76894-86-5; **20**, 76894-75-2; **21**, 76894-77-4; **22**, 76894-78-5; **23**, 76894-79-6; **24**, 76894-80-9; **25**, 76894-81-0; **26**, 76894-82-1; **27**, 76894-83-2; **28**, 76894-84-3; **29**, 76894-85-4; **30**, 85602-50-2; 5-chloro-3-[(dimethylamino)methyl]-1*H*-indole, 830-94-4; 2-methyl-1*H*-indole, 95-20-5; 2-cyclopropyl-1*H*-indole, 40748-44-5; 5-methyl-1*H*-indole, 614-96-0; 5-methoxy-1*H*-indole, 1006-94-6; 5-bromo-1*H*-indole; 5-(dimethylamino)-1*H*-indole, 6843-23-8; imidazole, 288-32-4; ethyl bromoacetate, 105-36-2; acrylonitrile, 107-13-1; ethyl propiolate, 623-47-2; thromboxane synthetase, 61276-89-9.

Ribose-Modified Adenosine Analogues as Adenosine Receptor Agonists

Michael D. Taylor,*† Walter H. Moos,† Harriet W. Hamilton,† Deedee S. Szotek,† William C. Patt,† Edward W. Badger,† James A. Bristol,† Robert F. Bruns,‡ Thomas G. Heffner,‡ and Thomas E. Mertz‡

Departments of Chemistry and Pharmacology, Warner-Lambert/Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan 48105. *Received January 23, 1985*

Analogues of the potent adenosine receptor agonist (*R*)-*N*-(1-methyl-2-phenylethyl)adenosine (*R*-PIA), modified at N9, were prepared and evaluated for adenosine A_1 and A_2 receptor binding and in vivo central nervous system and cardiovascular effects. The modifications at N9 include deoxy sugars, 5′-substituted-5′-deoxyriboses, non-ribose sugars, sugar ring homologues, and acyclic sugar analogues. Most of the derivatives have poor affinity for adenosine receptors. Only minor modifications at C5′ and C3′ maintain potent binding. In general, those derivatives exhibiting in vivo behavioral or cardiovascular effects also have the highest affinity for adenosine receptors.

A wealth of recent evidence has revealed the prominent role of endogenous adenosine as a regulatory substance, distinct from endocrine hormones and the common neurotransmitters.[1] The number and variety of effects attributable to adenosine are remarkable, particularly since it may elicit opposite effects in different tissues. For example, adenosine causes vasodilation and hypotension in peripheral blood vessels[2] while in the kidney vasoconstriction results.[3] Other smooth muscle tissues are sensitive to adenosine including lung,[4] ileum,[5] and taenia coli.[6] Effects on coronary blood flow,[7] contractility of cardiac muscle,[8] and fat metabolism[9] are well documented. Some evidence suggests that adenosine may act as a neurotransmitter or neuromodulator in the brain.[10]

The observed physiological effects of adenosine are the result of its interaction with specific receptors. Direct binding studies with radiolabeled ligands with high affinity for adenosine receptors[11] have facilitated the identification of receptors in various tissues. At least two extracellular adenosine receptors are coupled to adenylate cyclase. One, termed A_1, is a high-affinity site that exerts an inhibitory effect on adenylate cyclase. The second, A_2, is a low-affinity site that activates adenylate cyclase.[12]

Antagonists of adenosine such as theophylline have long been known and considerably more potent derivatives such as 8-(2-amino-4-chlorophenyl)-1,3-dipropyl-1*H*-purine-2,6-dione have been developed.[13] No significant selectivity for either receptor subtype has been reported. Similarly, a number of adenosine analogues, particularly N^6-alkyl derivatives, are potent adenosine agonists. Several, such as (*R*)-*N*-(1-methyl-2-phenylethyl)adenosine (*R*-PIA, **1**),[12,14] produce dramatic hypotensive and negative chronotropic effects in vivo.[15] These derivatives are generally selective for A_1 receptors.

Our efforts in this area are directed toward the development of novel, selective adenosine agonists as potential therapeutic agents. Recently, we reported adenosine analogues having modified heterocyclic ring systems.[16] In this report, we detail the preparation and evaluation of *R*-PIA analogues modified at the ribose moiety. The modifications at N9 include deoxy sugars, 5′-substituted-5′-deoxyriboses, non-ribose sugars, sugar ring homologues, and acyclic sugar analogues. This work differs from previous structure–activity relationship studies in two ways. First, evaluating *R*-PIA analogues rather than adenosine analogues should eliminate the potential complicating effect of adenosine deaminase in the biological preparations and utilizes a substitution at N^6 known to improve affinity for the adenosine receptor. Second, affinity for adenosine receptors was determined by displacement of

† Department of Chemistry.
‡ Department of Pharmacology.

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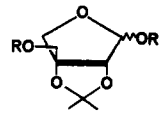
radioactive ligands. The previous studies[17,18] involving ribose-modified adenosine analogues measured adenosine receptor mediated adenylate cyclase activity.

Chemistry. Alkylation of 6-chloropurine at N9 followed by substitution at C6 with *l*-amphetamine ((*R*)-α-methylbenzeneethanamine) or, alternatively, direct alkylation of (*R*)-*N*-(1-methyl-2-phenylethyl)-1*H*-purin-6-amine (**2**) provided access to derivatives **3**–**8** (Table II). The former approach was used to prepare **2** and **5** from the known 6-chloropurine precursors. Acid-catalyzed alkylation of 6-chloropurine with 2,3-dihydrofuran[19] or 2,3-dihydropyran followed by *l*-amphetamine substitution produced **6** and **7**, respectively, as a mixture of 1′-*R*,*S*-diastereomers. The 2′,3′-dihydroxypropane derivatives **3** and **4** derived from alkylation of **2** with (*R*)- or (*S*)-2,2-dimethyl-1,3-dioxolane-4-methanol 4-methylbenzenesulfonate with subsequent acid-catalyzed hydrolysis. The glycol **9** was prepared by osmium tetraoxide oxidation of the corresponding cyclohexenyl precursor **8**, which in turn was prepared by alkylation of **2** with 3-bromocyclohexene. Since **8** was produced as a mixture of diastereomers, **9** was also a mixture of two compounds. These were assigned structures with hydroxyls trans to the purine, a result of steric control in the formation of the osmate ester.[20] One of these derivatives, the exact configuration of which remains unknown,[21] could be obtained in pure form by fractional crystallization. The corresponding diastereomer, however, could not be separated from the remaining mixture. The 2′,3′-diacetate and the 2′,3′-dibenzoate derivatives of **9** were prepared by standard methods, but these diastereomeric mixtures were also inseparable by TLC, reverse-phase HPLC, or fractional crystallization.

The deoxy analogues **10** and **11** (Table I) were prepared from **1** via a multistep deoxygenation procedure previously used for the preparation of 3′-deoxyadenosine.[22] The key step in this sequence was the selective silylation of 5′-*O*-(4,4′-dimethoxytriphenylmethyl)-*N*-(1-methyl-2-phenylethyl)adenosine in the presence of silver nitrate. The mixture thus produced was a 2:1 mixture of the 2′-*tert*-butyldimethylsilyl and 3′-*tert*-butyldimethylsilyl derivatives. Treatment of the mixture with thiocarbonyldiimidazole followed by tri-*n*-butyltin hydride gave a 2:1 mixture of 2′- and 3′-deoxy products, which could be separated by flash chromatography. Each derivative was individually deprotected with fluoride ion and mild acid treatment to yield **10** and **11**. The 2′-deoxy derivative **10** could also be prepared, albeit in poor yield, from 2′-deoxyinosine.[23] Attempts to prepare the 5′-deoxy analogue **12** from **1** via several reported deoxygenation procedures[24] failed. However, glycosylation of **2** with 5-deoxyribofuranose 1,2,3-triacetate[25] followed by deprotection produced **12** in reasonable yield.

