Alternating Dependency of Cytokinin Activity on the Number of Methylene Units in ω -Phenylalkyl Derivatives of Some Purine Cytokinins and 4-Substituted Pyrido[3,4-*d*]pyrimidine

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ω -Phenylalkyl derivatives of N^6 -substituted adenine, N^6 -substituted adenosine and 6-alkoxy-purine with odd numbers of methylenes had relatively high activity, while the corresponding 2-methyl-4-substituted-aminopyrido[3,4-*d*]pyrimidines with even numbers of methylenes had high activity in an *Amaranthus* betacyanin test and lettuce seed germination test. These results suggest that the ω -phenyl groups of the cytokinins play a specific role for cytokinin-receptor binding and that the pyrido[3,4-*d*]pyrimidines interact with a receptor in a different binding mode.

Such physical properties of a series of ω, ω' -dicarboxylic acids as melting point and solubility in water vary alternately with the increase of the number of methylenes.¹⁾ Such an alternation has also been observed in biological systems. For instance, ω -fluoro-substituted carboxylic acids¹⁾ and substituted diphenyl ethers of ω, ω' -glycol²⁾ show a similar alternation in toxicity against mice and schistosomidal activity, respectively. The former case belongs to metabolism *in vivo*, i.e., β -oxidation, while the latter one belongs, probably, to the intrinsic substrate-receptor interaction. The

alternation of biological activity due to substrate-receptor interaction is interesting from the standpoint of a structure-activity study, since such a terminal functional group may play an important role in biological activity by a weak, but specific interaction with a group or groups of a receptor responsible for substrate-recognition. Unfortunately, reasonable explanations for this alternation in biological systems have not been made.

Our efforts in recent several years have been directed to structure-activity studies of cytokinins, including both the purine type and

non-purine type, to reveal fundamental aspects of cytokinin–receptor interaction.^{3~7)} In the course of these studies, we have found an interesting alternation in the biological activity of both cytokinins. As far as we know, there has been no report on the alternation of cytokinin activity since the discovery of kinetin in 1955. In this paper, we report an alternating dependency on the even and odd numbers of methylene units in ω -phenylalkyl derivatives of N^6 -substituted adenine (**1**), its riboside (**4**), 6-alkoxypurine (**2**) and 2-methyl-4-substituted-aminopyrido[3,4-*d*]pyrimidine (**3**).

RESULTS

i) N^6 -(ω -Phenylalkyl)adenines (**1**)

In an *Amaranthus* betacyanin test, **1a**, **1b** (N^6 -benzyladenine), **1c** and **1e** exhibited the activity expected from previous results in other bioassays.^{8,9)} The activity of **1d** was five times higher than that of **1c**. Cytokinin activity

decreased in the order of **1b** > **1d** > **1a** > **1c** $\gg$ **1e**, compound **1e** being inactive (Table I). The homologs with odd numbers of methylenes showed stronger activity than those with even numbers of methylenes. Therefore, these compounds exhibited an alternation of activity with respect to the methylene length (Fig. 1). In a lettuce seed germination test, the decreasing order of activity, **1b** > **1d** > **1a** > **1c** $\gg$ **1e**, was observed, which coincided with that in the *Amaranthus* betacyanin test. Similar results were obtained in a tobacco callus test (Table II).

ii) 6-(ω -Phenylalkoxy)purines (**2**)

6-Alkoxypurines are relatively potent cytokinins that have oxygen linkage in the 6-position.^{10,11)} Compounds **2a**~**2e** with 0~4 methylenes were bioassayed to learn whether or not such an alternation could be observed for these purine derivatives. In both an *Amaranthus* betacyanin test and lettuce seed germi-

TABLE I. SUMMARY OF THE CYTOKININ ACTIVITY OF ω -PHENYLALKYL DERIVATIVES OF N^6 -SUBSTITUTED ADENINE, 6-ALKOXPURINE, 2-METHYL-4-SUBSTITUTED-AMINOPYRIDO[3,4-*d*]PYRIMIDINE AND N^6 -SUBSTITUTED ADENOSINE

