac), 2.17 (3 H, s, Ac), 2.38 (2 H, t, C≡CCH_2), 4.41–4.42 (2 H, m, H-5'a,b), 4.47 (1 H, dd, H-4'), 5.58 (1 H, dd, H-3'), 5.81 (1 H, t, H-2'), 6.31 (1 H, d, H-1'), 8.30 (1 H, s, H-8).

9-(2,3,5-Tri-*O*-acetyl-1-β-D-ribofuranosyl)-6-chloro-2-(4-cyclohexyl-1-butyn-1-yl)purine (9f). From **7** with 3-cyclohexyl-1-butyne (**13b**) (0.16 g, 1.2 mmol) for 1 h, 490 mg of **9f** (89% as an oil) was obtained: IR (KBr) 2240 cm^{-1}; NMR ($CDCl_3$) δ 0.88–1.77 (13 H, m, c-C_6H_{11}), 2.08 (3 H, s, Ac), 2.16 (3 H, s, Ac), 2.17 (3 H, s, Ac), 2.49 (2 H, t, C≡CCH_2), 4.41 (2 H, m, H-5'a,b), 4.47 (1 H, dd, H-4'), 5.57 (1 H, dd, H-3'), 5.80 (1 H, t, H-2'), 6.32 (1 H, d, H-1'), 8.31 (1 H, s, H-8).

9-(2,3,5-Tri-*O*-acetyl-1-β-D-ribofuranosyl)-6-chloro-2-(5-cyclohexyl-1-pentyn-1-yl)purine (9g). From **7** with 5-cyclohexyl-1-pentyne (**13c**) (0.18 g, 1.2 mmol) for 1 h, 510 mg of **9g** (91% as an oil) was obtained: IR (KBr) 2235 cm^{-1}; NMR ($CDCl_3$) δ 0.84–1.72 (15 H, m, c-$C_6H_{11}CH_2CH_2$), 2.08 (3 H, s, Ac), 2.16 (3 H, s, Ac), 2.17 (3 H, s, Ac), 2.46 (2 H, t, C≡CCH_2), 4.41 (2 H, m, H-5'a,b), 4.47 (1 H, dd, H-4'), 5.57 (1 H, dd, H-3'), 5.80 (1 H, t, H-2'), 6.33 (1 H, d, H-1'), 8.31 (1 H, s, H-8).

9-(2,3,5-Tri-*O*-acetyl-1-β-D-ribofuranosyl)-6-chloro-2-[2-(1-hydroxycyclopentyl)-1-ethyn-1-yl]purine (9j). From **7** with 1-ethynyl-1-cyclopentanol (0.14 mL, 1.2 mmol) for 1 h, 450 mg of **9j** (86% as an oil) was obtained: IR (KBr) 2235 cm^{-1}; NMR ($CDCl_3$) δ 1.77–1.94 (8 H, m, c-C_5H_8), 2.09 (3 H, s, Ac), 2.13 (3 H, s, Ac), 2.18 (3 H, s, Ac), 2.85 (1 H, s, OH), 4.43–4.52 (3 H, m, H-4', 5'a,b), 5.72 (1 H, dd, H-3'), 5.90 (1 H, t, H-2'), 6.22 (1 H, d, H-1'), 8.28 (1 H, s, H-8).

9-(2,3,5-Tri-*O*-acetyl-1-β-D-ribofuranosyl)-6-chloro-2-[2-(1-hydroxycyclohexyl)-1-ethyn-1-yl]purine (9k). From **7** with 1-ethynyl-1-cyclohexanol (0.15 g, 1.2 mmol) for 1 h, 500 mg of **9k** (93% as an oil) was obtained: IR (KBr) 2230 cm^{-1}; NMR ($CDCl_3$) δ 1.64–2.13 (10 H, m, c-C_6H_{10}), 2.10 (3 H, s, Ac), 2.12 (3 H, s, Ac), 2.17 (3 H, s, Ac), 2.90 (1 H, s, OH), 4.46–4.51 (3 H, m, H-4', 5'a,b), 5.75 (1 H, dd, H-3'), 5.89 (1 H, t, H-2'), 6.21 (1 H, d, H-1'), 8.26 (1 H, s, H-8).