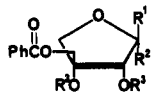
Direct chlorination of **1** with thionyl chloride produced **13**.[26] The 5′-deoxy-5′-methylthio derivative **14** was prepared by treatment of **1** with dimethyl disulfide and tributylphosphine.[27]

The non-ribose nucleosides **15**–**17** were prepared by glycosylation of **2**. An acid-catalyzed fusion reaction of **2** with tetra-*O*-benzoyl-L-lyxofuranose[28] or tetra-*O*-acetyl-L-lyxopyranose[29] gave **15** and **16**, respectively, in moderate yields after deprotection. The apiofuranosyl analogue **17** proved to be the most problematic of the compounds prepared. A successful route began with 2,3-*O*-(1-methylethylidene)-β-D-apiofuranose, **18**, which is readily available in four steps from D-mannose.[30] To maintain stereochemical integrity at C3, the sugar was converted to the dibenzoyl derivative **19**. Acid-catalyzed hydrolysis



18 R = H
19 R = COPh

removed the isopropylidene and the anomeric benzoate blocking groups to give **20**. Acetylation under a variety of standard conditions failed to give **21**. After several attempts, treatment of **20** with 1-methyl-3-acetylimidazolium chloride[31] produced, in low yield, a mixture of **21** and **22**. The anomeric configurations were not immediately assigned. The major acetate (**21**), when treated with the N^6,9-bis(trimethylsilyl) derivative of **2** and trimethylsilyl triflate, produced the protected nucleoside, which was not isolated but stirred with methanolic ammonium hydroxide to yield **17**, in low yield. The β-configuration of **17** was assigned based on the $J_{1',2'}$ coupling constant of 7.2 Hz, in good agreement with a value of 7.5 Hz observed for the corresponding adenine apionucleoside.[32] Under similar glycosylation conditions, the minor acetate **22** did not react but decomposed after an extended reaction period. On the basis of the observed reactivity and the well-known directing and rate-enhancing effects for β-acetoxy sugars containing a trans 2-acetoxy group,[33]



20 R^1,R^2 = H,OH; R^3 = H
21 R^1 = $OCOCH_3$; R^2 = H; R^3 = $COCH_3$
22 R^1 = H; R^2 = $OCOCH_3$; R^3 = $COCH_3$

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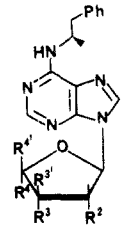
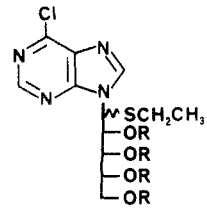
Table I. Modified-Sugar *R*-PIA Analogues



compd	R^2	R^3	$R^{3'}$	R^4	$R^{4'}$
1	OH	OH	H	H	CH_2OH
10	H	OH	H	H	CH_2OH
11	OH	H	H	H	CH_2OH
12	OH	OH	H	H	CH_3
13	OH	OH	H	H	CH_2Cl
14	OH	OH	H	H	CH_2SCH_3
15	OH	OH	H	CH_2OH	H
17	OH	OH	CH_2OH	H	H

21 was assigned the β-anomeric configuration and **22** the α-configuration.

The ring-opened ribose analogues (Table II) were prepared by separate approaches. The 2′,3′-seco analogue **23** was prepared from **1** by sequential treatment with sodium metaperiodate and sodium borohydride.[34] Coupling[35] of 6-chloropurine with 2,3,4,5-tetra-*O*-acetylribose dithioacetal[36] gave the thionucleoside **24**, which was deprotected with mild base treatment, producing **25**. The amphetamine side chain was installed in the usual way and Raney nickel desulfurization produced the desired 1′,4′-*O*-secoribose analogue **27**.



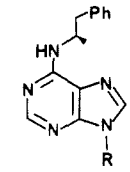
24 R = $COCH_3$
25 R = H

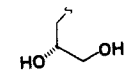
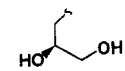
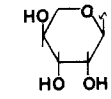
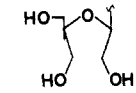
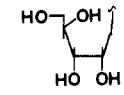
Biological Evaluation. Biological testing results are summarized in Table III. All of the compounds were evaluated for adenosine A_1 receptor affinity as measured by the ability to displace tritiated *N*-cyclohexyladenosine (CHA).[11a] In addition, a recently developed assay for A_2 receptor affinity[37] was employed which allowed us to determine receptor subtype selectivity. Two in vivo assays were used to evaluate the central nervous system (CNS) and cardiovascular effects of these compounds. The mouse activity and screen tests measure inhibition of spontaneous locomotor activity and screen fall-off[38] as indices of severe depression, discoordination, or CNS toxicity after ip dosing of the test substance. Cardiovascular activity was determined by measuring the effects of each compound on blood pressure and heart rate in anesthetized, vagotomized rats following iv dosing.

Discussion

The range of structural variation examined provides a number of insights into structure–activity relationships with regard to adenosine receptor binding. Also, although most of the compounds were not active in vivo, the data give some indication of the predictive value of receptor binding with respect to in vivo activity.

Table II. Non-Sugar *R*-PIA Analogues



Compound	R	Compound	R
2	H		
3		8	
4		9	
5	$-CH_2OCH_2CH_2OH$	16	
6		23	
7		27	

R-PIA, **1**, is among the most selective of adenosine receptor agonists, being very potent at the A_1 receptor (K_i = 1.1 nM) and only moderately potent at the A_2 receptor (K_i = 120 nM). This 110-fold selectivity compares to the 700-fold selectivity observed for *N*-cyclopentyladenosine, the most A_1 selective compound reported to date.[39] These results are consistent with the published selectivity of **1** for A_1 receptor mediated inhibition and A_2 mediated stimulation of adenylate cyclase.[12]

The ribose moiety of adenosine is critical for effective binding to both A_1 and A_2 receptors, as evidenced by the poor affinity of adenine.[2a,40] *R*-PIA similarly has substantially better affinity than the aglycone **2**. Furthermore, since adenine and 9-methyladenine are reported to be weak adenosine antagonists,[40] **2** may also be an antagonist. This could not be confirmed in the in vivo agonist models where **2** is essentially inactive.

All of the ring-opened analogues (**3–5**, **23**, and **27**) are less than one-thousandth as active as **1** at both A_1 and A_2 receptors. Also inactive are the α-L-lyxofuranosyl (**15**) and D-apio-β-D-furanosyl (**17**) analogues. Conformational differences relative to adenosine may be significant for the lyxofuranosyl derivative and certainly for the apiofuranosyl derivative. For the latter, the conformation of 9-(β-D-β-apiofuranosyl)adenine has been shown to be significantly different than adenosine.[32] The closely related 9-α-L-lyxofuranosyladenine and 4′-(hydroxymethyl)adenosine are reported to be inactive at the A_2 receptor of human fibroblasts.[18] Compounds containing a six-membered ring at N9 (**7**, **9**, **16**) exhibit extremely weak affinity for adenosine receptors and all of the compounds above are inactive

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Table III. Receptor Binding, CNS, and Cardiovascular Effects of *R*-PIA Analogues[a]

	adenosine receptor binding: $K_i \pm$ SE, nM			CNS activity[b]		cardiovascular activity[d]	
compd	A_1	A_2	A_2/A_1	inhibn of mouse locomotor act.: LAD,[c] mg/kg	screen test failure: LAD,[c] mg/kg	heart rate: ED_{20},[e] mg/kg	blood pressure: ED_{20},[f] mg/kg
1	1.1 ± 0.2	120 ± 9	110	1	3	0.006[g]	0.005[g]
2	9600	39000 ± 4000	4.1	100	100	>10	8
3	>10000	>100000		>100	>100	>10	>10
4	>10000	>100000		>100	>100	NT[h]	NT
5	68000	NT		>30	>30	NT	NT
6	1500 ± 60	8200 ± 700	5.5	>100	>100	>3	>3
7	12000	38000 ± 8000	3.2	100	>100	NT	NT
9	15000	>100000	>6.7	>100	>100	>3	>3
10	1900 ± 100	NT		>30	>30	NT	NT
11	29 ± 8	6900 ± 1700	240	100	100	0.40	0.80
12	25 ± 2	3300 ± 400	130	30	100	>0.3	0.05
13	1.6 ± 0.2	1900 ± 800	1200	10	100	0.08	0.10
14	29 ± 1	5600 ± 1400	190	>100	>100	3	0.023
15	20000	>100000	>5	>100	>100	>10	>10
16	5700	>100000	>18	NT	NT	NT	NT
17	>10000	>50000		NT	NT	NT	NT
23	>10000	>100000		>100	>100	>10	0.9
27	2200 ± 200	>100000	>45	>100	>100	>10	10

[a] See Experimental Section for detailed procedures. [b] Nine mice per observation. [c] Lowest dose producing a 60% reduction in locomotor activity or 60% screen test failure. [d] Two rats per determination. [e] 20% decrease in rate. [f] 20% decrease in blood pressure. [g] Four rats per determination. [h] Not tested.

in the in vivo behavioral and cardiovascular screens.