Compound	Betacyanin biosynthesis		Lettuce seed germination	
	$C_{0.1\mu\text{MBA}},^a \mu\text{M}$	$pC_{0.1\mu\text{MBA}}$	$E_{50},^b \mu\text{M}$	pE_{50}
1a	0.48	0.32	0.74	0.13
1b	0.10	1.00	0.10	1.00
1c	0.89	0.05	2.5	-0.39
1d	0.16	0.79	0.40	0.40
1e	Inactive		Inactive	
2a	309	-2.49	154	-2.19
2b	0.33	0.48	0.19	0.71
2c	9.3	-0.97	20.9	-1.32
2d	0.71	0.15	0.66	0.18
2e	Inactive		Inactive	
3a	2.5	-0.40	0.81	0.09
3b	380	-2.58	Inactive	
3c	89	-1.95	Inactive	
3d	Inactive		Inactive	
4a	1.55	-0.19	0.98	0.01
4b	0.16	0.81	0.08	1.10
4c	2.1	-0.32	6.9	-0.84
4d	0.25	0.60	0.20	0.70
4e	45	-1.65	Inactive	

^a Concentration at which the sample formed the same amount of betacyanin ($\Delta\text{Abs}_{542\sim 620\text{nm}}$) as that of 0.1 μM BA.

^b Concentration at which the sample showed 50% germination after 4 days incubation at $31(\pm 1)^\circ\text{C}$ in the dark.

TABLE II. CYTOKININ ACTIVITY OF N^6 -(ω -PHENYLALKYL)ADENINES AND THEIR RIBOSYL DERIVATIVES IN A TOBACCO CALLUS TEST

Compound	C_K , ^a μ M	pC_K
1a	0.12	0.92
1b	0.013	1.90
1c	0.54	0.27
1d	0.12	0.92
1e	Inactive	
4a	—	—
4b	0.057	1.24
4c	0.53	0.27
4d	0.19	0.72
4e	13	-1.10

^a Concentration at which the sample gave the same yield (fresh weight) as half of the maximum yield promoted by kinetin.

FIG. 1. Alternation of Cytokinin Activity of N^6 -(ω -Phenylalkyl)adenines.

●—●, *Amaranthus* betacyanin test ($pC_{0.1\mu M BA}$); ○—○, lettuce seed germination test (pE_{50}); △—△, tobacco callus test (pC_K).

nation test, the activity decreased in the order of **2b** > **2d** > **2c** > **2a** > **2e**, **2e** being inactive. Compound **2d** was more active than **2c** by a factor of approximately ten in the former test, and by a factor of three in the latter test. Additionally, **2a** was less active than **2d**. Irrespective of the different linkage in the 6-position, **2** showed the same type of alternation as that observed for **1** (Fig. 2).

iii) 2-Methyl-4-(ω -phenylalkylamino)pyrido[3,4-*d*]pyrimidines (**3**)

The cytokinin activity of 4-substituted

FIG. 2. Alternation of Cytokinin Activity of 6-(ω -Phenylalkoxy)purines.

●—●, *Amaranthus* betacyanin test ($pC_{0.1\mu M BA}$); ○—○, lettuce seed germination test (pE_{50}).

FIG. 3. Alternation of Cytokinin Activity of 2-Methyl-4-(ω -Phenylalkylamino)pyrido[3,4-*d*]pyrimidines.

●—●, *Amaranthus* betacyanin test ($pC_{0.1\mu M BA}$); ○—○, lettuce seed germination test (pE_{50}).

pyrido[3,4-*d*]pyrimidines was first found in our systematic studies on pyridopyrimidines, *i.e.*, 1,3-*X*-triazanaphthalenes (*X*=5, 6, 7 and 8).^{6,7,12} The activity of **3a**~**3d** was studied to compare with that of purine cytokinins **1** and **2**. In the *Amaranthus* betacyanin test, the phenylamino derivative **3a** was the most active, and **3c** was thirty-five times less active than **3a**, but four times more active than the benzylamino derivative **3b**. Compound **3d** was inactive. Thus, the activity decreased in the order of **3a** > **3c** > **3b** > **3d**. The difference of activity between **3b** and **3c** was ascertained by several repetitions of the assay. The homologs

FIG. 4. Alternation of Cytokinin Activity of N^6 -(ω -Phenylalkyl)adenosines.

