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7-DEAZA-9-PHENYLADENINES

A NEW CLASS OF ADENOSINE RECEPTOR ANTAGONISTS

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Abstract—A series of twelve 7-deaza-9-phenyladenines and of related 9-aralkyl-, 9-alkyl-, and 9-alkenyl-analogs and of 7-deaza-9-phenylhypoxanthines inhibited binding of [^{3}H]phenylisopropyladenosine to rat brain A_1-adenosine receptors and antagonized activation of adenylate cyclase elicited by interaction of *N*-ethylcarboxamidoadenosine with A_2-adenosine receptors in rat pheochromocytoma PC12 cell membranes. A subset of seven compounds, encompassing the range of major structural variations, antagonized inhibition of adenylate cyclase elicited by interaction of *R*-phenylisopropyladenosine with A_1-adenosine receptors in rat fat cell membranes. 7-Deaza-9-phenyladenine had a K_i value of 3 μM at the brain A_1-receptor and a K_B value of 17 μM at the PC12 A_2-receptor and was thus about 5-fold more potent than theophylline at the former and nearly equipotent with theophylline at the latter. It had a K_B value of 4.6 μM at the fat cell A_1-receptor. The presence of methyl groups at the 7- and 8-positions reduced activity at all receptors several fold. Aryl substituents in a series of 7-deaza-7,8-dimethyl-9-phenyladenines did not have major effects on affinities for the brain A_1- or the PC12 cell A_2-adenosine receptors. The absence of the 9-phenyl substituent in the 7,8-dimethyl series reduced activity several fold, while replacement with arylalkyl (—$CH_2C_6H_4F$), alkyl (—$(CH_2)_5CH_3$) or alkenyl (—CH_2CH=CH_2) substituents had only modest effects on potency at the brain A_1-receptor and the PC12 cell A_2-receptor. 7-Deaza-7,8-dimethylhypoxanthine was nearly equipotent to the analogous 7-deazaadénine at the brain and fat cell A_1-receptors, but was several fold more potent than the analogous 7-deazaadenine at the A_2-receptor. 7-Deaza-7,8-dimethyl-9-(2,4-dibromophenyl)hypoxanthine was less potent than the analogous 7-deazaadenine at both the brain A_1- and the PC12 cell A_2-adenosine receptors. 7-Deaza-9-phenyl-7,8-benzohypoxanthine was the most potent of the present series of antagonists and was somewhat selective for the A_2-adenosine receptor with a K_i of 0.9 μM at the brain A_1-receptor, a K_B of 1.4 μM at the fat cell A_1-receptor, and a K_B of 0.2 μM at the A_2-receptor.

Adenosine modulates a variety of physiological functions through at least two major subclasses of receptors; an A_1-adenosine receptor is inhibitory to adenylate cyclase and A_2-adenosine receptors are stimulatory to adenylate cyclase [1]. Other classes of adenosine receptors may exist and be coupled with potassium or calcium channels [2]. As yet no truly satisfactory antagonists with specificity for either of the subclasses of adenosine receptors have been developed in spite of extensive efforts at structural modification of xanthines, such as caffeine and theophylline. Some selectivity *in vivo* has been reported at A_1-receptors for certain 8-substituted-1,3-dipropylxanthines [3, 4] and at A_2-receptors for a caffeine analog [4]. Non-xanthine heterocycles have not been studied as extensively [5], but certain non-xanthine heterocycles, such as the 9-methyl-adenines [6] and a triazoloquinazoline (CGS 15943a) [7], do appear to have the potential for some selectivity towards either A_1- or A_2-adenosine receptors.

The present paper describes another class of heterocycles, namely 7-deaza-9-phenyladenines and 7-deaza-9-phenylhypoxanthines, that have antagonist activity at A_1- and A_2-adenosine receptors. Some members of this series are several fold more potent than theophylline, and some exhibit selectivity towards either A_1- or A_2-adenosine receptors.