Adenosine receptor affinity and in vivo activity are sensitive to the presence and stereochemistry of hydroxyl substitution on the furanose ring. The inactive derivatives, **15** and **17**, mentioned above, involve stereochemical modifications of the 5′-hydroxymethyl. 2′-Deoxy-*R*-PIA (**10**) exhibits very weak affinity for the A_1 receptor and is devoid of behavioral activity, paralleling results for 2′-deoxyadenosine.[17,18] Other deoxyadenosines (3′-, 5′-, and 5′-deoxy-5′-haloadenosines) act as partial agonists at the human fibroblast A_2 receptor, whereas 5′-deoxy-5′-(methylthio)adenosine is reportedly a pure antagonist.[18] The corresponding *R*-PIA derivatives, **11–14**, were the only compounds in this report to exhibit nanomolar affinity for the A_1 receptor. Of these, the 5′-deoxy-5′-chloro derivatives, **13**, has the highest affinity. This compound demonstrates A_1 affinity equivalent to **1** and A_1 selectivity of 1200-fold, which is slightly greater than the highly selective N^6-cyclopentyladenosine,[39] and 10 times the selectivity of *R*-PIA. The lower in vivo activity of **13** relative to **1** may be due to lower intrinsic activity; that is, it may act as a partial agonist. The 3′-deoxy (**11**) and 5′-deoxy (**12**) derivatives are approximately 25 times less potent than **1** at both A_1 and A_2 receptors and at least 30 times less potent in behavioral and cardiovascular screens. Like **11** and **12**, the 5′-methylthio derivative **14** is 25–50 times less potent than **1**. In contrast to the effects of 5′-deoxy-5′-(methylthio)adenosine in human fibroblasts,[18] **14** clearly shows agonist-like activity in its effects on blood pressure and heart rate in the rat. The maximum decrease in heart rate was 30% compared to 87% for **1**, suggesting that **14** may be a partial agonist. Surprisingly, **14** exhibits no inhibition of locomotor activity.

Since most of the derivatives have poor affinity for adenosine receptors, one must be circumspect in evaluating the predictive value of receptor affinity for in vivo effects. Nonetheless, a qualitative correlation of receptor affinity and cardiovascular and CNS effects is observed here. Compounds **1** and **11–13** produce both cardiovascular and CNS effects and are among the most potent at A_1 and A_2 receptors. Compound **14** is also very potent at adenosine receptors but surprisingly inactive in the CNS test, perhaps due to a difference in metabolism or absorption. Compound **2** has a weak effect on locomotor activity and blood pressure. The activity observed for **2** may reflect a small amount of glycosylation to **1** in vivo. Compounds that are inactive in vivo also have poor receptor binding activity. The marginal CNS activity of **7** and the cardiovascular effects of **23** and **27** may be due to a mechanism that does not involve adenosine receptors.

In conclusion, structural requirements for potent binding to adenosine receptors are strict with respect to the ribofuranosyl moiety. Only minor modifications at C3′ and C5′ are tolerated without significant loss of activity. A qualitative correlation between adenosine receptor affinity and in vivo physiological effects is observed.

Experimental Section

Chemistry. Melting points were determined in open glass capillary tubes on a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded as indicated on a Varian EM-360 (60 MHz), EM-390 (90 MHz), XL-200 (200 MHz), or XL-300 (300 MHz) spectrometer. IR spectra, reported in cm^{-1}, were obtained on Digilab FTS-14 or modified Nicolet FT IR spectrometers. Mass spectra were recorded on a Finnegan 4500 mass spectrometer with an INCOS data system or a VG 7070 E/HR mass spectrometer with an 11/250 data system. UV spectra were obtained on a Cary 118 UV/visible spectrophotometer. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. Elemental analyses were performed by the Warner-Lambert/Parke-Davis Analytical Chemistry Section. Silica gel 60 PF_{254} plates were used for thin-layer chromatography; spots were visualized with UV light, iodine vapor, or 5% ethanolic $H_3PO_4 \cdot 12MbO_3$. Flash chromatography refers to the method of Still and co-workers.[41] Radially accelerated preparative thin-layer chromatography was carried out on a Chromatotron obtained from Harrison Laboratories with disks prepared with silica gel 60 PF_{254}. Preparative HPLC was conducted on a Waters Prep 500 instrument using silica gel cartridges. Preparative MPLC employed Michel-Miller columns using 230–400-mesh silica gel or prepacked Lobar columns (Merck). Organic extracts were dried over $MgSO_4$. All concentrations and evaporations were performed in vacuo. Dry DMF and pyridine were obtained by distillation from calcium hydride. Dry THF was obtained by distillation from sodium and benzophenone.

(*R*)-*N*-(1-Methyl-2-phenylethyl)-9*H*-purin-6-amine (2). In 250 mL of ethanol were placed 7.73 g (50 mmol) of 6-chloro-

(41) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

1*H*-purine and 13.6 g (100 mmol) of *l*-amphetamine, and the solution was heated to reflux and stirred under N_2 atmosphere for 72 h. After the mixture cooled to 50 °C, the ethanol was removed under reduced pressure to give a slurry. The slurry was dissolved in 100 mL of chloroform and washed with 100 mL each of water and saturated brine. The chloroform was dried over $MgSO_4$ and concentrated to give 11 g of a white precipitate (87%): mp 190–193 °C; NMR (Me_2SO-d_6, 90 MHz) δ 1.18 (d, 3 H), 2.86 (m, 2 H), 4.65 (br m, 1 H), 7.21 (s, 5 H), 7.42 (d, 1 H, ex), 8.05 (s, 1 H), 8.12 (s, 1 H), 11.5 (br, 1 H, ex); $[\alpha]_D$ −114.8 (*c* 1.08, MeOH). Anal. ($C_{14}H_{15}N_5$) C, H, N.

[*R*-(*R,*R**)]-3-[6-[(1-Methyl-2-phenylethyl)amino]-9*H*-purin-9-yl]-1,2-propanediol (3).** To 125 mL of dry DMF was added 6.0 g (23.7 mmol) of **2** and 0.72 g (30 mmol) of mineral oil free sodium hydride. The solution was warmed to 80 °C and stirred for 2 h. To this solution was added, at once, 10.0 g (35 mmol) of (*R*)-2,2-dimethyl-1,3-dioxolane-4-methanol 4-methylbenzenesulfonate.[42] The new solution was then warmed to 100 °C and stirred under nitrogen overnight. The mixture was concentrated to give a slurry, which was then dissolved in 100 mL of methylene chloride and washed once each with water and brine. The organic layer was dried and concentrated. The residue was dissolved in the minimal amount of ethyl acetate, applied to a silica gel column, and eluted with ethyl acetate. The major component was isolated as a clear, viscous oil, 4.5 g (52%). A portion of this product (3.6 g, 10 mmol) was added to 100 mL of 6 N HCl and the resulting solution was heated at reflux for 6 h. Heating was discontinued and the solution stirred overnight. The solution was reduced in volume to 25 mL. The pH was adjusted to 7 with 5% NaOH and the neutral solution extracted with methylene chloride. The combined extracts were dried and evaporated to give 1.5 g of a white solid (46%): mp 153.5–155 °C; NMR (Me_2SO-d_6, 90 MHz) δ 1.15 (d, *J* = 6 Hz, 3 H), 2.90 (m, 2 H), 3.37 (br m, 2 H), 3.7–4.5 (m, 3 H), 4.72 (br m, 1 H), 4.83 (t, 1 H, ex), 5.10 (d, *J* = 5 Hz, 1 H, ex), 7.3 (s, 5 H), 7.58 (d, *J* = 9 Hz, 1 H, ex), 8.09 (s, 1 H), 8.24 (s, 1 H); $[\alpha]_D$ −70.9 (*c* 1.03, MeOH). Anal. ($C_{17}H_{21}N_5O_2$·0.1H_2O) H, N, C: calcd, 62.03; found, 61.55.

[*S*-(*R,*S**)]-3-[6-[(1-Methyl-2-phenylethyl)amino]-9*H*-purin-9-yl]-1,2-propanediol (4).** The product **4** was prepared via the procedure described for **3** from **2** and (*S*)-2,2-dimethyl-1,3-dioxolane-4-methanol 4-methylbenzenesulfonate[42] in 34% overall yield (alkylation 42%, hydrolysis 81%). The product was obtained as a white solid: mp 154.5–155.5 °C; NMR (Me_2SO-d_6, 90 MHz) δ 1.17 (d, 3 H), 2.86 (m, 2 H), 3.33 (br, 2 H), 3.7–4.45 (m, 3 H), 4.65 (br, 1 H), 4.8 (t, 1 H, ex), 5.05 (d, 1 H, ex), 7.22 (s, 5 H), 7.56 (d, 2 H, ex), 8.0 (s, 1 H), 8.13 (s, 1 H); $[\alpha]_D$ −108.2° (*c* 1.04, MeOH). Anal. ($C_{17}H_{21}N_5O_2$) C, H, N.