9-(2,3,5-Tri-*O*-acetyl-1-β-D-ribofuranosyl)-6-chloro-2-[2-(1-hydroxycycloheptyl)-1-ethyn-1-yl]purine (9l). From **7** with 1-ethynyl-1-cycloheptanol (0.17 g, 1.2 mmol) for 1 h, 500 mg of **9l** (91% as an oil) was obtained: IR (KBr) 2230 cm^{-1}; NMR ($CDCl_3$) δ 1.64–2.16 (12 H, m, c-C_7H_{12}), 2.10 (3 H, s, Ac), 2.12 (3 H, s, Ac), 2.17 (3 H, s, Ac), 2.82 (1 H, s, OH), 4.44–4.52 (3 H, m, H-4', 5'a,b), 5.75 (1 H, dd, H-3'), 5.90 (1 H, t, H-2'), 6.21 (1 H, d, H-1'), 8.27 (1 H, s, H-8).

9-(2,3,5-Tri-*O*-acetyl-1-β-D-ribofuranosyl)-6-chloro-2-[2-(1-hydroxycyclooctyl)-1-ethyn-1-yl]purine (9m). From **7** with 1-ethynyl-1-cyclooctanol (0.18 g, 1.2 mmol) for 1 h, 500 mg of **9m** (89% as an oil) was obtained: IR (KBr) 2230 cm^{-1}; NMR ($CDCl_3$) δ 1.52–2.14 (14 H, m, c-C_8H_{14}), 2.10 (3 H, s, Ac), 2.12 (3 H, s, Ac), 2.17 (3 H, s, Ac), 2.65 (1 H, s, OH), 4.44–4.51 (3 H, m, H-4', 5'a,b), 5.75 (1 H, dd, H-3'), 5.89 (1 H, t, H-2'), 6.20 (1 H, d, H-1'), 8.25 (1 H, s, H-8).

Conversion of 9 into 10. A solution of **9u** (490 mg, 0.95 mmol) in concentrated NH_4OH (30 mL) and 1,4-dioxane (60 mL) in a steel sealed tube was heated at 70 °C for 20 h. The solvent was removed in vacuo and the residue was purified by a silica gel column with $CHCl_3$/MeOH (5:1) to give 2-(1-octyn-1-yl)adenosine (**10u**, 320 mg, 90%): mp 101–103 °C (lit.[17] mp 101–103 °C).

Similarly **9a–g,j–m** were converted into **10a–g,j–m**.

2-(2-Cyclopentyl-1-ethyn-1-yl)adenosine (10a). From **9a** (430 mg, 0.85 mmol), **10a** (280 mg, 91%) was obtained: UV (H_2O) λ_{max} 270 nm (15 900), 286 sh (11 000), λ_{min} 247 (8000); UV (0.05 N HCl) λ_{max} 272 nm (17 000), 290 sh (12 000), λ_{min} 247 (7500); NMR (DMSO-d_6) δ 1.56–1.99 and 2.82–2.86 (9 H, m, c-C_5H_9), 3.52–3.70 (2 H, m, H-5'a,b), 3.95 (1 H, dd, H-4'), 4.12 (1 H, dd, H-3'), 4.52 (1 H, dd, H-2'), 5.18 (1 H, d, 2'- or 3'-OH), 5.22 (1 H, t, 5'-OH), 5.45 (1 H, d, 2'- or 3'-OH), 7.41 (2 H, br s, NH_2), 8.38 (1 H, s, H-8).

2-(3-Cyclopentyl-1-propyn-1-yl)adenosine (10b). From **9b** (480 mg, 0.92 mmol), **10b** (300 mg) was obtained: UV (H_2O) λ_{max} 271 nm (14900), 286 sh (10500), λ_{min} 246 (6800); UV (0.05 N HCl) λ_{max} 272 (16700), 293 (12000), λ_{min} 248 (6600), 284 (11600); NMR (DMSO-d_6) δ 1.29–2.10 (9 H, m, c-C_5H_9), 2.40 (2 H, d, $C{\equiv}CCH_2$), 4.12 (1 H, dd, H-3′), 4.53 (1 H, dd, H-2′), 5.12 (1 H, d, 2′- or 3′-OH), 5.25 (1 H, t, 5′-OH), 5.41 (1 H, d, 2′- or 3′-OH), 5.88 (1 H, d, H-1′), 7.36 (2 H, br s, NH_2), 8.39 (1 H, s, H-8).