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METHODS

Materials. *N*-Ethylcarboxamidoadenosine (NECA) and *R*-N^6-phenylisopropyladenosine (*R*-PIA) were from Research Biochemicals Inc. (Wayland, MA); [^{3}H]N^6-phenylisopropyladenosine (50 Ci/mmol) was from New England Nuclear (Boston, MA); and [α-^{32}P]ATP (30 Ci/mmol) from Amersham (Arlington Heights, IL). Rolipram was provided by Schering AG (Berlin).

The synthesis of 4-amino-5-6,dimethyl-7-phenyl-7H-pyrrolo[2,3-d]pyrimidine (**2**) [8]; 2,4-diamino-5,6-dimethyl-7-phenyl-7H-pyrrolo[2,3-d]pyrimidine (**4**) [9]; 4-amino-5,6-dimethyl-7-*n*-hexyl-7H-pyrrolo[2,3-d]pyrimidine (**14**) [8]; 4-amino-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine (**16**) [10]; and 5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4(3*H*)-one (**17**) [10] have been described.

Procedures for the synthesis of the compounds **5–13, 15, 18–20** are provided below. Melting points (°C) were determined in open capillaries and are uncorrected. The ^{1}H-NMR spectra were determined on Varian T 60 and Bruker-AC 80 spectrometers

with tetramethylsilane as the internal reference and [$^2H_6$]Me_2SO as solvent. Chemical shifts are reported in delta (δ) units. All compounds analyzed correctly for carbon, hydrogen and nitrogen.

General synthetic methods. 3-Hydroxy-2-butanone (0.2 mol), the appropriate aromatic or aliphatic amine (0.2 mol), and *p*-toluenesulfonic acid (0.1 g) were dissolved in dry benzene (100 ml) and refluxed with the aid of a Dean–Stark trap. When 3.6 ml of water was collected, the reaction was stopped. The solution was cooled to 50–60°. Through a dropping funnel malononitrile (0.2 mol), dissolved in hot benzene, was added in such a manner so as to maintain gentle boiling. The solvent then was removed on a rotary evaporator. Normally the oily residue crystallized spontaneously, and the product was recrystallized from ethanol. All products analyzed correctly for carbon hydrogen and nitrogen. The resulting intermediates were 1-substituted 2-amino-4,5-dimethyl-1H-pyrrole-3-carbonitriles, as for example 2-amino-4,5-dimethyl-1-(2,4-dibromophenyl)-1H-pyrrole-3-carbonitrile (**20**), m.p. 185°.

The pyrrole (20 mmol) was dissolved in a mixture of formamide (30 ml), *N,N*-dimethylformamide (10 ml) and formic acid 85% (4.0 ml) and refluxed for 4–8 hr. The resulting crystalline product was collected by filtration and recrystallized, from an ethanolic solution of potassium hydroxide, to yield 4-amino-5,6-dimethyl-7-substituted-7H-pyrrolo[2,3-d]pyrimidines (**5–15**) with the following properties: (**5**) m.p. 208°, ^{1}H-NMR δ 2.0 (s, 3H, 6-CH_3), 2.4 (s, 3H, 5-CH_3), 6.6 (s, 2H, NH_2), 7.4–7.6 (m, 4H, aromatic), 7.9 (s, 1H, H2); (**6**) m.p. 210°; (**7**) m.p. 250°; (**8**) m.p. 245°, ^{1}H-NMR δ 1.98 (s, 3H, 6-CH_3), 2.35 (s, 3H, 5-CH_3), 3.7 (s, 3H, OCH_3), 5.0 (s, 2H, NH_2), 7.05–7.3 (m, 4H, aromatic), 8.2 (s, 1H, H2); (**9**) m.p. 235°; (**10**) m.p. 225°; (**11**) m.p. 233–235°, ^{1}H-NMR δ 2.05 (s, 3H, 6-CH_3), 2.45 (s, 3H, 5-CH_3), 5.5 (s, 2H, NH_2), 7.2–7.8 (m, 4H, aromatic), 8.2 (s, 1H, H2); (**12**) m.p. 242°, ^{1}H-NMR δ 1.95 (s, 3H, 6-CH_3), 2.4 (s, 3H, 5-CH_3), 6.5 (s, 2H, NH_2), 7.2–8.05 (m, 3H, aromatic), 7.9 (s, 1H, H2); (**13**) m.p. 195°, ^{1}H-NMR δ 2.15 (s, 3H, 5-CH_3), 2.31 (s, 3H, 6-CH_3), 5.37 (s, 2H, —CH_2—), 6.44 (s, 2H, NH_2), 6.60–7.29 (m, 4H, aromatic), 7.97 (s, 1H, H2); (**15**) m.p. 152°, ^{1}H-NMR δ 2.19 (s, 3H, 5-CH_3), 2.29 (s, 3H, 6-CH_3), 4.44–4.92 (m, 4H, —CH_2CH=CH_2), 5.51–5.98 (m, 1H, —CH=CH_2), 6.19 (s, 2H, NH_2), 7.70 (s, 1H, H2).