(*R*)-2-[[6-[(1-Methyl-2-phenylethyl)amino]-9*H*-purin-9-yl]methoxy]ethanol (5). A mixture of 400 mg (1.75 mmol) of 2-[(6-chloro-9*H*-purin-9-yl)methoxy]ethanol,[43] 505 mg (1.78 mmol) of *l*-amphetamine *l*-tartrate, and 1.1 mL (4.6 mmol) of tri-*n*-butylamine in 12.5 mL of absolute ethanol was heated at reflux under nitrogen for 56 h and then concentrated to a yellow oil. This oil was purified by MPLC (Merck Lobar RP-8 size B column, 1/1/1 methanol/acetonitrile/water) to give a glass (1.26 g, 100%). The yield was corrected for the presence of tartrate and amine as determined by NMR and microanalysis. NMR (1/1/1 $CDCl_3$/Me_2SO-d_6/acetone-d_6, 60 MHz) δ 1.15 (d, *J* = 7 Hz, 3 H), 3.57 (s, 4 H), 5.69 (s, 2 H), 7.22 (s, 5 H), 8.3 (s, 2 H), additional multiplets obscured by tri-*n*-butylamine hydrochloride and water; mass spectrum (EI), *m*/*z* (relative intensity) 328 (M^+, 2), 236 (32), 162 (100), 91 (36). Anal. ($C_{17}H_{21}N_5O_2$·0.4*n*-Bu_3NHCl·1.4*l*-tartrate·5.5H_2O) C, H, N, Cl.

(*R*)-*N*-(1-Methyl-2-phenylethyl)-9-(tetrahydro-2-furanyl)-9*H*-purin-6-amine (6). A solution of 5.0 g (22 mmol) 6-chloro-9-(tetrahydro-2-furanyl)-9*H*-purine,[43] 16 g (44 mmol) of *l*-amphetamine, and 3.4 mL (24 mmol) of triethylamine in 250 mL of absolute ethanol was heated at reflux for 60 h. After cooling, the mixture was concentrated to an orange oil, which was purified by column chromatography (silica gel, 2 × 75 cm, ethyl acetate/2-propanol, 4/1). The major component was obtained as a pale orange glass: 4.6 g (56%); NMR (Me_2SO-d_6, 90 MHz) δ 1.25 (d, *J* = 6.0 Hz, 3 H), 1.2–3.2 (m, 4 H), 3.8–4.3 (m, 3 H), 4.5–5.0 (m, 1 H), 5.4–5.6 (m, 1 H), 6.1–6.3 (dd, *J* = 6.0, 4.0 Hz, 1 H), 7.2 (s, 5 H), 7.7 (s, 1 H), 8.3 (s, 1 H); measured mass 323.1734 ($C_{18}H_{21}N_5O$ requires 323.1746). Anal. ($C_{18}H_{21}N_5O$) C, H; N: calcd, 21.66; found, 19.21.

(*R*)-*N*-(1-Methyl-2-phenylethyl)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-amine (7). A solution of 2.40 g (10.0 mmol) 6-chloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine,[43] 4.1 g (30 mmol) of *l*-amphetamine, and 5 mL (0.12 mmol) triethylamine in 50 mL of absolute ethanol was heated at reflux under nitrogen for 3 days. Additional triethylamine (3 mL) was added and after 1 more day the solution was concentrated to an oil. The oil was purified by flash chromatography (120 g silica gel, 5/1 chloroform/methanol) affording 3.83 g (100%) of a golden oil: NMR ($CDCl_3$, 90 MHz) δ 1.29 (d, *J* = 7 Hz, 3 H), 1.6–2.3 (m, 5 H), 2.6–3.2 (m, 2 H), 3.6–4.3 (m, 2 H), 4.6–5.0 (m, 1 H), 5.77 (m, 2 H), 7.27 (s, 5 H), 7.95 (s, 1 H), 8.40 (s, 1 H). Anal. ($C_{19}H_{23}N_5O$·0.45H_2O) C, H, N.

[*R*-(1β,2α,3α)]-9-(2,3-Dihydroxycyclohexyl)-*N*-(1-methyl-2-phenylethyl)-9*H*-purin-6-amine (9). A solution of 5.0 g (20 mmol) of **2** in 60 mL of DMF was treated with 2.8 g (20 mmol) of sodium hydride and stirred 5 min. After addition of 3.3 mL (20 mmol) of 3-bromocyclohexene, the solution was stirred 6 h whereupon another 3.3 mL of 3-bromocyclohexene was added. The mixture was stirred at 25 °C for 60 h and 65 °C for 26 h. The solution was poured into 150 mL of water and extracted with chloroform (2 × 150 mL). The organic extracts were washed twice with water, dried, and concentrated to an orange oil. Flash chromatography (250 g of silica gel, 5% methanol in chloroform) produced 1.9 g of the 9-(3-cyclohexenyl)-9*H*-purine (28%) as an off-white solid and 1.7 g (34%) of recovered **2**.

A solution of 1.8 g (5.4 mmol) of the 9-(3-cyclohexenyl)-9*H*-purine in 10 mL of acetone and 5 mL of water was added to a solution containing 0.88 g (6.5 mmol) of *N*-methylmorpholine *N*-oxide monohydrate and 0.28 g (1.1 mmol) of osmium tetraoxide in 10 mL of acetone and 5 mL of water. A brown precipitate formed and 15 mL of acetone was added to redissolve it. After solution was stirred overnight, a slurry of 1.5 g of sodium bisulfite, 5 g of magnesium silicate, and 35 mL of water was added. The mixture was stirred 15 min and filtered and the cake washed with several portions of acetone. The filtrate was concentrated to a brown residue (1.9 g). Flash chromatography (125 g, 5% methanol in chloroform) produced 1.3 g (65%) of a chromatographically homogeneous mixture of two diastereomers in a 1:1 ratio by NMR spectroscopy. Recrystallization from 35 mL of ethyl acetate produced 0.59 g of a single diastereomer of unknown configuration at C-1′: mp 131–135 °C; NMR ($CDCl_3$, 200 MHz) δ 1.22 (d, *J* = 6.5 Hz, 3 H), 1.64 (d, *J* = 11.6 Hz, 2 H), 1.7–2.2 (m, 4 H), 2.71 (dd, *J* = 13.7, 7.3 Hz, 1 H), 3.01 (dd, *J* = 13.7, 5.5 Hz, 1 H), 3.8–4.15 (m, 2 H), 4.25 (s, 1 H), 4.5–4.9 (m, 3 H), 5.74 (d, *J* = 7.6 Hz, 1 H), 7.24 (m, 5 H), 7.69 (s, 1 H), 8.27 (s, 1 H). Anal. ($C_{19}H_{23}N_5O_4$) C, H, N.

Additional crops were contaminated by the other isomer and attempts to crystallize this isomer from the mother liquor were unsuccessful as were attempts at chromatographic purification.

(*R*)-2′- and 3′-Deoxy-*N*-(1-methyl-2-phenylethyl)adenosine (10 and 11). (a) 5′-*O*-(4,4′-Dimethoxytriphenylmethyl)-*N*-(1-methyl-2-phenylethyl)adenosine. With use of the procedure of Ogilvie and co-workers,[20] the protected product was prepared in 91% as a white foam: NMR (Me_2SO-d_6, 90 MHz) δ 1.21 (d, *J* = 7 Hz, 3 H), 2.6–3.1 (m, 2 H), 3.22 (m, 2 H), 3.71 (s, 6 H), 4.05 (m, 1 H), 4.27 (m, 1 H), 4.68 (m, 1 H), 5.17 (d, *J* = 6 Hz, 1 H), 5.48 (d, *J* = 5 Hz, 1 H), 5.90 (d, *J* = 4 Hz, 1 H), 6.80 (d, *J* = 9 Hz, 4 H), 7.1–7.4 (m, 14 H), 7.62 (d, *J* = 8 Hz, 1 H), 8.11 (s, 1 H), 8.20 (s, 1 H).

