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Synthesis and Biological Activities of Some N^6-(Nitro- and -aminobenzyl)adenosines†

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Synthesis and biological activities of 12 analogs of N^6-benzyladenosine are described. The compounds were prepared by two methods: (1) direct alkylation of adenosine with an appropriately substituted benzyl bromide to give the N^1-substituted derivative which was then rearranged in base to give the N^6-substituted compound, and (2) by nucleophilic displacement of chlorine in 6-chloropurine ribonucleoside, 6-chloro-2-aminopurine ribonucleoside, and 6-chloro-2-aminopurine with an amine. These analogs were examined for their growth inhibitory effect in cultured leukemic cells and also for their effect on adenosine aminohydrolase activity. N^6-*p*-Nitrobenzyladenosine and its 2′-deoxy analog were competitive inhibitors (K_i 65, 22 μM). The 2-amino-N^6-*p*-nitrobenzyladenine and its ribonucleoside were found to be noncompetitive inhibitors of adenosine aminohydrolase. In cultured L1210 leukemia, 2-amino-6-*p*-nitrobenzylaminopurine and the corresponding ribonucleoside were better growth inhibitors than N^6-benzyladenosine, while N^6-*p*-nitrobenzyladenosine, its 2′-deoxy analog, and N^6-*p*-fluorobenzyladenosine were as active as N^6-benzyladenosine.

The clinical usefulness of N^6-benzyladenosine in neoplastic disease[1] prompted the synthesis and exploration of the biological activity of nitro and aminobenzyl analogs of this compound. N^6-Benzyladenosine has been shown to possess growth inhibitory activity in tumor cell systems in vitro and in vivo.[2,3] Some of the N^6-benzyladenosine derivatives have exhibited inhibitory activity toward the uptake of purines and pyrimidines in cultured cells.[4,5] It stimulates the growth of tobacco pith tissue in vitro[6] and in cell-free systems acts as a competitive inhibitor of adenosine aminohydrolase.[7] Reported herein are the syntheses of 12 analogs of N^6-benzyladenosine, their growth inhibitory properties in three cell lines in culture, and their effect on adenosine aminohydrolase activity.

Chemistry. N^6-*p*-Nitrobenzyladenosine (2) was synthesized by a reaction of adenosine with *p*-nitrobenzyl bromide in DMF to furnish the N^1-*p*-nitrobenzyladenosine derivative. The latter was rearranged in base to give N^6-*p*-nitrobenzyladenosine.[8] Similarly *o*- and *m*-nitrobenzyladenosine (3 and 4) and *p*-fluorobenzyladenosine (9) were prepared starting from adenosine and an appropriately substituted benzyl bromide. 2′-Deoxyadenosine was used as the starting material for the preparation of 2′-deoxy-N^6-benzyladenosine (13)[9] and 2′-deoxy-N^6-*p*-nitrobenzyladenosine (5). Catalytic reduction of N^6-*p*-nitrobenzyladenosine gave N^6-*p*-aminobenzyladenosine (7), which was isolated as the HCl salt. Acetylation of the latter afforded N^6-*p*-acetamidobenzyladenosine (8). Reaction of methyl isocyanate with 2′,3′,5′-tri-*O*-acetyl-N^6-benzyladenosine followed by deacetylation gave a more soluble compound, *N*-[(9-β-D-ribofuranosylpurin-6-yl)-*N*-benzylcarbamoyl]methylamine (10). Treatment of N^6-benzyladenosine (1) with methanolic hydrogen chloride gave the N^6-benzyladenosine hydrochloride (14), which was more soluble in water than the parent compound. However, it was less stable. Nucleophilic displacement of chlorine in 6-chloro-2-aminopurine and 6-chloro-2-aminopurine ribonucleoside with *p*-nitrobenzylamine[10,11] gave 2-amino-6-*p*-nitrobenzylaminopurine (12) and 2-amino-6-*p*-nitrobenzylaminopurine ribonucleoside (11), respectively. N^6-(2-Methoxy-5-nitro)phenyladenosine (6) was similarly prepared starting from 6-chloropurine ribonucleoside and 2-methoxy-5-nitroaniline. The structures of all these compounds were confirmed by their uv, ir, and NMR spectra as well as from their correct elemental analyses. The physical properties of these analogs are listed in Table I.