5,6-*dimethyl*-7-(2-*chlorophenyl*)-7*H*-*pyrrolo*[2,3-*d*]*pyrimidine* - 4(3*H*) - *one* (**18**). 2-Amino - 4,5 - dimethyl-1-(2-chlorophenyl)-pyrrolo-3-carbonitrile (30 mmol) prepared by the general method (see above) was dissolved in 60 ml of formic acid (85%) and refluxed for 8 hr. After cooling, the precipitate was collected by filtration and recrystallized from ethanol to afford **18** (m.p. 263°) in 80% yield.

9-*Phenyl*-9*H*-*pyrimido*[4,5-*b*]*indole*-4(3*H*)-*one* (**19**). 2-Amino-4,5,6,7-tetrahydro-1-phenyl-1H-indole-3-carbonitrile (5 mmol) prepared by the general method (see above) was dissolved in 10 ml of formic acid (85%) and refluxed for 8 hr. After cooling, the precipitate was collected by filtration and recrystallized from ethanol to afford 9-phenyl-5,6,7,8 - tetrahydro - 9H - pyrimido[4,5 - b]indole-4(3H)-one (m.p. 320°) in 80% yield. This pyrimidoindole was dissolved in a 1:30 mixture of nitric acid (65%) and ethanol and refluxed for 12 hr. After cooling, the precipitate was collected by filtration and recrystallized from ethanol to afford **19** (m.p. 355°) in 68% yield. ^{1}H-NMR δ 7.25–7.5 (m, 4H, indole), 7.6 (s, 5H, aromatic), 8.15 (s, 1H, H2), 12.4 (broad, 1H, NH).

4-*Amino*-7-*phenyl*-7-*pyrrolo*[2,3-*d*]*pyrimidine*-5,6-*dicarboxylic acid* (**3**). Compound 2 (5.0 g, 21 mmol) was added slowly and with stirring to sulfuryl chloride (70.0 g, 520 mol). The mixture was stirred until a solid mass was formed. After addition of 100 ml H_2O, the mixture was heated. The resulting acidic solution was neutralized with sodium acetate until a precipitate was formed. The latter was collected by filtration and washed with water and recrystallized from ethanol to afford 4-amino-7-phenyl-7H - pyrrolo[2,3,d]pyrimidine - 5,6 - dicarboxaldehyde (m.p. 253°) in a 90% yield. ^{1}H-NMR δ 7.6 (s, 5H, aromatic), 8.1 (s, 2H, NH_2), 8.2 (s, 1H, H2), 10.1 (s, 1H, 6-CHO), 10.5 (s, 1H, 5-CHO).

The 5,6-dicarboxaldehyde (1.0 g, 3.5 mmol) was added to a stirred mixture of 30% hydrogen peroxide (30 g) and 10% sodium hydroxide in water (10 g) in a 1-liter beaker. After cooling, the mixture was acidified with hydrochloric acid (10%). The precipitate was collected by filtration and washed with water to afford **3** (m.p. 293°) in 86% yield.

