Search for New Purine- and Ribose-Modified Adenosine Analogues as Selective Agonists and Antagonists at Adenosine Receptors†

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The binding affinities at rat A_1, A_{2a}, and A_3 adenosine receptors of a wide range of derivatives of adenosine have been determined. Sites of modification include the purine moiety (1-, 3-, and 7-deaza; halo, alkyne, and amino substitutions at the 2- and 8-positions; and N^6-CH_2-ring, -hydrazino, and -hydroxylamino) and the ribose moiety (2′-, 3′-, and 5′-deoxy; 2′- and 3′-O-methyl; 2′-deoxy 2′-fluoro; 6′-thio; 5′-uronamide; carbocyclic; 4′- or 3′-methyl; and inversion of configuration). (−)- and (+)-5′-Noraristeromycin were 48- and 21-fold selective, respectively, for A_{2a} vs A_1 receptors. 2-Chloro-6′-thioadenosine displayed a K_i value of 20 nM at A_{2a} receptors (15-fold selective vs A_1). 2-Chloroadenin-9-yl(β-L-2′-deoxy-6′-thiolyxofuranoside) displayed a K_i value of 8 μM at A_1 receptors and appeared to be an antagonist, on the basis of the absence of a GTP-induced shift in binding vs a radiolabeled antagonist (8-cyclopentyl-1,3-dipropylxanthine). 2-Chloro-2′-deoxyadenosine and 2-chloroadenin-9-yl(β-D-6′-thioarabinoside) were putative partial agonists at A_1 receptors, with K_i values of 7.4 and 5.4 μM, respectively. The A_{2a} selective agonist 2-(1-hexynyl)-5′-(*N*-ethylcarbamoyl)adenosine displayed a K_i value of 26 nM at A_3 receptors. The 4′-methyl substitution of adenosine was poorly tolerated, yet when combined with other favorable modifications, potency was restored. Thus, N^6-benzyl-4′-methyladenosine-5′-(*N*-methyluronamide) displayed a K_i value of 604 nM at A_3 receptors and was 103- and 88-fold selective vs A_1 and A_{2a} receptors, respectively. This compound was a full agonist in the A_3-mediated inhibition of adenylate cyclase in transfected CHO cells. The carbocyclic analogue of N^6-(3-iodobenzyl)adenosine-5′-(*N*-methyluronamide) was 2-fold selective for A_3 vs A_1 receptors and was nearly inactive at A_{2a} receptors.

Introduction

The adenosine receptors are members of the superfamily of receptors coupled to guanyl nucleotide-binding proteins (G-proteins). The are composed of seven transmembrane helical domains.[1] Adenosine mediates a wide variety of physiological functions including vasodilatation, vasoconstriction in the kidney, cardiac depression, inhibition of lipolysis, inhibition of platelet aggregation, inhibition of lymphocyte functions, inhibition of insulin release and potentiation of glucagon release in the pancreas, inhibition of neurotransmitter release from nerve endings, stimulation of steroidogenesis, and potentiation of histamine release from mast cells.[1-5] The A_1, A_{2a}, A_{2b}, and A_3 adenosine receptors have been cloned from several species, including in each case rat, dog, mouse, and human.[6] Activation of A_1 and A_3 receptors causes the inhibition of adenylate cyclase, activation of phospholipase C, activation of potassium channels, and inhibition of calcium channels.[4,5] The A_{2a} and A_{2b} receptors activate adenylate cyclase via G-protein coupling.[5]

Numerous structure–activity relationship studies of adenosine responses have been published (see ref 1). The objectives of these studies have been to discover highly potent analogues of adenosine, long-acting and nonmetabolizable agonists and antagonists, and analogues which are specific for a subtype of adenosine receptors. The recent discovery of the novel rat A_3 adenosine receptor subtype[7] prompted us to undertake a detailed examination of a variety of nucleoside analogues as ligands for A_3 and other adenosine receptors. Agents selective for A_3 receptors[8-10] have promise as agents for treating ischemia of the brain and heart,[11,12] inflammation, and asthma.[13] This study is a survey of some known and some novel modifications of adenosine to identify structural changes that result in selectivity.

Since some adenine and adenosine derivatives have been shown to be adenosine receptor antagonists,[15,26]

† Abbreviations: AB-MECA, N^6-(4-aminobenzyl)adenosine-5′-(*N*-methyluronamide; CGS 21680, 2-[[[4-(2-carboxyethyl)phenyl]ethyl]-amino]-5′-(*N*-ethylcarbamoyl)adenosine; CHA, N^6-cyclohexyladenosine; CHO, Chinese hamster ovary; CPA, N^6-cyclopentyladenosine; CPX, 8-cyclopentyl-1,3-dipropylxanthine; DMAP, 4-(dimethylamino)pyridine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; EtOH, ethanol; HE-NECA, 2-(1-hexynyl)-5′-(*N*-ethylcarbamoyl)adenosine; HMDS, hexamethyldisilazane; MeOH, methanol; MeCN, acetonitrile; NECA, 5′-(*N*-ethylcarbamoyl)adenosine; PIA, (*R*)-N^6-(phenylisopropyl)-adenosine; THF, tetrahydrofuran; TMS, trimethylsilyl; TMS-OTf, trimethylsilyl trifluoromethanesulfonate; Tris, tris(hydroxymethyl)-aminomethane.