2-(4-Cyclopentyl-1-butyn-1-yl)adenosine (10c). From **9c** (460 mg, 0.86 mmol), **10c** (290 mg, 87%) was obtained: UV (H_2O) λ_{max} 270 nm (14300), 286 sh (9400), λ_{min} 246 (7200); UV (0.05 N HCl) λ_{max} 271 nm (16300), 290 (10300), λ_{min} 245 nm (7700); NMR (DMSO-d_6) δ 1.09–1.95 (11 H, m, c-$C_5H_9CH_2$), 2.40 (2 H, t, $C{\equiv}CCH_2$), 3.53–3.68 (2 H, m, H-5′a,b), 3.95 (1 H, dd, H-4′), 4.15 (1 H, dd, H-3′), 4.53 (1 H, dd, H-2′), 5.16 (1 H, d, 2′- or 3′-OH), 5.21 (1 H, t, 5′-OH), 5.43 (1 H, d, 2′- or 3′-OH), 5.85 (1 H, d, H-1′), 7.41 (2 H, br s, NH_2), 8.38 (1 H, s, H-8).

2-(2-Cyclohexyl-1-ethyn-1-yl)adenosine (10d). From **9d** (480 mg, 0.92 mmol), **10d** (290 mg, 84%) was obtained: UV (H_2O) λ_{max} 270 nm (14700), 285 sh (10500), λ_{min} 246 (6900); UV (0.05 N HCl) λ_{max} 271 nm (15800), 294 (12000), λ_{min} 247 (6600), 284 (11300); NMR (DMSO-d_6) δ 1.29–1.84 and 2.59–2.65 (11 H, m, c-C_6H_{11}), 3.54–3.68 (2 H, m, H-5′a,b), 3.95 (1 H, dd, H-4′), 4.12 (1 H, dd, H-3′), 4.51 (1 H, dd, H-2′), 5.86 (1 H, d, H-1′), 7.43 (2 H, br s, NH_2), 8.39 (1 H, s, H-8).

2-(3-Cyclohexyl-1-propyn-1-yl)adenosine (10e). From **9e** (450 mg, 0.84 mmol), **10e** (290 mg, 89%) was obtained: UV (H_2O) λ_{max} 270 nm (13700), 286 sh (9500), λ_{min} 246 (6200); UV (0.05 N HCl) λ_{max} 272 nm (15400), 292 (10700), λ_{min} 247 (6200), 285 (10600); NMR (DMSO-d_6) δ 1.02–1.83 (11 H, m, c-C_6H_{11}), 2.31 (2 H, d, $C{\equiv}CCH_2$), 3.53–3.68 (2 H, m, H-5′a,b), 3.95 (1 H, dd, H-4′), 4.11 (1 H, dd, H-3′), 4.53 (1 H, dd, H-2′), 5.18 (1 H, d, 2′- or 3′-OH), 5.23 (1 H, t, 5′-OH), 5.45 (1 H, d, 2′- or 3′-OH), 5.85 (1 H, d, H-1′), 7.41 (2 H, br s, NH_2), 8.38 (1 H, s, H-8).

2-(4-Cyclohexyl-1-butyn-1-yl)adenosine (10f). From **9f** (490 mg, 0.89 mmol), **10f** (310 mg, 86%) was obtained: UV (H_2O) λ_{max} 270 nm (14600), 285 sh (10200), λ_{min} 246 (6800); UV (0.05 N HCl) λ_{max} 272 nm (17000), 288 sh (11500), λ_{min} 247 (7200); NMR (DMSO-d_6) δ 0.87–1.76 (13 H, m, c-$C_6H_{11}CH_2$), 2.41 (2 H, t, $C{\equiv}CCH_2$), 3.53–3.68 (2 H, m, H-5′a,b), 3.95 (1 H, dd, H-4′), 4.12 (1 H, dd, H-3′), 4.53 (1 H, dd, H-2′), 5.16 (1 H, d, 2′- or 3′-OH), 5.22 (1 H, t, 5′-OH), 5.44 (1 H, d, 2′- or 3′-OH), 5.85 (1 H, d, H-1′), 7.41 (2 H, br s, NH_2), 8.38 (1 H, s, H-8).