4 - *Amino* - 7*H* - *pyrrolo*[2,3 - *d*]*pyrimidine* - 4 - *amine* (**1**). Compound **3** (1.5 g, 5 mmol) was melted slowly in a porcelain basin. After cooling, 10 ml of a solution of 10% sodium hydroxide in water was added. The water phase was extracted with ether. The ethereal layer was concentrated on a rotary evaporator, and the residue was recrystallized from ethanol to yield **1** (m.p. 178–180°) in 24% yield. ^{1}H-NMR δ 6.8 (d, 1H, H5), 7.2 (s, 2H, NH_2), 7.4–7.8 (m, 6H, H6 and aromatic), 7.6 (d, 1H, H6), 8.2 (s, 1H, H2).

Binding assay. Rat cerebral cortical membranes were prepared and binding of [^{3}H]N^6-*R*-phenylisopropyladenosine was assayed as described [11]. Briefly, binding of 1 nM [^{3}H]N^6-*R*-phenylisopropyladenosine was measured in a total volume of 1 ml of 50 mM Tris buffer (pH 7.4) with 0.2 units adenosine deaminase and brain membranes (100 μg protein) after incubation for 90 min at 37° in the absence or presence of various concentrations of antagonists. Nonspecific binding was determined in the presence of 5 mM theophylline. All assays were done in triplicate. Separation was by addition of 4 ml of ice-cold buffer followed by rapid filtration through Whatman GF/B glass fiber filters in a Brandel M-24R manifold (Brandel Instruments, Gaithersburg, MD), followed by washing twice with 5 ml of ice-cold buffer.

Adenylate cyclase assay. Rat pheochromocytoma PC12 cell membranes and rat fat cell membranes were prepared, and adenylate cyclase activity was assayed as described [12]. Briefly, assays were in a total volume of 100 μl of 50 mM Tris–HCl, pH 7.4, containing 0.1 mM [α-^{32}P]ATP (0.3 μCi/tube), 0.1 mM cyclic AMP, 1 μg/ml adenosine deaminase, 0.1 mM rolipram, 5 mM creatine phosphate, 0.4 mg/ml creatine kinase, and 2 mg/ml bovine serum albumin. Concentrations of GTP and $MgCl_2$ were,

respectively, 10 μM and 0.5 mM for PC12 cell membranes (5–10 μg protein/tube) and 10 μM and 1.0 mM for rat fat cell membranes (5 μg protein/tube). In the case of rat fat cell membranes, 150 mM NaCl was included in the assay. Incubations were for 5 min at 37°. [^{32}P]Cyclic AMP formation was determined as described [13]. Dose–response curves for activation of PC12 adenylate cyclase by NECA or inhibition of rat fat cell adenylate cyclase by *R*-PIA were carried out in the absence or presence of the antagonist. Each experiment was repeated three times. None of the antagonists showed any agonist activity in either the PC12 or fat cell membrane assays.

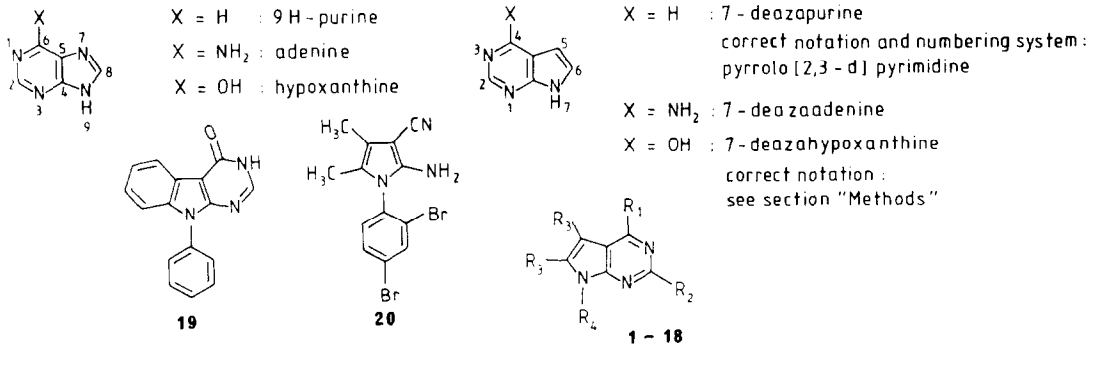
Data analysis. The EC_{50} or IC_{50} values were obtained from concentration–response curves. K_i values for binding were obtained from IC_{50} values by the Cheng–Prusoff equation [14] using a K_D for [^{3}H]N^6-*R*-phenylisopropyladenosine of 1.0 nM. K_B values for adenylate cyclase were calculated using the Schild equation [15] and the ratio of EC_{50} values for NECA activation or the ratio of IC_{50} values for *R*-PIA inhibition in the presence and absence of antagonist.