Experimental Section

Melting points were determined by a Mel-Temp laboratory model melting point apparatus and are uncorrected. Uv spectra were recorded on a Cary 14 and Beckman Acta-V spectrophotometer. NMR spectra were recorded on a Varian A-60A spectrometer in DMSO-d_6 solution using Me_4Si as an internal standard. Elemental analyses were carried out by Heterocyclic Chemical Corporation, Harrisonville, Mo. Homogeneity of all the compounds was checked by thin-layer chromatography in three solvent systems: (a) *i*-PrOH–concentrated NH_4OH–H_2O (7:1:2 v/v); (b) EtOAc–2-ethoxyethanol–16% HCO_2H (4:1:2 v/v, upper phase); and (c) EtOAc–*n*-PrOH–H_2O (4:1:2 v/v, upper phase).

N^6-*p*-Nitrobenzyladenosine (2). Method A. To a solution of 1.33 g of adenosine (5.0 mmol) in 25.0 ml of freshly distilled anhydrous DMF was added 3.24 g (15.0 mmol) of *p*-nitrobenzyl bromide and the mixture stirred in a stoppered flask at room temperature for 48 hr. The reaction mixture was then evaporated to dryness in vacuo at 45°. The gummy residue was triturated three times with 50 ml of hot acetone. The crude residue was dissolved in 50 ml of distilled water and the pH of the solution was adjusted to 9.0–9.5 by careful addition of diluted aqueous NH_4OH. The mixture was then heated on a steam bath for 3 hr. The pH of the solution was maintained within the range of 9.0–9.5 by addition of diluted aqueous NH_4OH from time to time. The reaction mixture was evaporated to a small volume and kept at 4° for 20 hr. A yellow crystalline product was collected on a filter and washed with H_2O. Two recrystallizations from absolute EtOH furnished 1.25 g (62.2%) of pure product: mp 174–176°; NMR δ 8.53 (s, 1, 8-H), 8.33 (s, 1, 2-H), 8.27 and 7.67 (pair of doublets, 4, J = 8 Hz in each case, protons of phenyl ring), 5.98 (d, 1, J = 6 Hz, 1′-H), 5.43 (d, 2, J = 7 Hz, $-CH_2C_6H_5$). Anal. ($C_{17}H_{18}N_6O_6$) C, H, N.

N^6-*p*-Aminobenzyladenosine Hydrochloride (7). To a solution of compound 2 (500 mg) in 125 ml of MeOH was added 500

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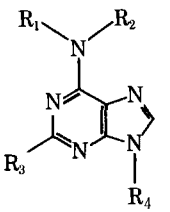
Table I. Properties of Some Nitro and Amino Derivatives of N^6-Benzyladenosine



Compd no.	R_1	R_2	R_3	R_4	Mp, °C	Molecular formula	Method of synthesis	Yield, %	Uv max, nm ($\epsilon \times 10^{-3}$) 0.1 *N* HCl	Water	0.1 *N* NaOH
2	$-CH_2C_6H_4$-*p*-NO_2	H	H	D-Ribose	174–176	$C_{17}H_{18}N_6O_6$	A	62.2	269 (22.3)	269 (22.2)	270 (23.1)
3	$-CH_2C_6H_4$-*o*-NO_2	H	H	D-Ribose	212–214	$C_{17}H_{18}N_6O_6$	A	29.8	264 (23.0)	266 (23.3)	266 (24.0)
4	$-CH_2C_6H_4$-*m*-NO_2	H	H	D-Ribose	163–165	$C_{17}H_{18}N_6O_6$	A	61.2	265 (26.6)	267 (26.6)	267 (27.2)
5	$-CH_2C_6H_4$-*p*-NO_2	H	H	D-2′-Deoxyribose	153–155	$C_{17}H_{18}N_6O_5 \cdot 0.5H_2O$	A	82.1	264 (20.6)	268 (19.8)	268 (20.7)
6[a]	2-OCH_3-5-NO_2-C_6H_3-	H	H	D-Ribose	224–225	$C_{17}H_{18}N_6O_7$	B	31.1	279 (23.2)	296 (26.7)	298 (26.4)
7	$-CH_2C_6H_4$-*p*-NH_2	H	H	D-Ribose	130–133	$C_{17}H_{20}N_6O_4 \cdot HCl$	*d*	89.7	264 (20.2)	268 (20.7)	268 (22.3)
8	$-CH_2C_6H_4$-*p*-$NHCOCH_3$	H	H	D-Ribose	212–214	$C_{19}H_{22}N_6O_5 \cdot 0.5H_2O$	*d*	77.3	263 (26.3)	267 (26.5)	267 (26.7)
9	$-CH_2C_6H_4$-*p*-F	H	H	D-Ribose	170–172	$C_{17}H_{18}N_5O_4F$	A	55.8	263 (22.3)	268 (22.9)	267 (23.3)
10	$-CH_2C_6H_5$	CH_3NHCO-	H	D-Ribose	165–167	$C_{19}H_{22}N_6O_5$	C	90.4	273 (17.5)	273 (17.3)	273 (16.2)
11	$-CH_2C_6H_4$-*p*-NO_2	H	NH_2	D-Ribose	105–106 dec	$C_{17}H_{19}N_7O_6 \cdot 2H_2O$	B	60.2	288 (21.7), 250–265 (plateau)	283 (23.9), 260 (sh)	283 (25.4), 260 (sh)
12[b]	$-CH_2C_6H_4$-*p*-NO_2	H	NH_2	H	263–264 dec	$C_{12}H_{11}N_7O_2 \cdot H_2O$	B	80.0	282 (24.6), 245 (16.8)	282 (22.5), 250–260 (plateau)	288 (22.2)
13[c]	$-CH_2C_6H_5$	H	H	D-2′-Deoxyribose	153–155	$C_{17}H_{19}N_5O_3 \cdot 0.5H_2O$	A	82.0	264 (20.6)	268 (19.8)	268 (20.7)