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we have examined potential new leads for adenosine derivatives as selective antagonists. A selective antagonist at the rat A_3 receptor is lacking. Several xanthine analogues that act as the potent antagonists at rat, rabbit, and human A_1 and A_2 receptors only weakly displaced the binding of radioligand from cloned rat A_3 receptors.[16]

Results

Chemistry. Adenosine analogues containing a variety of structural modification (compounds **1**−**44**) were examined in this study. The affinity of the adenosine analogues at A_1, A_{2a}, and A_3 receptors was established in binding assays[17−19] (Table 1). Physical data for new adenosine analogues are listed in Table 2. Compounds **10b**[24b] and **12b**[52] were prepared according to literature-known procedures.

The synthesis of the carbocyclic derivative **12c** is shown in Scheme 1. Using a procedure that has been employed to couple cyclopentyl acetates with nucleophiles in the presence of Pd(0) catalysis to give *cis*-oriented products,[20] reaction of (+)-**45** with 2,6-dichloropurine gave (+)-**46**. Standard vicinal glycolization of (+)-**46** to (−)-**47** was followed by exchanging the 6-chloro group with NH_4OH to give **48**. Heating **48** with phenylethylamine gave **12c**.

3′-*C*-Methyladenosine, **29a**, and 4′-*C*-methyladenosine, **29b**, were prepared according to known procedures.[49,50] The 4′-*C*-methyl modification was combined with other substitutions known to favor A_3 selectivity (Scheme 2). The methyl 4-methyl-D-ribofuranoside uronate **49** was prepared previously as an intermediate in the chemoenzymatic synthesis of methyl 4-methyl-D-ribofuranoside from cyclopentadiene.[21] This methyl uronate was transformed into the corresponding nucleoside. Direct amidation proceeded smoothly with methylamine in MeOH to give the methyl amide **50**, which was converted to the diacetate **51** by treatment with HCl/MeOH and acetylation with acetic anydride and pyridine. When the β-methyl glycoside **51** was subjected to Vorbrüggen conditions[22] (N^9-TMS-6-chloropurine, TMS-OTf, CH_3CN, 50 °C), a significant amount of the α-nucleoside was initially formed even though the 2-acetyl group is β-directing. Apparently the carbonyl of the uronamide can participate as an α-director. However, upon heating to 80 °C for 6−12 h, the thermodynamically more stable β-nucleoside **52** was formed in good yield as the sole product. When the displacement of the chloro group with benzylamine was conducted in methanol at 70 °C, 1−2% of the 6-methoxy derivative contaminated the product. The use of *tert*-butyl alcohol instead of methanol as cosolvent suppressed this type of reaction and gave clean *N*-benzyladenosinuronamide **41**.

An N^6-substituted 5′-uronamide, **42**, was synthesized following the approach of Gallo-Rodriguez et al.[8] via the action of furfurylmethylamine on 6-chloropurine-5′-(*N*-methyluronamido)riboside 2′,3′-dimethylacetal, **53**. Deblocking the 2′,3′-dimethylacetal protecting group was sluggish due to the acid-sensitive nature of the furfuryl group.

The synthesis of the carbocyclic analogue (±)-**44** (Scheme 3) began by heating (±)-**54** with methylamine to provide (±)-**55**. Reaction of **55** with 5-amino-4,6-dichloropurine gave intermediate **56**. Heating **56** with methyl dimethoxyacetate followed by acidic treatment gave **57**. The 6-chloro group of **57** was displaced by 3-iodobenzylamine to give **44**.

Synthesis of **12a** (Scheme 4) was accomplished by employing a standard procedure for preparing carbocyclic nucleosides.[56] Thus, reaction of (±)-*trans*-2-aminocyclopentanol with 2-amino-4,6-dichloropyrimidine yielded **65**, which was subjected to C-5 diazo coupling with 4-(chlorophenyl)diazonium chloride to result in **66**. Completion of the preparation of **12a** followed a routine sequence:[56] reduction of **66** to amine **67**, ring closure with trimethyl orthoformate to prepare precursor **68**, and, finally, displacement of chlorine by ammonia to give **12a**.