RESULTS AND DISCUSSION

The present series of 7-deaza-9-phenyladenines represents a new class of adenosine receptor antagonists, perhaps analogous to the 9-methyladenines, another class of nonxanthine adenosine receptor antagonists [6]. Most of the present series of 7-deaza-9-phenyladenines (see Scheme I and Table 1) contained methyl groups at the 7- and 8-position, and this disubstitution resulted in a 6-fold reduction in potency at the A_1-receptor and almost a 4-fold reduction in potency at the A_2-receptor (compare **2** with **1**). A 7,8-unsubstituted analog (**1**) had a K_i value of about 3 μM at the A_1-receptor and was thus nearly 5-fold more potent than theophylline (K_i, 15 μM) [11] at this receptor, while the K_B value of 17 μM at the A_2-receptor made **1** almost equipotent at the A_2-receptor of PC12 cells with theophylline (K_B 14 μM) [12]. Further analogs in a 7,8-unsubstituted series might be expected to yield potent A_1-selective adenosine antagonists. 9-Methyladenine was much less potent (K_i 106 μM) [6] at the A_1-receptor than **1** and slightly less potent (K_B 24 μM) [6] at the A_2-receptor than **1**. At present it is uncertain whether interactions of 7-deaza-9-phenyladenines and 9-methyladenines with adenosine receptors are similar or whether the 9-phenyl moiety in the 7-deaza-series markedly alters the mode of binding. In the 9-methyladenines, N^6-substituents can markedly enhance affinity for A_1-receptors [6]. Whether N^6-substituents in the 7-deaza-9-phenyladenines would have similar effects is unknown. The presence of carboxy substituents in the 7- and 8-position of 7-deaza-9-phenyladenine reduced activity to an even greater extent than did methyl substituents (compare **1**, **2** and **3**).

In the 7-deaza-7,8-dimethyl-9-phenyladenine series, the presence of a 2-amino group reduced activity at the A_1-receptor, but not at the A_2-receptor (compare **4** and **2**). Substituents on the 9-phenyl moiety did not have marked effects on potency in this series except for a *m*-chloro moiety (**6**) which significantly increased potency at the A_1-receptor (K_i 6.5 μM) and the A_2-receptor (K_B 8.8 μM). Unlike the unsubstituted parent (**2**), the *m*-chloro-substituted analog showed no selectivity for the A_1-receptor. The effect of polar aryl substituents (—CO_2^-, SO_3^-) on activity has not been assessed as yet. An analog in which the 9-phenyl substituent was replaced with a 9-*o*-fluorobenzyl substituent (**13**) was about 2-fold more potent, having a K_i value of 6.8 μM at the A_1-receptor and a K_B value of 27 μM at the A_2-receptor. Analogs with a 9-*n*-hexyl substituent (**14**) or a 9-allyl substituent (**15**) replacing the 9-phenyl group were several fold less potent at the A_1-receptor and slightly more potent at the A_2-receptor (compare **14** and **15** with **2**). Replacement of the 9-phenyl substituent with hydrogen (**16**) reduced activity by 3-fold or more at both adenosine receptors. However, unlike the 9-methyladenine series where absence of the methyl in adenine itself reduces activity many fold at the A_1-receptor and by 20-fold at the PC12 cell A_2-receptor [6], comparison of the 9-allyl-analog (**15**) with the corresponding analog (**16**) lacking the 9-allyl moiety revealed no change in potency at the A_1-receptor and only a 5-fold reduction in activity at the A_2-receptor of PC12 cells.