[a] This compound was prepared by the reaction of 6-chloropurine ribonucleoside with 2-methyl-5-nitroaniline in the presence of calcium carbonate as an acid acceptor. [b] 2-Amino-6-chloropurine was used as the starting material for this compound and the final product was crystallized from hot DMF. [c] This compound was also prepared by Robins and Trip.[9] [d] See the Experimental Section.

Table II. Biological Activities of Analogs of N^6-Benzyladenosine

Compd no.	Enzyme[a] K_i, μM	Antiproliferative act. in culture[b] Nc 37	RPMI 6410	L1210
1[c]	550	++, + at 10^{-5}	>++, + at 10^{-5}	++
2	65	±	±	++
3	530	NA	±	NA
4	280*	+	±	++
5	22	±	±	++
6	∞	+	+	++
7	∞	+	+	+
8	∞	+		NA
9	∞	++	+	++ at 48 hr, ± at 72 hr
10	∞	+		NA
11	80*	+, NA at 10^{-5}	+, NA at 10^{-5}	>++, + at 10^{-5}
12	400*	+, ± at 10^{-5}	+	>++, + at 10^{-5}
13	∞	±	±	NA

[a] K_m = 40 μM adenosine. An asterisk after an entry indicates noncompetitive inhibition. Inhibition was competitive in all other instances. Absence of detectable inhibition is indicated by ∞, i.e., K_i is infinitely large. [b] Experimental details are in the text. Viable cell density relative to controls is 30–60%, ++; 60–80%, +; 80–90%, ±; NA, 90–110°; after 72 hr of incubation at a drug concentration of 10^{-4} M except where indicated as otherwise. [c] Compound 1 refers to N^6-benzyladenosine. Structures of all the other compounds correspond to Table I.

mg of 10% Pd/C and the mixture was hydrogenated at room temperature under atmospheric pressure. The hydrogenation was continued for 16 hr and then the catalyst was removed by filtration. The clear colorless solution was cooled at −5° and 0.3 ml of 5.2 N HCl–MeOH was added to it and the mixture stirred at 0° for 1 hr. The solution was then evaporated to dryness at 40°; the residue was dissolved in 15 ml of anhydrous EtOH, filtered, concentrated to a small volume, and kept at 0° for 16 hr. The crystalline product was collected on a filter and washed with EtOH. The product was recrystallized once from absolute EtOH: yield 456 mg (89.7%); mp 130–133° dec. Anal. ($C_{17}H_{20}N_6O_4$·HCl) C, H, N.

N^6-*p*-Acetamidobenzyladenosine (8). To a solution of compound 7 (100 mg) in 10 ml of H_2O was added 100 mg of sodium acetate followed by addition of 2 ml of Ac_2O. The mixture was stirred at room temperature for 2 hr and then carefully neutralized to pH 7.0 by slow addition of 1 N NaOH solution. The neutral solution was allowed to stand at 4° for 16 hr. The crystalline product was collected on a filter, washed with water, and recrystallized once from absolute EtOH: yield 80 mg (77.3%); mp 212–214°. Anal. ($C_{19}H_{22}N_6O_5$·0.5H_2O) C, H, N.