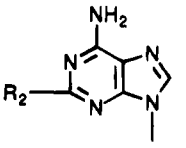
The synthesis of the carbocyclic **15b** began with the reaction of *N*-[4-(1-butyl)phenyl]guanidine nitrate with diethyl allylmalonate to give **58** (Scheme 5) plus a small amount of the isomeric **59**.[53] To achive successful chlorination of **58** to **60**, it was necessary to add tetraethylammonium chloride to the phosphorus oxychloride. In our hands, the standard ozonolysis approach for converting the allyl side chain of **60** to the acetaldehyde substituent of **61** could not be accomplished, apparantly due to susceptibility of the arylamino side chain to the reaction conditions. Thus, treatment of **60** with osmium tetraoxide in the presence of sodium periodate yielded **61** that was, in turn, readily converted into its dimethyl acetal derivative **62**. Reaction of **62** with (±)-4α-amino-2β,3α-dihydroxy-1α-cyclopentanemethanol[54] provided **63**. The latter product was not fully characterized but was ring closed under acidic conditions to **64** that was then converted into the target derivative **15b** by heating with methanolic ammonia.

Biology. 2-Chloroadenosine, **1**, was much more potent than 1-deaza-2-chloroadenosine, **2**, at A_1 receptors and nearly equipotent at A_3 receptors. Thus, the 1-deaza modification is well tolerated at rat A_3 receptors. Among 2-halo analogues, the difference in affinity between 2-chloro- and 2-fluoroadenosine was most pronounced at A_3 receptors, at which the 2-fluoro analogue **3** was 5.5-fold less potent. As shown previously, certain 8-position substitution, such as bromo, **4**, was not well tolerated at A_3 receptors, and the potencies of the 8-amino and 8-butylamino analogues[23] **5** and **6**, respectively, were consistent with this observation. There was a slight tendency toward A_{2a} selectivity among compounds **4**−**6**.

Carbocyclic nucleosides have found wide application in the antiviral area.[24] At adenosine receptors, there are few reports of the affinity of carbocyclic derivatives of adenosine. Francis et al.[25] reported that the carbocyclic analogue of CGS 21680, an A_{2a} selective agonist, retained that selectivity. Racemic aristeromycin was reported to have activity at A_{2b} receptors.[26] Enantiomerically pure aristeromycin, **7**, isolated from *Streptomyces citricolor*,[27] showed essentially no displacement of radioligand from A_1 or A_{2a} receptors but was weakly potent at A_3 receptors. The 5′-deoxy modification of adenosine, shown previously to be tolerated at A_1, A_{2a}, and A_3 receptors, was somewhat compatible with the carbocyclic modification at A_{2a} and A_3 receptors. 5′-Deoxyaristeromycin,[28] **9**, was only 7-fold less potent than 5′-deoxyadenosine, **8**, at A_{2a} receptors and of comparable potency to aristeromycin, **7**, at A_3 receptors. Curiously, by deleting the 5′-methylene group of aristeromycin, as in compound **10a** ((−)-5′-noraristeromycin), the potency was greatly enhanced at A_1 and A_{2a}

Table 1. Affinities of Adenosine Derivatives in Radioligand Binding Assays at Rat Brain A_1, A_{2a}, and A_3 Receptors[a-c,g]

a. Non-N^6-substituted Derivatives



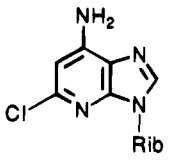
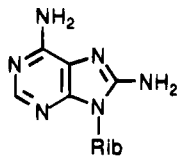
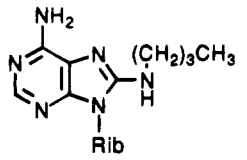
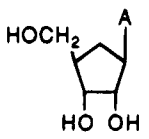
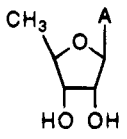
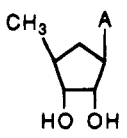
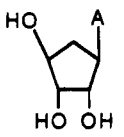
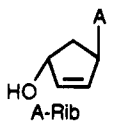
Compound	Structure	R_2=	$K_i(A_1)$[a]	$K_i(A_{2a})$[b]	$K_i(A_3)$[c]	Reference
			K_i (μM) or % displacement at 10^{-4} M[g]			
1	A-Rib	Cl	0.0093	0.063	1.89[d]	9
2		-	0.226 ±0.028	0.163 ±0.040	2.48±0.36	42
3	A-Rib	F	0.0059	0.028	10.4±2.3	43
4		-	41%	22.7	31%[d]	9
5		-	53%[h]	24.1	26%	23,38
6		-	11.4[h]	11.5	31%	23,38
7		H	3±1%	0%	200±8	-
8		H	0.269	0.596	2.83[d]	9
9		H	12±4%	4.30±0.41	66±2%	28
10a		H	33.0±6.8	0.692 ±0.096	68±1%	20,24
10b		H	37±7%	41.4±11.0	122±17	24b
11	A-Rib	ϕ-$(CH_2)_2$ NH-	0.98[e] (IC_{50})	0.068[f] (IC_{50})		25