2-(5-Cyclohexyl-1-pentyn-1-yl)adenosine (10g). From **9g** (510 mg, 0.91 mmol), **10g** (320 mg, 85%) was obtained: UV (H_2O) λ_{max} 270 nm (13800), 285 sh (9700), λ_{min} 246 (6200); UV (0.05 N HCl) λ_{max} 272 nm (16900), 290 sh (11600), λ_{min} 246 (6900); NMR (DMSO-d_6) δ 0.86–1.71 (15 H, m, c-$C_6H_{11}CH_2CH_2$), 2.38 (2 H, t, $C{\equiv}CCH_2$), 3.55–3.68 (2 H, m, H-5′a,b), 3.95 (1 H, dd, H-4′), 4.12 (1 H, dd, H-3′), 4.53 (1 H, dd, H-2′), 5.18 (1 H, d, 2′- or 3′-OH), 5.24 (1 H, t, 5′-OH), 5.45 (1 H, d, 2′- or 3′-OH), 5.85 (1 H, d, H-1′), 7.42 (2 H, br s, NH_2), 8.39 (1 H, s, H-8).

2-[2-(1-Hydroxycyclopentyl)-1-ethyn-1-yl]adenosine (10j). From **9j** (450 mg, 0.86 mmol), **10j** (300 mg, 93%) was obtained: UV (H_2O) λ_{max} 270 nm (7500), 289 (9100), λ_{min} 247 (6600), 281 (9100); UV (0.05 N HCl) λ_{max} 272 nm (14100), 295 (10300), λ_{min} 248 (6600), 283 (9500); NMR (DMSO-d_6) δ 1.66–1.94 (8 H, m, c-C_5H_8-H), 3.53–3.69 (2 H, m, H-5′a,b), 3.95 (1 H, dd, H-4′), 4.12 (1 H, dd, H-3′), 4.49 (1 H, dd, H-2′), 5.16–5.18 (2 H, m, OH × 2), 5.42 (1 H, br s, OH), 5.46 (1 H, d, OH), 5.87 (1 H, d, H-1′), 7.43 (2 H, br s, NH_2), 8.41 (1 H, s, H-8).

2-[2-(1-Hydroxycyclohexyl)-1-ethyn-1-yl]adenosine (10k). From **9k** (500 mg, 0.93 mmol), **10k** (310 mg, 85%) was obtained: UV (H_2O) λ_{max} 270 nm (14400), 287 sh (9600), λ_{min} 246 (7100); UV (0.05 N HCl) λ_{max} 271 nm (15600), 294 (10800), λ_{min} 247 (7300), 284 (10300); NMR (DMSO-d_6) δ 1.25–1.87 (10 H, m, c-C_6H_{10}-H), 3.56–3.71 (2 H, m, H-5′a,b), 3.97 (1 H, dd, H-4′), 4.15 (1 H, dd, H-3′), 4.50 (1 H, dd, H-2′), 5.11 (1 H, d, OH), 5.20 (1 H, t, 5′-OH), 5.44 (1 H, d, OH), 5.50 (1 H, d, OH), 5.89 (1 H, d, H-1′), 7.41 (2 H, br s, NH_2), 8.39 (1 H, s, H-8).

2-[2-(1-Hydroxycycloheptyl)-1-ethyn-1-yl]adenosine (10l). From **9l** (500 mg, 0.91 mmol), **10l** (320 mg) was obtained: UV (H_2O) λ_{max} 270 nm (13100), 289 (9000), λ_{min} 246 (6100), 283 (8800); UV (0.05 N HCl) λ_{max} 272 (14300), 296 (10300), λ_{min} 247 (6300), 284 (9500); NMR (DMSO-d_6) δ 1.49–2.00 (12 H, m, c-C_7H_{12}-H), 3.53–3.69 (2 H, m, H-5′a,b), 3.95 (1 H, dd, H-4′), 4.12 (1 H, dd, H-3′), 4.50 (1 H, dd, H-2′), 5.15–5.17 (2 H, m, OH × 2), 5.41 (1 H, br s, OH), 5.45 (1 H, d, OH), 5.88 (1 H, d, H-1′), 7.44 (2 H, br s, NH_2), 8.41 (1 H, s, H-8).

2-[2-(1-Hydroxycyclooctyl)-1-ethyn-1-yl]adenosine (10m). From **9m** (500 mg, 0.89 mmol), **10m** (330 mg, 89%) was obtained: UV (H_2O) λ_{max} 271 nm (13000), 289 (9100), λ_{min} 246 (6000), 282 (8900); UV (0.05 N HCl) λ_{max} 272 nm (13900), 295 (10200), λ_{min} 248 (6200), 283 (9400); NMR (DMSO-d_6) δ 1.45–1.93 (14 H, m, c-C_8H_{14}-H), 3.54–3.68 (2 H, m, H-5′a,b), 3.95 (1 H, dd, H-4′), 4.12 (1 H, dd, H-3′), 4.50 (1 H, t, H-2′), 5.87 (1 H, d, H-1′), 7.45 (2 H, br s, NH_2), 8.41 (1 H, s, H-8).