2-Amino-6-*p*-nitrobenzylamino-9-(β-D-ribofuranosyl)purine (11). Method B. To a suspension of 1.51 g (8.0 mmol) of *p*-nitrobenzylamine hydrochloride in 30 ml of hot absolute EtOH was added 0.448 g (8.0 mmol) of KOH dissolved in 5 ml of absolute EtOH. A pellet of KOH was held by a pair of tweezer and stirred in this mixture until the deep blue color of *p*-nitrobenzylamine anion just persisted. Then a few milligrams of *p*-nitrobenzylamine hydrochloride was added until the yellow color of neutral *p*-nitrobenzylamine came back. The precipitated KCl was removed by filtration and 1.21 g (4.0 mmol) of 2-amino-6-chloropurine ribonucleoside was added to the filtrate. The reaction mixture was refluxed for 18 hr and then chilled at 4° for 1 hr. The dark gummy solid was collected on a filter and repeatedly triturated with hot benzene until it turned into a yellow powder. The crude material was recrystallized twice from absolute EtOH: yield 1.09 g (60.2%); mp 105–106° dec; ir (KBr) max 3400 (OH), 3300 (NH), 1520, 1400, 1340, (NO_2), and 1490 cm^{-1} (C=N, C=C). Anal. ($C_{17}H_{19}N_7O_6$·2H_2O) C, H, N.

N-[(9-β-D-Ribofuranosylpurin-6-yl)-N-benzylcarbamoyl]methylamine (10). Method C. To a solution of 893 mg (2.50 mmol) of N^6-benzyladenosine[2] (1) in 5 ml of anhydrous pyridine was added 2 ml of Ac_2O and the mixture was stirred at room temperature for 2 hr. MeOH (5 ml) was then added to the reaction mixture, which was then stirred for another 15 min and then evaporated to dryness. The residue was dissolved in 10 ml of anhydrous pyridine and again evaporated to dryness. The crude product was found to be homogenous by TLC in solvents B and C and it had the same uv spectra as N^6-benzyladenosine in water, 0.1 N HCl, and 0.1 N NaOH solutions. The gummy residue was redissolved in 10 ml of anhydrous pyridine and 0.570 g (10 mmol) of methyl isocyanate was added and the mixture was heated at 90° for 6 hr in a glass bomb with stirring. The reaction mixture was then evaporated to dryness and the last traces of pyridine were removed by repeated azeotropic distillation with anhydrous toluene. The gummy residue was dissolved in 40 ml of 4.0 N NH_3–MeOH and the solution stirred at 4° for 16 hr. A white crystalline product that gradually precipitated was filtered, washed with MeOH, and recrystallized once from absolute EtOH: yield 936 mg (90.4%); mp 165–167°; NMR δ 8.75 (s, 1, 8-H), 8.72 (s, 1, 2-H), 7.33 (s, 5, $-C_6H_5$), 6.01 (d, 1, J = 6 Hz, 1′-H), 5.95 (s, 2, $-CH_2C_6H_5$), and 2.92 ppm (d, 3, J = 3 Hz, $-NHCH_3$). Anal. ($C_{19}H_{22}N_6O_5$) C, H, N.

N^6-Benzyladenosine Hydrochloride (14). A solution of 1.0 g of N^6-benzyladenosine[2] (1) (dried under high vacuum at 100° for 16 hr) in 1000 ml of anhydrous MeOH was cooled to −5° in an ice–salt bath and 0.54 ml of 5.2 N HCl–MeOH was added to it. The mixture was stirred at 0° for 1 hr and then evaporated to dryness at 30°. The residue was dissolved in 25 ml of anhydrous MeOH and the solution was diluted with 250 ml of ether. The precipitated product was collected on a filter, washed with ether, and recrystallized from MeOH–ether: yield 943 mg (83.5%); mp 108–110°; uv λ max 265 (0.1 N HCl), 270 (water), and 270 nm (0.1 N NaOH). Anal. ($C_{17}H_{19}N_5O_4$·HCl·0.5H_2O) C, H, N.