Table 1 (Continued)

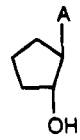
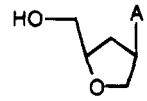
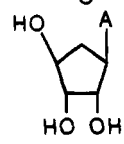
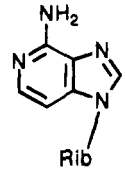
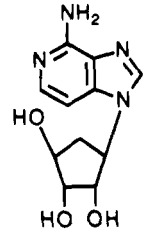
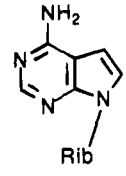
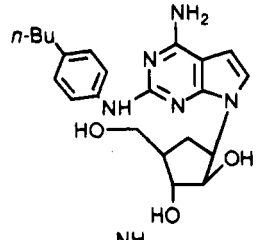
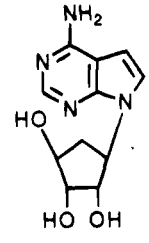
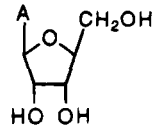
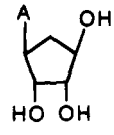
Compound	Structure	R_2=	K_i (μM) or % displacement at 10^{-4} M[e] $K_i(A_1)$[a]	$K_i(A_{2a})$[b]	$K_i(A_3)$[c]	Reference
12a		NH_2	30±1%	20.8±3.7	199±26	-
12b		NH_2	0%	16±5%	198±33	52
12c[j]		ϕ-$(CH_2)_2$ NH-	0.946 ±0.179	1.82±0.20[i]	59.2±9.2	-
13		-	21.5	59.8	61.7[d]	9
14[j]		-	4%	8%	20%	44
15a		-	>100	48%	39%[d]	9
15b		-	29±6%	11±2%	70.4±2.2	-
16[j]		-	0%	8%	19%	20,44
17		H	29.0	25%	10%[d]	9
18		H	180±40	8.54±1.77	24±1%	24

Table 1 (Continued)

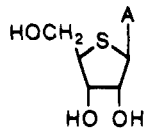
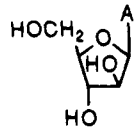
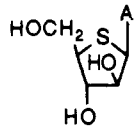
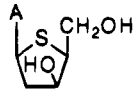
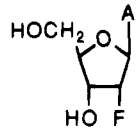
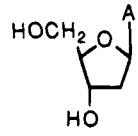
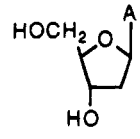
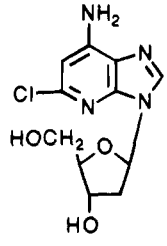
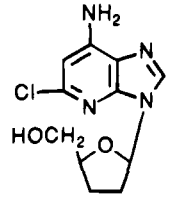
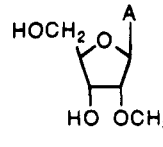
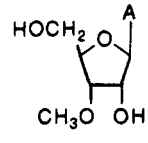
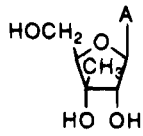
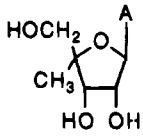
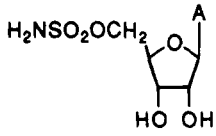
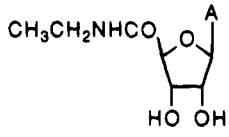
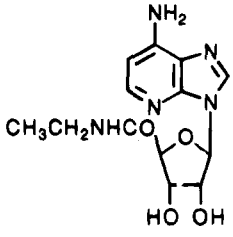
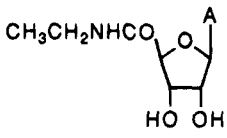
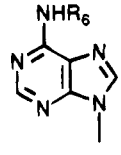
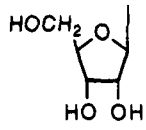
Compound	Structure	R_2 =	K_i (μM) or % displacement at 10^{-4} M[a] $K_i(A_1)$[a]	$K_i(A_{2a})$[b]	$K_i(A_3)$[c]	Reference
19		Cl	0.300 ±0.053	0.0198 ±0.0046	1.09±0.11	29
20		H	20%	26%	24%[d]	9
21		Cl	5.36±0.87	7.12±1.36	49.3±2.2	29
22		Cl	7.99±1.38	12.8±2.4	32%	29
23		Cl	0.640 ±0.107	0.897 ±0.178	82.4±5.2	30
24		H	31%	39%	28%[d]	9
25		Cl	7.32±0.96	20.4±3.5	207±8	46
26		-	29.0±4.4	35±3%	21%	31
27		-	101±19	55.5±2.8	16%	32
28a		H	29%	49%	43%[d]	9
28b		H	0%	8%	11%	-

Table 1 (Continued)