●—●, *Amaranthus* betacyanin test ($pC_{0.1\mu M BA}$); ○—○, lettuce seed germination test (pE_{50}); △—△, tobacco callus test (pC_K).

with even numbers of methylenes showed higher activity than those with odd numbers of methylenes, which was quite different from the alternation of the purine cytokinins **1** and **2** (Fig. 3). In the lettuce seed germination test, only **3a** was active.

iv) N^6 -(ω -Phenylalkyl)adenosines (**4**)

In the *Amaranthus* betacyanin test, cytokinin activity decreased in the order of **4b** > **4a** > **4d** > **4c** > **4e**, the decreasing order being consistent with that of the corresponding bases **1** (Fig. 4). The lettuce seed germination test and tobacco callus test gave the same results.

DISCUSSION

An alternation of cytokinin activity of N^6 -(ω -phenylalkyl)adenosines (**1**), which had been extensively studied in 1950s, was found for the first time in three different bioassays: an *Amaranthus* betacyanin test, lettuce seed germination test and tobacco callus test. Kuraishi earlier reported that **1a** and **1c** were almost as active as **1b**, and **1d** was weak in promoting leaf growth of *Raphanus sativus*.⁸⁾ Furthermore, Skinner *et al.* reported that **1b**, **1c** and **1d** were equally active in stimulating seed germination in a variety of lettuce.⁹⁾ The results obtained in this study did not coincide with the previous results. The discrepancy, particularly

in the order of activity between **1c** and **1d** may have arisen from the difference in accuracy or sensitivity of the assay methods.

N^6 -(ω -Phenylalkyl)adenosines (**4**) showed a similar alternation. This is reasonable since N^6 -substituted adenines and their ribosyl derivatives exert similar substituent effects on cytokinin activity.¹³⁾ 6-(ω -Phenylalkoxy)-purines (**2**) also exhibited the same type of alternation, as expected from their structural resemblance to **1**; the benzyloxy derivative **2b** was the most active, as reported earlier.^{10,11)} Such an alternation of cytokinin activity of closely related 6-(ω -phenylalkylthio)purines can be found in the literature,⁹⁾ the homologs with odd numbers of methylenes having stronger activity. These results imply that the four kinds of purine derivatives exert their cytokinin action similarly, irrespective of the linkage in the 6-position.

In contrast, 2-methyl-4-(ω -phenylalkyl-amino)pyrido[3,4-*d*]pyrimidines (**3**), a non-purine type of cytokinin, exhibited an alternation different from that of the purine type of cytokinin. The present study and the previous one⁷⁾ show that the substituent effects were not the same between the pyrido[3,4-*d*]pyrimidines and the purine cytokinins, suggesting different modes of interaction with a receptor for these two types of cytokinins.

Among N^6 -(ω -substituted-alkyl)adenosines, **1** with a phenyl group as the ω -substituent showed alternation, while N^6 -(ω -hydroxy-alkyl)adenosines, N^6 -*n*-alkyladenosines, N^6 -iso-alkyladenosines and N^6 -alkoxyalkyladenosines did not.¹²⁾ Thus, we believe at present that the ω -phenyl group and the purine ring or the pyrido[3,4-*d*]pyrimidine ring which interact with a receptor simultaneously (multiple recognition by the receptor) are necessary for the alternation of activity. The necessity of a planar phenyl group for potent cytokinin activity, which ensures favorable interaction with the receptor, has been found for 6-styryl-purines and their related compounds.⁵⁾ From the results in a gas chromatographic study of acyclic and cyclic hydrocarbons, Endo *et al.*¹⁴⁾ have recently proposed a "structure

similarity hypothesis" that claims compounds or groups having similar structures interact preferably with each other. The alternation in cytokinin activity specific for the ω -phenylalkyl derivatives of the cytokinins, and the preferable interaction between structurally similar groups, strongly suggest that the substituent recognition site of the cytokinin receptor(s) in *Amaranthus* cotyledons, lettuce seed and tobacco callus has an aromatic planar nature.