(b) Silylation and Imidazoylthiocarbonylation.[44] 5′-(4,4′-Dimethoxytriphenylmethyl)-*R*-PIA (8.0 g, 11.6 mmol) was dissolved in 130 mL of dry THF and treated with 3.5 g (44 mmol) of pyridine and 2.3 g (15 mmol) crushed silver nitrate. After the mixture was stirred for 30 min, 2.3 g (15 mmol) of chloro-*tert*-

(42) Baer, E.; Hemendra, B. *Can. J. Biochem.* **1969**, *47*, 955.
(43) Barrio, J. R.; Bryant, J. D.; Keyser, G. E. *J. Med. Chem.* **1980**, *23*, 572.
(44) Ogilvie, K. K.; Hakimelahi, G. H.; Proba, Z. A.; Usman, N. *Tetrahedron Lett.* **1983**, *24*, 865.

butyldimethylsilane was added, giving an immediate white precipitate. After 24 h, additional portions of silver nitrate (1.0 g) and silane (1.0 g) were added, and the mixture was stirred an additional 24 h. The mixture was filtered and concentrated to a clear waxy oil. Flash chromatography (275 g silica gel, 35% ethyl acetate in hexane) provided 7.2 g (8.9 mmol, 77%) of a waxy solid. The NMR spectrum showed the product to be a 2:1 mixture of isomers by integration of the respective purine ring protons. This mixture was dissolved in 30 mL of dry DMF and treated with 4.8 g (27 mmol) of thiocarbonyldiimidazole. The orange solution was stirred overnight in a stoppered flask. Concentration of the solution yielded an orange residue, which was dissolved in 200 mL of ethyl acetate and washed with water and brine. The organic fraction was dried and concentrated to yield 8.5 g (104%) of an orange foam.

(c) Deoxygenation. The crude foam was dissolved in 100 mL of toluene and treated with 1.0 g of AIBN. The flask was flushed with nitrogen and 9.0 mL (33 mmol) of tributyltin hydride was added via syringe. The solution was heated at reflux for 3 h, cooled, and concentrated. The residue was purified by flash chromatography (200 g silica gel, 20–30% ethyl acetate in hexane) to yield first 3.43 g (48.4%) of a white solid assigned the 3′-deoxy-2′-*O*-[(1,1-dimethylethyl)dimethylsilyl] structure by NMR analysis, followed by 1.80 g (25.4%) of the 2′-deoxy-3′-*O*-[(1,1-dimethylethyl)dimethylsilyl] derivative. Total yield was 73.8%.

(d) Deprotection of 3′-Deoxy Derivative. The major component was dissolved in 25 mL of dry tetrahydrofuran and treated with 7 mL of 1 M tetrabutylammonium fluoride. After stirring 15 min, the mixture was diluted with 50 mL of toluene and concentrated. The residue was dissolved in 25 mL of 80% acetic acid, stirred 45 min, and then concentrated. The residue was purified by flash chromatography (130 g of silica gel, 5% methanol in chloroform) to obtain 1.36 g (85%) of a white foam. Recrystallization from 10/1 isopropyl ether/methanol produced 1.28 g (80%) of **11** as fine-white needles: mp 143–144 °C; NMR ($CDCl_3$, 200 MHz) δ 1.21 (d, J = 6.6 Hz, 3 H), 1.20 (m, 1 H), 1.45 (m, 1 H), 2.77 (dd, J = 14.6, 7.4 Hz, 1 H), 3.02 (dd, J = 14.6, 5.6 Hz, 1 H), 3.53 (dd, J = 12.7, 2.5 Hz, 1 H), 3.94 (dd, J = 12.7, 1.6 Hz, 1 H), 4.50 (m, 1 H), 4.60 (br, 1 H), 4.93 (dd, J = 14.7, 7.4 Hz, 1 H), 5.1–6.2 (br, 1 H), 5.65 (d, J = 5.3 Hz, 1 H), 6.06 (d, J = 7.9 Hz, 1 H, C-1′), 7.24 (m, 6 H), 7.75 (s, 1 H), 8.22 (s, 1 H). Anal. C, H, N.

(e) Deprotection of 2′-Deoxy Derivative. In the same manner, 1.8 g (2.3 mmol) of the 2′-deoxy derivative obtained above gave 0.50 g (59%) of **10** after flash chromatography. Recrystallization from 10/1 isopropyl ether/methanol produced 0.34 g (40%) of analytically pure **10** as a white crystalline solid: mp 140.5–142 °C; NMR ($CDCl_3$, 90 MHz) δ 1.26 (d, J = 10 Hz, 3 H), 2.29 (dd, J = 7.5, 2.4 Hz, 2 H), 2.6–3.3 (complex m, 4 H), 3.6–4.25 (complex m, 2 H), 4.22 (br, 1 H), 4.71 (d, J = 2.1 Hz, 1 H), 5.82 (d, J = 4.1 Hz, 1 H), 6.32 (dd, J = 4.9, 2.4 Hz, 1 H, C-1′), 6.85 (d, J = 5.0 Hz), 7.24 (s, 5 H), 7.77 (s, 1 H), 8.32 (s, 1 H). Anal. ($C_{19}H_{23}N_5O_4$) C, H, N.

(*R*)-5′-Deoxy-*N*-(1-methyl-2-phenylethyl)adenosine (12). A mixture of 4.6 g of 5′-deoxyribofuranose 1,2,3-triacetate[23] and 4.5 g of **2** was melted and stirred at 150 °C under a nitrogen atmosphere. To this mixture was added one drop of concentrated sulfuric acid. The solution was stirred until no more acetic acid was evolved (~4 h). The mixture was cooled to room temperature and dissolved in 50 mL of methylene chloride. The solution was washed with water, dried, and concentrated to give a black foam. This foam was dissolved in ethyl acetate and purified by silica gel chromatography. The major component was obtained from the fastest band to give 2.3 g. The compound was placed in 200 mL of methanol and 0.3 g of sodium methoxide was added. The solution was stirred at room temperature for 4 h. The reaction was quenched with 10 mL of water, neutralized to pH 7 with Dowex 50 (H^+ form), and concentrated to give 1.8 g (27%) of a tan foam: NMR (Me_2SO-d_6, 200 MHz) δ 1.16 (d, J = 6.4 Hz, 3 H), 1.26 (d, J = 6.2 Hz, 3 H), 2.76 (m, 1 H), 3.0 (m, 1 H), 3.93 (m, 2 H), 4.62 (m, 2 H), 5.5 (br, 2 H), 5.80 (d, J = 5.0 Hz, 1 H), 7.23 (s, 5 H), 7.66 (d, J = 8.0 Hz, 1 H), 8.17 (s, 1 H), 8.29 (s, 1 H); measured mass 369.1791 ($C_{19}H_{23}N_5O_3$ requires 369.1801).

(*R*)-5′-Chloro-5′-deoxy-*N*-(1-methyl-2-phenylethyl)-adenosine (13). To 50 mL of hexamethylphosphoramide were added 15.9 g (134 mmol) of thionyl chloride and 9.6 g (13 mmol) of **1** under nitrogen. The mixture was stirred at room temperature overnight. The pH of the solution was adjusted to 7 with concentrated ammonium hydroxide. A gum formed and the mixture was set aside for 2 h to settle. The aqueous solution was decanted and the gum was dissolved in 500 mL of ethanol. The mixture was concentrated to give a white solid, which was washed with ether and dried. The crude product was stirred in hot acetone and filtered while still warm and then concentrated to give 2.6 g (26%) of a white solid: mp 83–86 °C; NMR (Me_2SO-d_6, 90 MHz) δ 1.2 (d, J = 6 Hz, 3 H), 2.88 (m, 2 H), 3.75–4.3 (m, 4 H), 4.71 (br, 2 H), 5.43 (br, 2 H), 5.9 (d, J = 5 Hz, 1 H), 7.29 (s, 5 H), 7.62 (d, J = 9 Hz, 1 H, ex), 8.15 (s, 1 H), 8.27 (s, 1 H). Anal. ($C_{19}H_{22}N_5O_3Cl$) C, H, N, Cl.