Compound	Structure	R_2 =	$K_i(A_1)$[a]	$K_i(A_{2a})$[b]	$K_i(A_3)$[c]	Reference
			K_i (μM) or % displacement at 10^{-4} M[a]			
29a		H	51.0±5.5	13%	9%	49
29b		H	3%	0%	8%	50
30i		H	1.03±0.05	5.00±1.63	11.0±1.9	34
31		H	0.063	0.0103	0.113[d]	9
32		-	0.051	0.58[f]	0.703 ±0.035	35
33		C≡C-$(CH_2)_3CH_3$	0.130[e]	0.0022	0.0256 ±0.0032	36

b. N^6-Substituted Derivatives

A=  **Rib=** 

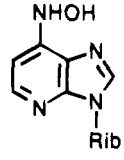
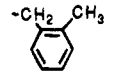
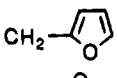
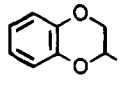
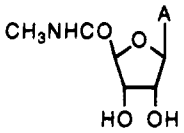
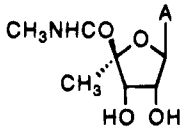
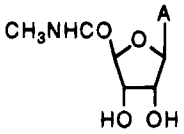
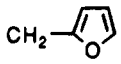
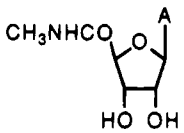
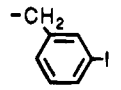
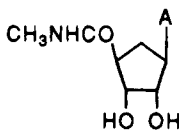
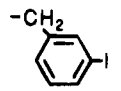
Compound	Structure	R_6 =	$K_i(A_1)$[a]	$K_i(A_{2a})$[b]	$K_i(A_3)$[c]	Reference
34	A-Rib	H_2N-	29.7±6.6	7.34±1.12	16.9±1.3	-
35		–	9.4[h]	10	56% (10^{-4})	48
36	A-Rib	φCH_2-	0.120	0.285	0.120[d]	9
37	A-Rib		0.0596 ±0.0143	0.0241 ±0.0018	0.36±0.21	37
38	A-Rib		0.236 ±0.005	0.129 ±0.039,	0.742 ±0.312	45
39	A-Rib		0.042 ±0.013	0.293 ±0.077	1.48 ±0.41	-

Table 1 (Continued)

Compound	Structure	R_6=	$K_i(A_1)$[a]	$K_i(A_{2a})$[b]	$K_i(A_3)$[c]	Reference
40		ϕCH_2-	0.898	0.597	0.016[d]	9
41		ϕCH_2-	62.4±6.1	53.6±14.6	0.604 ±0.143	21
42			8.61±2.55	6.22±2.71	0.720 ±0.250	-
43			0.054	0.056	0.0011	8
44			35.9±8.3	28±5%	19.5 ±4.7	-

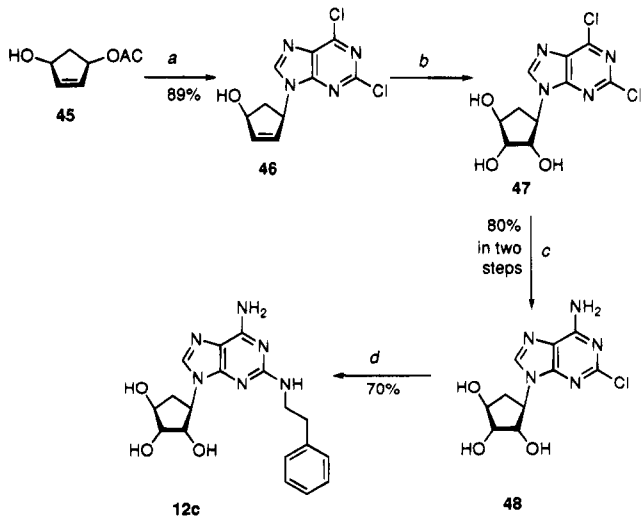
[a] Displacement of specific [^{3}H]PIA binding, unless noted, in rat brain membranes expressed as K_i ± SEM in μM (n = 3–6), or as a single average value if from a literature report. [b] Displacement of specific [^{3}H]CGS 21680 binding, unless noted, in rat striatal membranes expressed as K_i ± SEM in μM (n = 3–6), or as a single average value if from a literature report. [c] Displacement of specific binding of [^{125}I]-N^6-(4-amino-3-iodobenzyl)adenosine-5′-(*N*-methyluronamide),[19] unless noted, in membranes of CHO cells stably transfected with the rat A_3-cDNA expressed as K_i ± SEM in μM (n = 3–7). [d] Displacement of specific binding of [^{125}I]-N^6-(4-amino-3-iodophenethyl)adenosine[9] in membranes of CHO cells stably transfected with the rat A_3-cDNA expressed as K_i ± SEM in μM (n = 3–5). [e] Displacement of specific [^{3}H]-N^6-cyclohexyladenosine binding in rat brain membranes. [f] Displacement of specific [^{3}H]-5′-(*N*-ethylcarbamoyl)adenosine binding in rat striatal membranes. [g] When a percentage is given, it refers to the percent displacement of radioligand binding at 10^{-4} M. [h] Displacement of specific [^{3}H]-8-cyclopentyl-1,3-dipropylxanthine binding in rat brain membranes. [i] Radioligand binding increased at 10^{-4} M. [j] DMSO stock solution made fresh before assay.