ω -Phenylalkyl derivatives of **1**, **2**, **3** and **4**, which have specific substituent effects on cytokinin activity, are helpful for understanding the cytokinin-receptor interaction at the molecular level. Furthermore, these compounds may be used for distinguishing the true cytokinin binding proteins responsible for the activity from non-specific binding proteins, since the alternation is not related to their lipophilicity but is related to the three-dimensional structure of the receptor(s).

EXPERIMENTAL

General. Melting points (mp) are uncorrected. IR and UV spectra were recorded on a JASCO IR-G spectrophotometer and a Hitachi UV 200-10 spectrophotometer, respectively. $^1\text{H-NMR}$ spectra were measured with a Hitachi R-22 spectrometer using Me_4Si as an internal standard. Elemental analyses were performed at the Analytical Center of Kyoto University, Kyoto.

The following N^6 -substituted adenines were synthesized by refluxing 6-chloropurine with appropriate amines together with triethylamine in 1-butanol for 3–5 hr, and were recrystallized from ethanol: N^6 -phenyladenine (**1a**), mp 277–280°C (lit.¹⁵ 284–285°C), 70% yield; N^6 -(2-phenylethyl)adenine (**1c**), mp 225–227°C (lit.¹⁶ 239–240°C), 87%; N^6 -(3-phenylpropyl)adenine (**1d**), mp 185°C (lit.¹⁶ 161–164°C), 51%; and N^6 -(4-phenylbutyl)adenine (**1e**), mp 158–164°C (lit.¹⁶ 161–164°C), 65%. Similarly, the following 9-ribosyl derivatives were prepared from 6-chloro-9- β -D-ribofuranosylpurine: N^6 -phenyladenosine (**4a**), mp 196–197°C (from aqueous methanol, lit.¹⁷ 199°C), 63%; N^6 -benzyladenosine (**4b**), mp 167–168°C (aqueous methanol, lit.¹⁷ 183°C), 67%; and N^6 -(2-phenylethyl)adenosine (**4c**), mp 166–167°C (aqueous ethanol, lit.¹⁸ 165–167°C), 91%. 6-Phenoxypurine (**2a**), mp 221–223°C (aqueous methanol, lit.¹⁹ 217–218°C) and 6-benzoyloxypurine (**2b**), mp 172–173°C (aqueous methanol, lit.²⁰ 171–172°C) were prepared in 43% and 45% yields, respectively, by nucleophilic substitution of 6-chloro-

purine with the corresponding sodium alkoxides.²⁰ The structures of the known compounds were confirmed by their IR, UV and $^1\text{H-NMR}$ spectra. N^6 -Benzyladenine (**1b**) was a product of Kohjin Co.

Bioassay. An *Amaranthus* betacyanin test was carried out by the method of Biddington and Thomas.²¹ Cytokinin activity is expressed by $\text{pC}_{0.1\mu\text{MBA}}$ (logarithm of the reverse of the concentration (μM) at which the samples formed the same amount of betacyanin as that of 0.1 μM BA).⁴

A germination test was made by using lettuce seeds (Great Lakes 366) at $31(\pm 1)^\circ\text{C}$ for 4 days in the dark as reported.⁴ Similarly, cytokinin activity is expressed by pE_{50} (logarithm of the reverse of the concentration (μM) for 50% germination).

A tobacco callus test was conducted as reported^{3,22} and cytokinin activity is expressed by pC_K (logarithm of the reverse of the concentration (μM) at which the samples formed the same amount of callus (fresh weight) as 50% of the maximum yield of kinetin, a standard compound, after 30 days).