(*R*)-5′-Deoxy-*N*-(1-methyl-2-phenylethyl)-5′-(methylthio)adenosine (14). Into 25 mL of *N*,*N*-dimethylformamide were placed 5.0 g (12.9 mmol) of **1**, 6.1 g (65 mmol) of dimethyl disulfide, and 13.2 g (65 mmol) of tri-*n*-butylphosphine. The mixture was stirred under nitrogen for 72 h. The reaction was quenched with 20 mL of water and then concentrated with warming. The excess phosphine/disulfide mixture was removed by distillation (80 °C (1.2 mmHg)), leaving a black glass. The residue was dissolved in ethyl acetate, filtered, and purified by silica gel chromatography. After a minor impurity, the product was eluted to yield, after evaporation of solvent, 1.5 g (28%) of a hygroscopic foam: NMR (Me_2SO-d_6, 90 MHz) δ 1.18 (d, J = 6 Hz, 3 H), 2.05 (s, 3 H), 2.55–3.2 (m, 4 H), 4.04 (m, 2 H), 4.69 (m, 2 H), 5.22 (d, J = 5 Hz, 1 H), 5.39 (d, J = 6 Hz, 1 H), 5.82 (d, J = 5 Hz, 1 H), 7.19 (s, 5 H), 7.57 (d, J = 9 Hz, 2 H), 8.13 (s, 1 H), 8.26 (s, 1 H). Anal. ($C_{20}H_{25}N_5O_3S$) C, H, N, S.

(*R*)-9-α-L-Lyxofuranosyl-*N*-(1-methyl-2-phenylethyl)-9*H*-purin-6-amine (15). A mixture of 1.1 g (4.3 mmol) of **2**, 15 mL of hexamethyldisilazane, and 10 mg of anhydrous ammonium sulfate was heated at reflux under a drying tube overnight. The mixture, initially a white suspension, gradually became a clear solution. The solution was concentrated to a white, waxy solid, which was dried in vacuo for 3 h. The solid was then dissolved in 30 mL of dichloroethane and 2.4 g of α-L-lyxofuranose tetrabenzoate added.[26] The flask was flushed with nitrogen and 1.0 mL of trimethylsilyl triflate was added via syringe. The brown mixture was heated at reflux under nitrogen for 23 h after which it was poured into 75 mL of 5% aqueous bicarbonate solution and twice extracted with methylene chloride. The extracts were dried, treated with decolorizing carbon, and filtered through a 3 × 1 cm pad of silica gel. The filtrate exhibited a single major component by TLC (1/1 ethyl acetate/hexane), which was isolated by flash chromatography (100 g, 30–50% ethyl acetate/hexane) to give 1.2 g (40%) of the tribenzoylated nucleoside. Without further purification, this material was stirred with 120 mL of 5% ammonia in methanol for 3 days. The solution was concentrated and the residue purified by flash chromatography (50 g, 7–12% methanol in chloroform) to yield 0.56 g (84%) of a white powder: mp 188–194 °C. An analytical sample was recrystallized from 2-propanol (77% recovery) to yield very fine needles: mp 194–195 °C; NMR (Me_2SO-d_6, 200 MHz) δ 1.17 (d, J = 6.4 Hz, 3 H), 2.70 (dd, J = 13.3, 6.6 Hz, 1 H), 2.96 (dd, J = 13.3, 6.6 Hz, 1 H), 3.48 (dd, J = 11.2, 5.9 Hz, 1 H), 3.63 (dd, J = 11.2, 5.3 Hz, 1 H), 4.13 (br, 1 H), 4.39 (br, 1 H), 5.00 (dd, J = 6.2, 3.8 Hz, 1 H), 5.83 (d, J = 6.2 Hz, 1 H), 7.1–7.4 (complex m, 5 H), 7.68 (d, J = 8.4 Hz, 1 H), 8.18 (s, 1 H), 8.36 (s, 1 H); IR (KBr) 2600–2800 (br), 1621 (s), 1476 (m), 1056 (m). Anal. ($C_{19}H_{23}N_5O_4$) C, H, N.

(*R*)-9-α-L-Lyxopyranosyl-*N*-(1-methyl-2-phenylethyl)-9*H*-purin-6-amine (16). The 6,9-bis(trimethylsilyl) derivative of **2** was prepared from 0.78 g (3.0 mmol) of **2** in the same manner as for **15**. The resulting waxy glass (1.1 g, 90%) was dissolved in 15 mL of dichloroethane and treated with 1.0 g (3.0 mmol) of L-lyxopyranose tetraacetate.[25] After flushing with nitrogen, the solution was treated with 0.6 mL (6 mmol) of trimethylsilyl triflate. The mixture was heated at reflux for 20 h. The dark solution was poured into 5% aqueous bicarbonate solution and twice extracted with chloroform. The extracts were dried and concentrated to 1.6 g of a tan foam. The major component was obtained by flash chromatography (75 g, 1/1 ethyl acetate/hexane) as 0.5 g of a white foam. A portion of the product (0.26 g) was stirred in 20 mL of 5% ammonia in methanol for 2 h. After evaporation, the residue was dissolved in 40 mL of 20% methanol in chloroform and filtered through a silica gel pad. Concentration

gave 0.18 g (92% crude yield) of a tan solid. Purification using a 4-mm Chromatotron disk and eluting with 10–20% methanol in chloroform gave 0.14 g (70%) of a white powder which was impure by microanalysis but chromatographically homogeneous (HPLC) and spectroscopically consistent with the desired structure: NMR (Me_2SO-d_6, 200 MHz) δ 1.16 (t, J = 6.4 Hz, 3 H), 2.77 (dd, J = 14.1, 6.1 Hz, 1 H), 2.98 (dd, J = 14.1, 6.7 Hz, 1 H), 3.62 (s, 2 H), 3.89 (s, 1 H), 4.33 (complex m, 1 H), 4.95 (d, J = 7.8 Hz, 1 H), 5.10 (d, J = 4.7 Hz, 1 H), 5.24 (d, J = 3.6 Hz, 1 H), 5.64 (d, J = 9.5 Hz, 1 H), 7.1–7.4 (complex m, 5 H), 7.59 (d, J = 8.7 Hz, 1 H), 8.16 (s, 1 H), 8.26 (s, 1 H), ~2 H obscured by water peak; IR (KBr) 3600–2800 (br), 1621 (s), 1478 (m), 1087 (m); measured mass 385.1739 ($C_{19}H_{23}O_4N_5$ requires 385.1750).

(*R*)-9-(D-Apio-β-D-furanosyl)-*N*-(1-methyl-2-phenylethyl)-9*H*-purin-6-amine (17). A mixture of 1.0 g (4.0 mmol) of **2**, 0.01 g of ammonium sulfate, and 15 mL of hexamethyldisilazane was heated at reflux overnight. An aliquot (2.1 mL) containing 0.14 g (0.55 mmol) of **2** was concentrated at 70 °C and then placed under vacuum (<1 mmHg) for 45 min to give 0.51 g of a waxy solid. This material was dissolved in 10 mL of dichloroethane and added to a solution of 0.21 g (0.55 mmol) of **22** in 3 mL of dichloroethane. The flask was sealed and flushed with nitrogen and 0.2 mL of tin tetrachloride was added dropwise. After stirring overnight, the mixture was quenched with 20 mL of cold saturated aqueous sodium bicarbonate and extracted with methylene chloride. The extract was dried and concentrated to leave a brown gum, which was purified on a 2-mm Chromatotron disk eluting with 2–10% methanol in chloroform. Two UV-active bands were isolated. The first contained 73 mg (26%) of a white foam shown by NMR to be the desired nucleoside. The second band contained **2**. The protected nucleoside (50 mg, 0.09 mmol) was stirred overnight with 3 mL of methanol and 1 mL of concentrated ammonium hydroxide solution. The volatiles were evaporated, and the residue was purified by preparative thin-layer chromatography (20 × 20 cm × 1 mm, 80% methanol in chloroform). The single UV-active band was extracted with 10% methanol in ethyl acetate. The eluate was concentrated to leave 12.2 mg (36%) of transparent glass chromatographically homogeneous and exhibiting an R_f nearly identical with that of **1**: NMR ($CDCl_3$, 300 MHz) δ 1.25 (d, J = 6.7 Hz, 3 H), 2.83 (dd, J = 13.0, 7.2 Hz, 1 H), 3.05 (dd, J = 13.0, 5.7 Hz, 1 H), 3.71 (d, J = 11.2 Hz, 1 H), 3.78 (d, J = 11.2 Hz, 1 H), 3.80 (br, 1 H), 4.07 (d, J = 10.3 Hz, 1 H), 4.18 (m, 1 H), 4.24 (d, J = 10.3 Hz, 1 H), 4.45 (d, J = 7.1 Hz, 1 H), 4.69 (br, 1 H), 5.92 (br, 1 H), 6.03 (d, J = 7.1 Hz, 1 H), 7.23 (m, 6 H), 7.79 (s, 1 H), 8.30 (s, 1 H); measured mass 386.1820 ($C_{19}H_{24}N_5O_4$ (M + 1) requires 386.1830).