Only three analogs of hypoxanthine were investigated. It should be noted that 9-methyl-O^6-phenylhypoxanthines are essentially inactive at adenosine receptors [6]. The simplest hypoxanthine analog, namely 7-deaza-7,8-dimethylhypoxanthine



Scheme I

Table 1. Potencies of 7-deaza-9-phenyladenines and related heterocycles as antagonists at A_1- and A_2-adenosine receptors

No.	Compound: Substituent* R_1	R_2	R_3	R_4	A_1 K_i (μM) versus [^{3}H]PIA binding† Rat brain membrane	A_2 K_B (μM) versus NECA-stimulation of adenylate cyclase‡ Rat PC12 cell membrane
1	NH_2	H	H	$-C_6H_5$	3.1 ± 0.1	17 ± 2.5
2	NH_2	H	CH_3	$-C_6H_5$	18 ± 4.1	62 ± 4.1
3	NH_2	H	CO_2H	$-C_6H_5$	67 ± 5.9	150
4	NH_2	NH_2	CH_3	$-C_6H_5$	57 ± 6.5	53
5	NH_2	H	CH_3	*o*-C_6H_4Cl	31 ± 2.9	31 ± 0.4
6	NH_2	H	CH_3	*m*-C_6H_4Cl	6.5 ± 0.8	8.8 ± 1.6
7	NH_2	H	CH_3	*p*-C_6H_4Cl	16 ± 2.9	57 ± 9.9
8	NH_2	H	CH_3	*o*-$C_6H_4OCH_4$	58 ± 2.5	91
9	NH_2	H	CH_3	*m*-$C_6H_4OCH_3$	24 ± 2.4	56
10	NH_2	H	CH_3	*p*-$C_6H_4OCH_3$	45 ± 3.8	56
11	NH_2	H	CH_3	*o*-C_6H_4Br	63 ± 6.2	22
12	NH_2	H	CH_3	*o,p*-$C_6H_3Br_2$	15 ± 1.5	13 ± 1.4
13	NH_2	H	CH_3	$-CH_2-$(*o*)-C_6H_4F	6.8 ± 0.8	27 ± 4.9
14	NH_2	H	CH_3	$-(CH_2)_5CH_3$	60 ± 2.6	42 ± 1.9
15	NH_2	H	CH_3	$-CH_2CH=CH_2$	49 ± 8.0	40 ± 3.9
16	NH_2	H	CH_3	H	55 ± 4.6	190 ± 20
17	OH	H	CH_3	H	58 ± 5.4	33 ± 3
18	OH	H	CH_3	*o*-C_6H_4Cl	53 ± 3.3	23 ± 2.4
19	9-Phenyl-9H-pyrimido[4,5-b]indole-4(3H)-one*				0.88 ± 0.04	0.22 ± 0.06
20	2-Amino-4,5-dimethyl-1-(2,4-dibromophenyl)-1H-pyrrole-3-carbonitrile*				125 ± 14	41 ± 4.6

* Structures and substituents (R_1—R_4) are shown in Scheme I.

† Inhibition of binding of [^{3}H]N^6-phenylisopropyladenosine (PIA) assayed as described in Methods. Values are means ± SEM (N = 3).

‡ Inhibition of activation of adenylate cyclase by *N*-ethylcarboxamidoadenosine (NECA) assayed as described in Methods. Values are means ± SEM (N = 3 or are individual values from one experiment, each point determined in triplicate.