6-(2-Phenylethoxy)purine (2c). This compound was synthesized in a 78% yield by the method of Bowles *et al.*²⁰ Recrystallization from aqueous methanol gave a crystalline powder, mp 171–173°C. IR (KBr) 3100 (NH), 1610, 1580 ($\text{C}=\text{N}$, $\text{C}=\text{C}$) cm^{-1} ; UV: $\lambda_{\text{max}}^{\text{pH}1}$ 254 (12,000), $\lambda_{\text{min}}^{\text{pH}1}$ 221 (4,270), $\lambda_{\text{max}}^{\text{pH}7}$ 252 (11,900), $\lambda_{\text{min}}^{\text{pH}7}$ 218 (3,640), $\lambda_{\text{max}}^{\text{pH}13}$ 261 (10,900), $\lambda_{\text{min}}^{\text{pH}13}$ 231 (3,000) nm; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 3.12 (2H, t, $J=7\text{ Hz}$, $\text{Ph}-\text{CH}_2$), 4.74 (2H, t, $J=7\text{ Hz}$, $\text{O}-\text{CH}_2$), 7.29 (5H, broad s, phenyl), 8.34 (1H, s, 8-H), 8.45 (1H, s, 2-H). *Anal.* Calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_4 \cdot 0.2\text{H}_2\text{O}$: C, 64.03; H, 5.13; N, 22.97. Found: C, 64.28; H, 4.80; N, 22.77%.

6-(3-Phenylpropoxy)purine (2d). This compound was synthesized in a 65% yield and recrystallized from aqueous methanol to give plates, mp 121–123°C. IR (KBr) 3050 (NH), 1610, 1590 ($\text{C}=\text{N}$, $\text{C}=\text{C}$) cm^{-1} ; UV: $\lambda_{\text{max}}^{\text{pH}1}$ 254 (9,850), $\lambda_{\text{min}}^{\text{pH}1}$ 223 (4,030), $\lambda_{\text{max}}^{\text{pH}7}$ 253 (8,990), $\lambda_{\text{min}}^{\text{pH}7}$ 222 (3,950), $\lambda_{\text{max}}^{\text{pH}13}$ 261 (10,600), $\lambda_{\text{min}}^{\text{pH}13}$ 232 (2,790) nm; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 2.10 (2H, m, $\text{C}-\text{CH}_2-\text{C}$), 2.77 (2H, t, $J=7\text{ Hz}$, $\text{Ph}-\text{CH}_2$), 4.51 (2H, t, $J=7\text{ Hz}$, $\text{O}-\text{CH}_2$), 7.24 (5H, broad s, phenyl), 8.34 (1H, s, 8-H), 8.45 (1H, s, 2-H). *Anal.* Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_4 \cdot 0.2\text{H}_2\text{O}$: C, 65.20; H, 5.63; N, 21.72. Found: C, 65.02; H, 5.35; N, 21.46%.

6-(4-Phenylbutoxy)purine (2e). This compound was similarly prepared. After silica gel column chromatography by eluting with hexane–ethyl acetate (1:1) and following by removal of the solvents, **2e** was obtained as a colorless powder, mp 116–118°C, in an 84% yield. Recrystallization from benzene afforded a crystalline powder of the same melting point. IR (KBr) 3080 (NH), 1590, 1570 ($\text{C}=\text{N}$, $\text{C}=\text{C}$) cm^{-1} ; UV: $\lambda_{\text{max}}^{\text{pH}1}$ 254 (9,710), $\lambda_{\text{min}}^{\text{pH}1}$ 223 (3,580), $\lambda_{\text{max}}^{\text{pH}7}$ 252 (9,390), $\lambda_{\text{min}}^{\text{pH}7}$ 222 (3,030), $\lambda_{\text{max}}^{\text{pH}13}$ 254

(9,710), $\lambda_{\text{min}}^{\text{pH}13}$ 232 (2,310) nm; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 1.5~2.0 (4H, m, $\text{C-CH}_2\text{-CH}_2\text{-C}$), 2.65 (2H, broad t, $J=7$ Hz, Ph-CH_2), 4.56 (2H, broad t, $J=7$ Hz, O-CH_2), 7.20 (5H, broad s, phenyl), 8.34 (1H, s, 8-H), 8.46 (1H, s, 2-H). *Anal.* Calcd. for $\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}$: C, 67.15; H, 6.01; N, 20.88. Found: C, 67.01; H, 5.77; N, 20.58%.