5-*O*-Benzoyl-D-apio-β-D-furanose 1,2,3-Tri-*O*-acetate and 5-*O*-Benzoyl-D-apio-α-D-furanose 1,2,3-Tri-*O*-acetate (21 and 22). (a) Benzoylation. To 75 mL of dry pyridine was added 9.2 g (48.4 mmol) of 2,3-*O*-(1-methylethylidene)-D-β-apiofuranose.[28] The solution was chilled in an ice bath while 35 mL of benzoyl chloride was added with stirring, causing the solution to thicken with a white precipitate. After stirring overnight at room temperature, the mixture was poured onto 200 g of ice–water and extracted with chloroform. The extract was dried and concentrated to yield a clear, viscous syrup. The syrup was purified by flash chromatography (275 g, 5–10% methanol in chloroform) to yield 13.6 g (70.6%) of the dibenzoylated product (10.4 g (54.0%) and 3.2 g (16.6%) of the major and minor epimers). Each epimer gave satisfactory NMR, IR, and microanalytical data.

(b) Hydrolysis. A solution of 10.2 g of the epimeric mixture in 75 mL of 80% trifluoroacetic acid was stirred overnight in a stoppered flask. The solution was concentrated, dissolved in chloroform, and twice washed with 5% aqueous sodium bicarbonate and once with water. The organic fraction was dried and concentrated to leave a yellow oil. Flash chromatography (200 g, 10% methanol in chloroform) gave 1.72 g (26%) of **20** as a transparent oil. Anal. ($C_{12}H_{14}O_6$) C, H, N. The yield of this reaction was variable. Two other experiments on ~1/3 scale gave 52% and 54% of the product.

(c) Acetylation. To 70 mL of methylene chloride was added 2.45 mL (30.6 mmol) of 1-methyl-1*H*-imidazole followed by 2.2 mL (30.6 mmol) of freshly distilled acetyl chloride added dropwise with vigorous stirring. After 5 min, 1.3 g (5.1 mmol) of **20** in 100 mL of methylene chloride was added dropwise over 30 min. After stirring 72 h under a drying tube, the mixture was filtered and the white residue was washed with methylene chloride. The filtrate was concentrated and the residue was purified on a 4-mm Chromatotron disk eluting with 1% methanol in chloroform. The first band was collected and concentrated to yield 0.24 g (12.5%) of **21** (α-anomer) followed by the second band which contained 0.22 g (11.5%) of **22** (β-anomer), both as white films. **21**: NMR ($CDCl_3$, 200 MHz) δ 2.05 (s, 3 H), 2.08 (s, 3 H), 2.11 (s, 3 H), 4.26 (d, J = 10.6 Hz, 1 H), 4.47 (d, J = 10.6 Hz, 1 H), 4.79 (d, J = 12.4 Hz, 1 H), 4.97 (d, J = 12.4 Hz, 1 H), 5.58 (s, 1 H), 6.15 (s, 1 H), 7.48 (apparent t, J = 7.8 Hz, 2 H), 7.58 (apparent t, J = 8.6 Hz, 1 H), 8.80 (apparent d, J = 7.8 Hz, 2 H). **22**: NMR ($CDCl_3$, 200 MHz) δ 2.03 (s, 3 H), 2.09 (s, 3 H), 2.10 (s, 3 H), 4.31 (d, J = 8.8 Hz, 1 H), 3.42 (d, J = 8.8 Hz, 1 H), 4.62 (d, J = 11.6 Hz, 1 H), 4.88 (d, J = 11.6 Hz, 1 H), 5.46 (d, J = 4.8 Hz, 1 H), 6.40 (d, J = 4.8 Hz, 1 H), 7.44 (t, J = 7.2 Hz, 2 H), 7.58 (t, J = 7.2 Hz, 1 H), 8.00 (d, J = 7.2 Hz, 2 H).

(*R*)-2-[1-(6-Chloro-9*H*-purin-9-yl)-2-hydroxyethoxy]-1,3-propanediol. 6-Chloropurine ribonucleoside (7.5 g, 26.2 mmol) was dissolved in 1.2 L of water by warming to 40 °C with a hot air gun. After the solution cooled to room temperature, 70 mL of 0.5 M $NaIO_4$ was added, and the mixture was stirred 1 h in the dark. The resulting white suspension was vacuum filtered and then passed through a column containing 100 g of Amberlite IR-45 ion-exchange resin. The pH of the eluate was 10–11. The solution was treated, in portions, with 3 g of sodium borohydride and stirred for 45 min. The solution was treated with 75 mL of acetone and then glacial acetic acid until neutral. The solution was concentrated to a viscous oil, which was triturated with hot 2-propanol, filtered, and concentrated. The residue was purified by flash chromatography (200 g, 10–15% methanol in chloroform) to yield 3.45 g (49%) of a white solid: mp 139–140 °C; NMR (Me_2SO-d_6, 90 MHz) δ 2.9–3.6 (complex m, 5 H), 3.88 (br, 2 H), 4.30 (br, 1 H), 4.70 (br, 1 H), 5.10 (br, 1 H), 6.00 (t, J = 4.5 Hz, 1 H), 8.71 (s, 1 H), 8.76 (s, 1 H); IR (KBr) 3600–2700 (br), 1600 (s), 1560 (s), 1200 (s), 941 (s). Anal. ($C_{10}H_{23}ClN_4O_4$) C, H, N, Cl.

[*R*-(*R,*R**)]-2-[2-Hydroxy-1-[6-[(1-methyl-2-phenylethyl)amino]-9*H*-purin-9-yl]ethoxy]-1,3-propanediol (23).** A solution containing 3.0 g (10.4 mmol) of the seco nucleoside obtained above, 2.16 g (16 mmol) of *l*-amphetamine, and 4.3 mL of triethylamine in 40 mL of absolute ethanol was heated at reflux under a drying tube (Drierite) for 16 h. The solution was concentrated to a brown oil, which was purified by flash chromatography (200 g, 10% methanol in chloroform) to yield 2.8 g of a white solid. Recrystallization from acetonitrile gave 2.0 g (50%) of a white crystalline solid: mp 115–116 °C; NMR (Me_2SO-d_6, 90 MHz) δ 2.19 (d, J = 3.0 Hz, 3 H), 2.74 (dd, J = 5.8, 2.9 Hz, 1 H), 3.0–3.7 (complex m, 7 H), 3.89 (t, J = 2.5 Hz, 2 H), 4.48 (t, J = 2.9 Hz, 1 H, ex), 4.72 (t, J = 3.0 Hz, 1 H, ex), 5.14 (t, J = 2.3 Hz, 1 H, ex), 5.91 (t, J = 3.0 Hz, 1 H), 7.1–7.4 (complex m, 5 H), 7.66 (d, J = 3.6 Hz, 1 H, ex), 8.22 (s, 1 H), 8.28 (s, 1 H); IR (KBr) 3600–3000 (br), 1620 (s), 1475 (m), 1115 (m); 1070 (m). Anal. ($C_{19}H_{25}N_5O_4$) C, H, N.

(*R*)-1-Deoxy-1-[6-[(1-methyl-2-phenylethyl)amino]-9*H*-purin-9-yl]-D-ribitol (27). (a) Glycosylation. A mixture of 7.58 g (47.1 mmol) of 6-chloropurine, 20 g (47.1 mmol) of diethyl ribose diethyl dithioacetal tetracetate,[45] 11.9 g (47.2 mmol) of mercuric cyanide, 6.39 g (29.6 mmol) of mercuric oxide, 4.0 g of calcium sulfate, and 380 mL of nitromethane was heated at reflux for 5 h, stirred overnight at room temperature, and then heated an additional 4 h at reflux. The mixture was filtered while hot and the cake was washed with 2 × 50 mL of hot nitromethane. After cooling, the solution was concentrated to a brown gum. The gum was extracted with several portions of hot chloroform, which were combined and filtered. The filtrate was washed three times with 30% aqueous potassium iodide and three times with water, dried, and concentrated to a brown oil. Flash chromatography (375 g, 25–75% ethyl acetate in hexane) produced the product as 14.7 g (59%) of an amber syrup containing an anomeric mixture of nucleosides.

(b) Hydrolysis. The nucleoside mixture (14.2 g, 29.6 mmol) was dissolved in 100 mL of methanol and treated with 0.5 g of potassium carbonate. After stirring 1 h, the solution was con-

(45) Zinner, H. *Chem. Ber.* **1950**, *83*, 418.

centrated to an off-white foam, 8.6 g (91%).