Table 2. Characterization of Newly Synthesized Compounds

comp no.	formula	analysis	mp (°C)
12a	$C_{10}H_{14}N_6O$	C, H, N	214–215
12c	$C_{18}H_{22}N_6O_3$	C, H, N	200
15b	$C_{22}H_{29}N_5O_3 \cdot 2\ H_2O$	C, H, N	210–213
21	$C_{10}H_{12}ClN_5O_3S$	C, H, N	207
22	$C_{10}H_{12}ClN_5O_2S$	C, H, N	171–173
39	$C_{19}H_{22}N_5O_6 \cdot 0.5\ H_2O$	C, H, N	176–178
41	$C_{19}H_{22}N_6O_4$	C, H	125–130 (dec)
42	$C_{16}H_{17}N_6O_5$	C, H, N	200–203
44	$C_{19}H_{21}IN_6O_3$	C, H, N	foam
46	$C_{10}H_8Cl_2N_4O$	C, H, N	foam
48	$C_{10}H_{12}ClN_5O_3$	C, H, N	180
50	$C_{11}H_{19}NO_5$	C, H	oil
β-51	$C_{12}H_{19}NO_7$	C, H	oil
52	$C_{16}H_{18}ClN_5O_6$	C, H	foam
57	$C_{12}H_{14}ClN_5O_3$	C, H, N	foam
58	$C_{17}C_{21}N_3\ O_2 \cdot H_2O$	C, H, N	211–212
60	$C_{17}H_{19}Cl_2N_3$	C, H, N	70–72
61	$C_{16}H_{17}Cl_2N_3O$	C, H, N	80
62	$C_{18}H_{23}Cl_2N_3O_2$	C, H, N	52–55
64	$C_{22}H_{27}ClN_4O_3 \cdot H_2O$	C, H, N	172–175
65	$C_9H_{13}ClN_4O$	C, H, N	171–173
66	$C_{15}H_{16}Cl_2N_6O$	C, H, N	
68	$C_{10}H_{12}ClN_5O$	C, H, N	197–198

receptors. The K_i value of **10a** at A_{2a} receptors was 0.69 μM, and there was also selectivity vs A_1 (48-fold) and A_3 receptors. This prompted us to synthesize an analogue which contained a 2-(2-phenylethyl)amino group, found previously to be conducive to A_2 selectivity,[18,25] as in compound **11**. The two sets of modifications however were not additive at A_{2a} receptors, and the

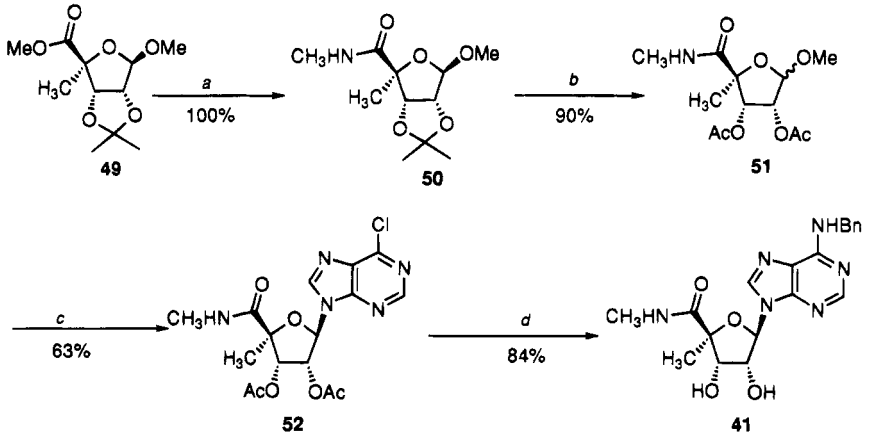
Scheme 1. Synthesis of Compound **12c**[a]



[a] Reaction conditions: (a) (i) NaH, 2,6-dichloropurine, THF, 0 °C; (ii) $Pd(PPh_3)_4$, PPh_3, 45, THF, 50 °C; (b) OsO_4, *N*-methylmorpholine *N*-oxide, THF/H_2O; (c) NH_4OH, MeOH; (d) phenylethylamine, EtOH, Et_3N, reflux.