2-Methyl-4-anilinopyrido[3,4-*d*]pyrimidine (**3a**). A mixture of 2-methyl-4-chloropyrido[3,4-*d*]pyrimidine⁷⁾ (180 mg, 1.0 mmol), aniline (162 mg, 2.0 mmol) and ethanol (20 ml) was stirred at 40~50°C for a few minutes. The solution was concentrated to a small volume, diluted with water and cooled in an ice bath. The resultant crystals were collected, washed with aqueous ethanol and dried. The crude product was recrystallized from the solvent to give fine needles, mp 232~233°C (232 mg, 98%). IR (KBr) 3300 (NH), 1620, 1600, 1570 (C=N , C=C) cm^{-1} ; UV: $\lambda_{\text{max}}^{\text{pH}1}$ 340 (11,600), 285 (5,990), $\lambda_{\text{max}}^{\text{pH}7}$ 344 (9,800), 289 (9,030), $\lambda_{\text{max}}^{\text{pH}12}$ 344 (9,700), 289 (9,060) nm; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 2.57 (3H, s, CH_3), 7.2~8.0 (5H, m, phenyl), 8.42 (1H, dd, $J=5$, 1 Hz, 5-H), 8.67 (1H, d, $J=5$ Hz, 6-H), 9.10 (1H, broad s, 8-H), 9.93 (1H, s, NH). *Anal.* Calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_4$: C, 71.16; H, 5.12; N, 23.72. Found: C, 71.17; H, 5.19; N, 23.60%.

2-Methyl-4-benzylaminopyrido[3,4-*d*]pyrimidine (**3b**). The UV data for **3b** were not reported in a previous paper.⁷⁾ UV: $\lambda_{\text{max}}^{\text{pH}1}$ 338 (8,810), 324 (11,400), 275 (7,630), $\lambda_{\text{max}}^{\text{pH}7}$ 330.5 (7,700), 282.5 (9,430), $\lambda_{\text{max}}^{\text{pH}13}$ 331 (7,570), 282.5 (9,500) nm.

2-Methyl-4-(2-phenylethylamino)pyrido[3,4-*d*]pyrimidine (**3c**). This compound, mp 118~119°C (from aqueous ethanol), was synthesized in a quantitative yield. IR (KBr) 3310 (NH), 1615, 1580 (C=N , C=C) cm^{-1} ; UV: $\lambda_{\text{max}}^{\text{pH}1}$ 338 (9,080), 324.5 (11,000), 284 (7,250), $\lambda_{\text{max}}^{\text{pH}7}$ 332 (8,020), 284.5 (9,020), $\lambda_{\text{max}}^{\text{pH}13}$ 332 (7,930), 284.5 (9,220) nm; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 2.49 (3H, s, CH_3), 2.97 (2H, t, $J=7$ Hz, Ph-CH_2), 3.75 (2H, q, $J=7$ Hz, N-CH_2), 7.31 (5H, broad s, phenyl), 8.06 (1H, dd, $J=5$, 1 Hz, 5-H), 8.52 (1H, d, $J=5$ Hz, 6-H), 8.57 (1H, broad s, NH), 8.99 (1H, broad s, 8-H). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{16}\text{N}_4 \cdot 2.0\text{H}_2\text{O}$: C, 63.98; H, 6.71; N, 18.65. Found: C, 64.07; H, 6.66; N, 18.66%.

2-Methyl-4-(3-phenylpropylamino)pyrido[3,4-*d*]pyrimidine (**3d**). This compound, mp 113~114°C (from aqueous ethanol), was synthesized in a 43% yield. IR (KBr) 3240 (NH), 2960, 2870 (CH), 1610, 1580 (C=N , C=C) cm^{-1} ; UV: $\lambda_{\text{max}}^{\text{pH}1}$ 338 (9,030), 324.5 (7,870), 276 (7,190), $\lambda_{\text{max}}^{\text{pH}7}$ 332.5 (8,010), 285 (9,150), $\lambda_{\text{max}}^{\text{pH}13}$ 332.5 (7,870), 285 (9,160) nm; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 1.97 (2H, m, $\text{C-CH}_2\text{-C}$), 2.50 (3H, s, CH_3), 2.68 (2H, t, $J=7$ Hz, Ph-CH_2), 3.60 (2H, q, $J=6$ Hz, N-CH_2), 7.27 (5H, broad s, phenyl), 8.24 (1H, dd, $J=5$, 1 Hz, 5-H), 8.60 (1H, d, $J=5$ Hz, 6-H), 9.02 (1H, broad s, 8-H), 9.13 (1H, broad, NH). *Anal.* Calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_4 \cdot 2.0\text{H}_2\text{O}$: C, 64.95; H, 7.05; N,