(c) Substitution. A mixture of 3.6 g (11.2 mmol) of the thionucleosides, 3.1 g (22.4 mmol) of *l*-amphetamine, and 5 mL of triethylamine in 80 mL of absolute ethanol was heated at reflux for 48 h. The mixture was cooled and concentrated to leave a clear viscous syrup, which was subjected to flash chromatography (140 g, 5% methanol in chloroform) to yield 3.1 g (62%) of an epimeric mixture of the 1′-ethylthio ribitol nucleosides. In addition, 1.25 g (35%) of the 6-chloropurine thionucleosides was recovered.

(d) Desulfurization. A solution of 2.7 g (6.0 mmol) of the thionucleosides in 30 mL of absolute ethanol was added to a stirred slurry of 55 g (wet paste) of Raney nickel[46] in 50 mL of ethanol and the mixture heated for 9 h at 70 °C. The mixture was then filtered while hot and the metal washed with 400 mL of hot ethanol. The filtrate was concentrated to yield 1.10 g (47%) of a white foam. To remove a trace of the starting material the product was subjected to flash chromatography (100 g, 5% methanol in chloroform) to yield 0.84 g (37%) of hygroscopic white foam: NMR (Me_2SO-d_6, 200 MHz) δ 1.19 (d, J = 6.5 Hz, 3 H), 2.78 (dd, J = 13.5, 6.4 Hz, 1 H), 3.06 (dd, J = 13.5, 7.4 Hz, 1 H), 3.42 (m, ~2 H partially obscured by water peak), 3.56 (m, 2 H), 3.95 (m, 1 H), 4.05–4.20 (m, 1 H), 4.45 (m, 2 H), 4.63 (br, 1 H), 4.72 (d, J = 5.0 Hz, 1 H), 5.02 (d, J = 3.1 Hz, 1 H), 5.04 (d, J = 3.1 Hz, 1 H), 7.15–7.42 (m, 6 H), 8.02 (s, 1 H), 8.18 (s, 1 H); IR (KBr) 3600–2800 (br), 1620 (s), 1480 (m), 1339 (m), 1299 (m). Anal. ($C_{19}H_{25}N_5O_4$) C, H, N.

***N*-Cyclohexyl[^{3}H]adenosine ([^{3}H]CHA) Binding in Rat Brain Membranes.** Rat brain (minus cerebellum and brain stem) membranes were prepared as described[11a] in the presence of adenosine deaminase. Incubations were in triplicate with 20 mg original tissue weight of membranes and 1 nM [^{3}H]CHA at 25 °C in 2 mL of 50 mM Tris-HCl at pH 7.7 with 0.1 unit/mL of adenosine deaminase (Sigma Type III) for 1 h alone or with test agents. The unbound [^{3}H]CHA was separated by rapid filtration under reduced pressure and the radiolabeled ligand retained by the filter was counted by liquid scintillation spectrophotometry. Specific binding for [^{3}H]CHA was determined as the total binding minus the binding obtained in the presence of 1 mM theophylline. IC_{50}'s were determined by the analysis of data from six doses which bracketed the IC_{50}, by the equation:

$$y = b - \frac{(b - n)c}{c + k}$$

where b = total binding, n = nonspecific binding, c = concentration of the drug, y = counts per minute, and $k = IC_{50}$. For all compounds, the Hill coefficient was close to 1.0, and the maximum extent of inhibition was the same as 1 mM theophylline. For compounds with IC_{50} values below 1 μM, IC_{50} determinations were performed at least twice. K_i values were calculated by multiplying IC_{50} values by 0.567, based on substituting a K_d of 1.31 nM for [^{3}H]CHA into the equation below where C is the concentration of [^{3}H]CHA:

$$K_i = \frac{IC_{50}}{1 + (C/K_d)}$$

[^{3}H]-1-(6-Amino-9*H*-purin-9-yl)-1-deoxy-*N*-ethyl-β-D-ribofuronamide ([^{3}H]NECA) Binding in Rat Striatal Membranes to Adenosine A_2 Receptors. [^{3}H]NECA binding to A_2 receptors[11d,37,39] was performed in the same way as [^{3}H]CHA binding with the following exceptions. The tissue was 5 mg original tissue wet weight of rat striatum, the radioligand was 4 nM [^{3}H]NECA, the volume was 1 mL, and the incubation contained 10 mM $MgCl_2$. A 50 nM concentration of *N*-cyclopentyladenosine was added to all incubations to eliminate A_1 binding of [^{3}H]NECA. Specific binding of [^{3}H]NECA was determined as the total binding minus the binding obtained in the presence of 100 μM *N*-cyclopentyladenosine. All active compounds had Hill coefficients close to 1.0 and gave the same maximal inhibition of [^{3}H]NECA binding as *N*-cyclopentyladenosine. K_i values were calculated by multiplying IC_{50} values by 0.674, based on substituting K_d values of 10.6 nM for [^{3}H]-NECA and 462 nM for *N*-cyclopentyladenosine into the equation below, where C_1 is the concentration of [^{3}H]NECA and C_2 is the concentration of CPA:

$$K_i = \frac{IC_{50}}{1 + (C_1/K_{d1}) + (C_2/K_{d2})}$$

Mouse Activity and Screen Test. Nine unfasted Swiss–Webster male mice (Buckberg Labs) weighing 20–30 g were equally divided into three groups for each drug dose tested. That is, data for each dose level were generated by three separate groups of three mice each. A minimum of three dose levels (10, 30, and 100 mg/kg) were tested for each drug. Treatments were administered intraperitoneally 1 h prior to testing. All dosages were calculated as parent compound and given in volumes of 10 mL/kg. Compounds were dissolved or suspended in 0.2% Methocel. Control animals were injected with Methocel. A two-part testing procedure was started 1-h postinjection. First, the screen test was performed.[38] Briefly this test consists of placing mice on individual wire screens, which are then rotated 180° at the start of a 60-s observation period. The number of mice falling off the inverted screen is recorded. Immediately following the screen test, the final phase of testing is initiated by placing each group of three mice in one actophotometer.[47] The actophotometer consists of a cylindrical chamber whose center is occupied by another cylinder which contains the illumination for six photocells located on the perimeter of the chamber. Six light-beam interruptions equals one count. Locomotor activity is recorded by computer at 10-min intervals for 60 min.

The data obtained from the screen test are expressed as percent of mice falling off the screen. Data derived from locomotor activity of drug-treated mice are compared to the activity of vehicle-treated animals and are expressed as percent inhibition of spontaneous locomotion. All percentages reported for inhibition of locomotion are based upon data accumulated for 1 h.

Determination of Blood Pressure and Heart Rate Effects. Male Sprague–Dawley rats (325–400 g) were anesthetized with sodium pentobarbital (50 mg/kg iv). Polyethylene catheters were inserted into the carotid artery (PE50) and jugular vein (PE10) for recording blood pressure and heart rate and for intravenous drug administration, respectively. Bilateral vagotomy was performed to minimize reflexogenic heart rate responses. A tracheal cannula was inserted, and the rats were respired with room air on a Harvard Apparatus Rodent Respirator. The tidal volume used was 2 mL and the cycle frequency was adjusted based upon body weight according to the Harvard Ventilation Chart. All surgical procedures are completed within 15 min following induction of anesthesia. A supplemental dose of sodium pentobarbital (50 mg/kg) was administered subcutaneously into the right flank upon completion of surgery, thereby eliminating the need for additional anesthetic during the course of the experiment. Body temperature was monitored with a rectal thermistor thermometer and was maintained between 37 and 38 °C with a heating pad. A 20-min stabilization period was allowed after surgery. All drugs were administered intravenously as solutions in a volume of 1 mL/kg. The preferred vehicle was 0.9% saline, but, when necessary, the test compound was initially dissolved in a few drops of 1 N HCl, 1 N NaOH, and/or 100% ethanol before dilution in 0.9% saline. Rising doses of the test agent were administered intravenously over 2 min at 10-min intervals. Successive doses of the test agent were given in log or half-log increments starting at 0.3 μg/kg and continuing up to 10 mg/kg until a dose was reached where either blood pressure decreased to ≤50 mmHg and/or heart rate decreased to ≤150 beats/min and remained at that level for at least 10 min after dose. Blood pressure and heart rate responses were measured 5 min after each dose and results expressed as percent of the initial control values. ED_{20} values, defined as doses that produced 20% decreases in mean blood pressure or heart rate, were determined graphically from these data.

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