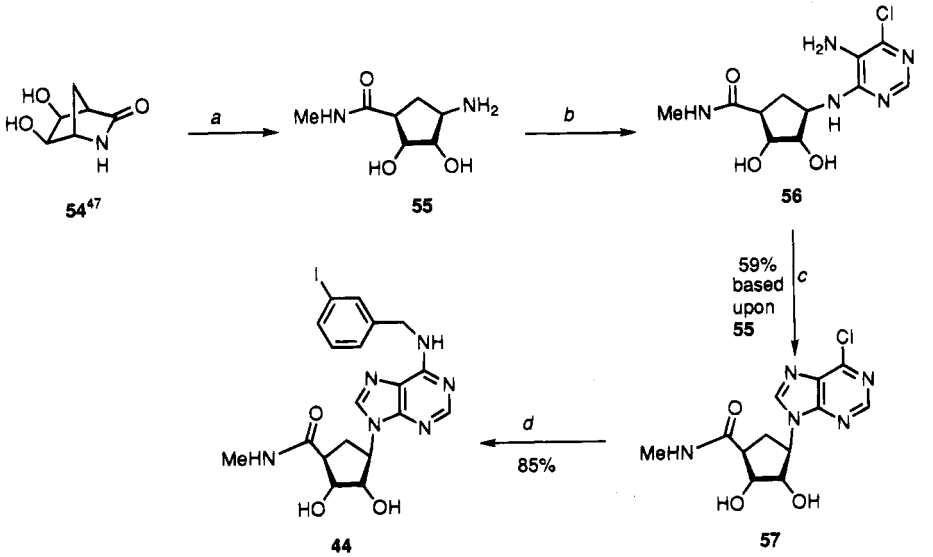
hybrid compound **12c** was nearly equipotent at A_1 and A_{2a} receptors. With the 2-(2-phenylethyl)amino group, there was no decrease in affinity at A_1 receptors from the 5′-norcarbocyclic modification. The same carbocyclic modification nearly abolished affinity at all adenosine receptors when combined with the 3-deaza modification

Scheme 2. Synthesis of Uronamide **41**[a]



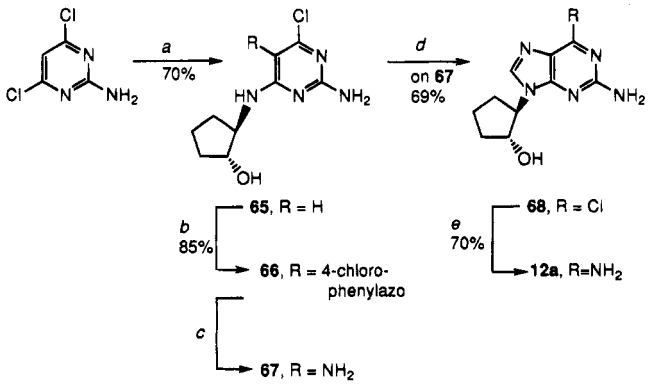
[a] Reaction conditions: (a) $MeNH_2$, MeOH; (b) (i) HCl, MeOH, (ii) Ac_2O, py; (c) N-TMS-6-Cl-purine, TMS-OTf, CH_3CN; (d) (i) NH_3, MeOH, 0 °C, (ii) $BnNH_2$, *t*-BuOH.

Scheme 3. Synthesis of Carbocyclic IB-MECA, **44**[a]



[a] Reaction conditions: (a) $MeNH_2$, THF, heat; (b) 5-amino-4,6-dichloropyrimidine, *n*-BuOH, Et_3N; (c) (i) $(MeO)_2CHOAc$, reflux, (ii) 1 N HCl; (d) 3-I-$PhCH_2NH_2$·HCl, Et_3N, EtOH, heat.

Scheme 4. Synthesis of Compound **12a**[a]