(**17**), was nearly equivalent in activity to a 9-(2,4-dibromophenyl)-7-deaza-7,8-dimethylhypoxanthine (**18**), quite unlike the situation in the 7-deaza-7,8-dimethyladenines where "deletion" of the 9-(2,4-dibromophenyl) moiety resulted in a marked reduction in activity (compare **12** and **16**). The most potent of the present compounds was a 7-deaza-9-phenylhypoxanthine with a fused benzo-ring at the 7,8-positions (**19**); not only was this analog very potent but it was somewhat selective (4-fold) for the rat PC12 A_2-receptor (K_B 0.22 μM) compared to the rat brain A_1-receptor (K_i 0.88 μM). Antagonists that are highly selective for A_2-adenosine receptors are not yet available. The most selective antagonists at present are at most only about 10-fold selective [5,7,16,17]. Thus, further investigation of analogs related to **19** may provide potent and more selective antagonists for A_2-adenosine receptors. One compound (**20**) lacking the fused pyrimidine ring was relatively weak at the A_1-receptor, but remarkably retained significant activity at the rat PC12 cell A_2-receptor being only 3-fold less active than that of the corresponding 7-deaza-7,8-dimethyl-9-aryladenine (compare **20** and **12**).

A representative series of seven compounds were assayed as antagonists versus A_1-adenosine receptor-mediated inhibition of adenylate cyclase in rat fat cell membranes (Table 2). These compounds were chosen to encompass the range of major structural alterations in the 9-deaza-9-phenyladenines and related heterocycles. All compounds tested were, indeed, antagonists in this adenylate cyclase assay

Table 2. Potencies of 7-deaza-9-phenyladenines and related heterocycles as antagonists at an A_1-adenosine receptor inhibitory to adenylate cyclase in rat fat cell membranes

Compound No.*	A_1 K_B (μM) versus *R*-PIA inhibition of adenylate cyclase† Rat fat cell membrane
1	4.6 ± 0.2
2	22 ± 1.3
3	52 ± 3.6
15	170 ± 20
16	110 ± 27
17	300 ± 70
19	1.4 ± 0.3

* For structures, see Table 1 and Scheme I.

† Antagonism of inhibition of adenylate cyclase by *R*-N^6-phenylisopropyladenosine (*R*-PIA) assayed as described in Methods. Values are means ± SEM (N = 3).

as they had been for the A_2-adenosine receptor in adenylate cyclase assay with PC12 cell membranes. None showed agonist activity (data not shown). The potencies as antagonists for A_1-adenosine receptor in fat cell membranes were for the 7-deaza-9-phenyladenines (**1, 2, 3**) comparable to the respective potencies as inhibitors of binding of [^{3}H]PIA to brain A_1-adenosine receptors (compare Tables 1 and 2). The 7-deazadenines with either a 9-allyl (**15**) or no substituent at the 9-position (**16**) were less potent in the fat cell assay as was the 7,8-dimethyl-7-deazahypoxanthine (**17**). The 7-deaza-9-phenylhypoxanthine with a fused benzo-ring at the 7,8-position (**19**) showed comparable high potency at the A_1-receptors of fat cells (Table 2) and brain (Table 1).

In summary, the present results document the potencies of a new series of non-xanthine heterocycles as antagonists of binding of [^{3}H]phenylisopropyladenosine to A_1-receptors of rat brain membranes and of NECA-stimulated activation via an A_2-receptor of adenylate cyclase in rat PC12 cell membranes. In addition, the potencies were determined for a selected set of these non-xanthine heterocycles as antagonists of *R*-PIA-elicited inhibition via an A_1-receptor of adenylate cyclase in rat fat cell membranes. Certain of the 7-deaza-9-phenyladenines (**1, 6, 12**) were antagonists with potencies comparable or, in the case of **1**, greater than theophylline: **1** was somewhat selective towards the A_1-receptors. A 7-deaza-9-phenylhypoxanthine (**19**) with a fused benzo-ring at the 7,8-position had very high potency and was somewhat selective for A_2-receptors. Further structure–activity studies in analogs lacking the 7,8-dimethyl substituents or with a fused benzo-ring or with polar substituents appear warranted.

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