Adenosine Receptor Binding Assay. The A_1 and A_2 receptor binding assays were done by previously described methods.[16] Briefly, the A_1 receptor binding assay was done in rat brain membranes using [^{3}H]CHA as a radioligand. The reaction mixture containing [^{3}H]CHA, adenosine deaminase, a test compound solution, and the A_1 receptor preparation was incubated at 23 °C for 2 h. After the incubation, the reaction mixture was filtrated with a glass fiber filter under reduced pressure. Nonbound radioactivity was removed by washing the filter with ice-cold buffer. The radioactivity of the glass fiber filter was counted in a liquid scintillation counter. The A_2 receptor binding assay was done in rat striatal membranes using [^{3}H]NECA in the presence of 50 nM CPA. Nonspecific binding of [^{3}H]CHA and [^{3}H]NECA were defined as binding in the presence of 10 mM (*R*)-phenylisopropyladenosine and 100 μM CPA, respectively. IC_{50} values were calculated from a nonlinear, log transformation of specific binding data from the ligand binding assay and converted to K_i values as described previously.[16]

Blood Pressure and Heart Rate. Effects of the compound on BP and HR in iv administration were measured in anesthetized male SHR as described previously.[16]

The solution of the test compound (0.03–100 μg/mL) was administered iv at 5-min intervals in a cumulative manner. Changes in BP and HR were expressed in terms of percent changes of their control values. The relative potency to decrease BP was estimated on the basis of the ED_{30} value, the mean dose that produced a 30% decrease in BP of SHR. Similarly, the relative potency to decrease HR was estimated on the basis of the ED_{10} value, the mean dose that produced a 10% decrease in HR of SHR. Antihypertensive effect of the compound in oral administration was also examined in conscious SHR as described previously.[16]

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Registry No. **8**, 35109-88-7; **9a**, 141345-24-6; **9b**, 141345-25-7; **9c**, 141345-26-8; **9d**, 141345-27-9; **9e**, 141345-28-0; **9f**, 141345-29-1; **9g**, 141345-30-4; **9j**, 141345-31-5; **9k**, 141345-32-6; **9l**, 141345-33-7; **9m**, 141345-34-8; **9u**, 133560-14-2; **10a**, 141345-09-7; **10b**, 141345-10-0; **10c**, 141345-11-1; **10d**, 141345-12-2; **10e**, 141345-13-3; **10f**, 141345-14-4; **10g**, 141345-15-5; **10h**, 90596-70-6; **10i**, 141345-16-6; **10j**, 141345-17-7; **10k**, 141345-18-8; **10l**, 141345-19-9; **10m**, 141345-20-2; **10o**, 141345-21-3; **10p**, 141345-22-4; **10q**, 141345-23-5; **10u**, 90596-75-1; **11a**, 766-00-7; **11b**, 4442-79-9; **11c**, 1124-63-6; **12a**, 18928-94-4; **12b**, 1647-26-3; **12c**, 34094-21-8; **13a**, 141345-07-5; **13b**, 141345-08-6; **13c**, 5963-75-7; c-$C_5H_9C{\equiv}CH$, 930-51-8; c-$C_5H_9CH_2C{\equiv}CH$, 116279-08-4; c-$C_6H_{11}C{\equiv}CH$, 931-48-6; c-$C_6H_{11}CH_2C{\equiv}CH$, 17715-00-3; $PhC{\equiv}CH$, 536-74-3; $Ph(CH_2)_2C{\equiv}CH$, 16520-62-0; c-$C_5H_8(OH)C{\equiv}CH$, 17356-19-3; c-$C_6H_{10}(OH)C{\equiv}CH$, 78-27-3; c-$C_7H_{12}(OH)C{\equiv}CH$, 2809-78-1; c-$C_8H_{14}(OH)C{\equiv}CH$, 55373-76-7; $(CH_3)_2(OH)CC{\equiv}CH$, 115-19-5; $CH_3(CH_2)_2(OH)CHC{\equiv}CH$, 15352-98-4; $CH_3(CH_2)_4(OH)CHC{\equiv}CH$, 37911-28-7; $CH_3(CH_2)_5C{\equiv}CH$, 629-05-0; $LiC{\equiv}CH{\cdot}H_2NCH_2CH_2NH_2$, 50475-76-8.