17.82. Found: C, 64.93; H, 6.76; N, 17.64%.

N⁶-3-(Phenylpropyl)adenosine (4d). A mixture of 6-chloro-9- β -D-ribofuranosylpurine (287 mg, 1.0 mmol), 3-phenylpropylamine (155 mg, 1.2 mmol), triethylamine (0.5 ml) and 1-butanol (5 ml) was refluxed for 1.5 hr. The mixture was dried, dissolved in ethanol and allowed to crystallize in a refrigerator (5°C) to give colorless needles, mp 124~126°C (348 mg, 88%). IR (KBr) 3350, 3200 (NH, OH), 1630 (C=N), 1140, 1100, 1065 (C-O), 760, 705 (phenyl) cm^{-1} ; UV: $\lambda_{\text{max}}^{\text{pH}1}$ 263 (14,700), $\lambda_{\text{max}}^{\text{pH}7}$ 267 (15,800), $\lambda_{\text{max}}^{\text{pH}13}$ 267 (14,700) nm; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 1.87 (2H, m, $\text{C-CH}_2\text{-C}$), 2.63 (2H, broad t, $J=7$ Hz, Ph-CH_2), 3.5 (2H, m, N-CH_2 , overlapped by HOD signal), 3.52 and 3.65 (2H, m, 5'-H), 3.98 (1H, m, 4'-H), 4.16 (1H, m, 3'-H), 4.61 (1H, broad t, $J=6$ Hz, 2'-H), 5.92 (1H, d, $J=6$ Hz, 1'-H), 7.2 (5H, broad s, phenyl), 7.88 (1H, broad t, $J=6$ Hz, NH), 8.22 (1H, s, 8-H), 8.33 (1H, s, 2-H). *Anal.* Calcd. for $\text{C}_{19}\text{H}_{23}\text{N}_5\text{O}_4 \cdot 0.5\text{H}_2\text{O}$: C, 57.86; H, 6.13; N, 17.76. Found: C, 57.42; H, 6.23; N, 17.58%.

N⁶-(4-Phenylbutyl)adenosine (4e). This compound, mp 123~124°C (from ethanol) was synthesized in an 86% yield. IR (KBr) 3350, 3230 (NH, OH), 1630 (C=N), 1140, 1090, 1070 (C-O), 760, 710 (phenyl) cm^{-1} ; UV: $\lambda_{\text{max}}^{\text{pH}1}$ 263 (16,400), $\lambda_{\text{max}}^{\text{pH}7}$ 266 (15,100), $\lambda_{\text{max}}^{\text{pH}13}$ 267 (15,200) nm; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 1.5~1.8 (4H, m, $\text{C-CH}_2\text{-CH}_2\text{-C}$), 2.60 (2H, Ph-CH_2 , overlapped by $\text{DMSO-}d_6$ signal), 3.5 (2H, m, N-CH_2 , overlapped by HOD signal), 3.53 and 3.66 (2H, m, 5'-H), 3.98 (1H, m, 4'-H), 4.16 (1H, m, 3'-H), 4.63 (1H, m, 2'-H), 5.93 (1H, d, $J=6$ Hz, 1'-H), 7.25 (5H, broad s, phenyl), 7.88 (1H, broad t, $J=7$ Hz, NH), 8.23 (1H, s, 8-H), 8.32 (1H, s, 2-H). *Anal.* Calcd. for $\text{C}_{20}\text{H}_{25}\text{N}_5\text{O}_4 \cdot 0.5\text{H}_2\text{O}$: C, 68.81; H, 6.42; N, 17.15. Found: C, 59.24; H, 6.10; N, 17.14%.

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