Enzyme Assay. Adenosine aminohydrolase from calf intestinal mucosa (200 U/mg supplied as a suspension in 3.2 M ammonium sulfate pH 7.5) was obtained from Sigma Chemical Co. This preparation has been subjected to numerous structural studies[12,13] and has been used to evaluate the inhibitory properties of large numbers of synthetic purine analogs.[14–19] It has an isoelectric point of 4.85[12] and an invarient K_m of about 50 μM adenosine between pH 6 and 10.[15] The assay of Kalckar[20] as described by Kaplan[21] was used to determine enzyme activity in terms of rate of change of absorbance at 265 nm. Analysis of the kinetic data was performed by means of double reciprocal plots as described by Dixon and Webb.[22] The linear regressions were fitted by eye or a computer-program-generated least-squares fit assuming equal variances for the experimental reaction velocities.[23]

Growth Inhibition. Antiproliferative activity was evaluated in cell culture. Cells derived from the buffy coat of a normal individual (Nc 37) and from a patient with myeloblastic leukemia (RPMI 6410), as well as L1210 mouse leukemia cells, were cultured in suspension without agitation in RPMI No. 1640 medium supplemented with 20% fetal calf serum.[24] The tubes were inoculated with cells taken from stock cultures in logarithmic growth to a starting density previously determined to be near the minimum required for logarithmic growth of control cultures. At 24-hr intervals, 0.2 ml was removed and mixed with Trypan Blue to a final concentration of 0.05%, and total and viable cells were counted in a hemocytometer. Cells able to exclude the dye were scored as viable. The compounds were dissolved in DMSO and allowed to remain at 37° overnight. This achieved sterilization. Sterile medium was then

added to bring the concentration of DMSO to 0.5% and that of the compound to 10^{-4} M. At the concentration used, DMSO did not affect the growth of control cultures.

Results and Discussion

The highest affinity for the substrate binding site of adenosine aminohydrolase was shown by the competitive inhibitors N^6-p-nitrobenzyladenosine (2) and N^6-p-nitrobenzyl-2'-deoxyadenosine (5) (Table II). For this enzyme, K_m may be considered equivalent to the enzyme–substrate dissociation constant.[25] This allows comparison of K_i with K_m. Thus, our best inhibitor had an affinity for the substrate binding site comparable to the affinity of the enzyme for substrate (K_m = 40 μM adenosine). N^6-Benzyladenosine[26] (1) and N^6-o-nitrobenzyladenosine (3) had lower affinities. The following compounds were noncompetitive inhibitors: N^6-m-nitrobenzyladenosine (4), 2-amino-6-p-nitrobenzylaminopurine (12), and 2-amino-6-p-nitrobenzylaminopurine ribonucleoside (11). The basis for lack of binding of compounds 6–9 is not clear, but it is suggested that since N^6-p-aminobenzyladenosine (7) is not bound while the p-nitro compound 2 is a good inhibitor, that the alteration in electron distribution in the benzene ring produced by an electron-withdrawing group, i.e., NO_2, favors binding while an electron-donating group, i.e., NH_2, prevents it. On this basis, the poor binding of N^6-o-nitrobenzyladenosine (3) must be attributed to steric factors.

In order to possibly improve upon the antitumor activity of N^6-benzyladenosine (1), several modifications were made in the benzene ring and in the purine moiety of the compound (Table II). The N^6-p-nitrobenzyladenosine (2) and its 2'-deoxy analog 5 and the N^6-m-nitrobenzyladenosine (4) were as potent as the parent compound in L1210 leukemia cell line while in the Nc 37 and RPMI 6410, the compounds were less active than the parent compound. The 2'-deoxy-N^6-benzyladenosine (13) and N^6-o-nitrobenzyladenosine (3) were almost inactive. The 2-amino-6-p-nitrobenzylaminopurine (12) and the corresponding ribonucleoside 11 were better growth inhibitors of L1210 cells than the parent compound, N^6-benzyladenosine (1). The N^6-(2-methoxy-5-nitrophenyl)adenosine (6) was also active in L1210 cells. N^6-p-Aminobenzyladenosine (7) and its N-acetyl derivative 8 were less active than the parent N^6-benzyladenosine in three cell lines. N^6-p-Fluorobenzyladenosine (9) was also active in the same range as the parent compound in L1210 leukemia.

As adjuvants to β-D-arabinofuranosyladenine (Ara-A) chemotherapy in cancer, the enzyme inhibitors like N^6-p-nitrobenzyladenosine (2) and the corresponding 2'-deoxy analog 5 are of interest. Compounds of this type can be used, in high enough dosage levels because of their relative nontoxic nature, to protect Ara-A from being deaminated in vivo to the inactive arabinosyl hypoxanthine by adenosine aminohydrolase. In vivo evaluation of these compounds is in progress.

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