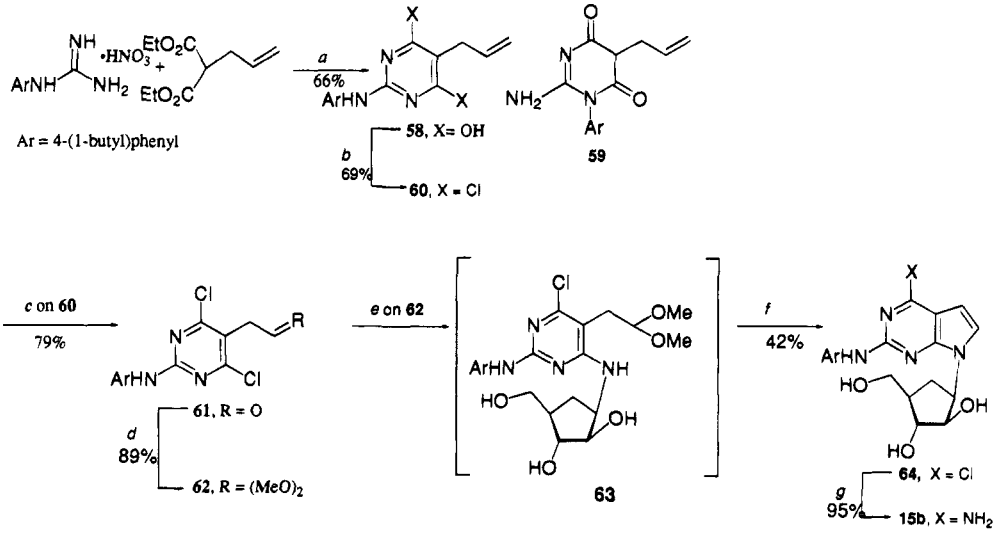


[a] Reaction conditions: (a) (±)-*trans*-2-aminocyclopentanol,[57] reflux in 1-BuOH; (b) (4-chlorophenyl)diazonium chloride; (c) Zn in AcOH/EtOH/H_2O, reflux; (d) $(MeO)_3CH$, concentrated HCl; (e) NH_3 in MeOH.

(cf. **13** and **14**). Didehydrodideoxy and dideoxy analogues of carbocyclic nucleosides **10b**[24b] and **12a** were inactive at A_1, and they were marginally active at A_{2a} and A_3 receptors. Dideoxy-3-oxa derivative **12b**[52] was nearly inactive at A_1 receptors, but it showed very weak binding affinity to A_{2a} and A_3 receptors. 3-Deazaadenosine, **13**, itself, was only weakly potent at the three subtypes. Similarly 7-deazaadenosine, **15a**, was only marginally potent, and in combination with the 5′- and carbocyclic modifications was essentially inactive in binding. 7-Deaza-2-(phenylbutyl)-*ara*-aristeromycin, **15b**, was only weakly potent at the three sybtypes, and there was also selectivity for A_3 vs A_1 and A_{2a} receptors.

β-L-Adenosine, compound **17**, was shown to bind weakly to A_1 receptors.[9] Curiously, compound **18** ((+)-5′-noraristeromycin), the L-analogue of compound **10a**, showed considerable potency at A_{2a} (>A_1 and A_3) receptors and was 21-fold selective for A_{2a} vs A_1 receptors. The 6′-thio modification of adenosine[29] was well tolerated in receptor binding. (The position corresponding to the carbohydrate 4′-oxygen is here numbered 6′, as in carbocyclic derivatives.) Compound **19** was 3.2-fold more potent than the corresponding oxygen analogue **1** at A_{2a} receptors, while at A_1 receptors affinity diminished by 32-fold. Compounds **1** and **19** were of similar potency at A_3 receptors. Thus, this thio modification, which provided 15-fold selectivity in **19**, may serve as a means of increasing A_{2a} selectivity in general. The 6′-thio and 2-chloro modifications of the arabinoside resulted in a substantial gain in potency at all three subtypes (cf. **21** and **20**). Surprisingly, even the 2′-

Scheme 5. Synthesis of 2-[[4-(1-Butyl)phenyl]amino]-*ara*-aristeromycin, **15b**[a]



[a] Reaction conditions: (a) NaOEt, EtOH; (b) $POCl_3$, Et_4NCl, *N,N*-diethylaniline in MeCN, 70 °C then 100 °C; (c) OsO_4, $NaIO_4$ in MeOH, acetone, H_2O; (d) NH_4Cl, pyridinium *p*-toluenesulfonate in absolute MeOH; (e) (±)-4a-amino-2β,3α-dihydroxy-1α-cyclopentanemethanol[54] in *n*-BuOH containing ET_3N, heat; (f) 2 N HCl in 1,4-dioxane; (g) NH_3–MeOH, heat.

deoxy-6′-thio-L-xylofuranoside analogue **22** had potency comparable to **21** at A_1 and A_{2a} receptors.

Compounds **23**–**29** contain 2′- and 3′-ribose modifications. The 2′-deoxy-2′-fluoro modification of 2-chloroadenosine,[30] **23**, had K_i values at A_1 and A_{2a} receptors in the micromolar range and was 2 orders of magnitude less potent at A_3 receptors. The degree of tolerance of the 2′-fluoro substituent (cf. compound **1**) was greatest at A_{2a} receptors. The corresponding 2′-deoxy analogue **25**[46] was less potent than **23** at A_1 and A_{2a} receptors by factors of 11 and 23. Thus at the 2′-position substituents in the order OH > F > H are favored in receptor binding at all three subtypes. For purposes of this comparison, it was essential to have the potency-enhancing 2-chloro substituent in order to obtain measurable K_i values (cf. compound **24**, which was nearly inactive).

The 1-deaza modification of adenosine was already shown to be tolerated in receptor binding (see compound **2**).[42] Deletion of the 2′-hydroxy group of **2**, resulting in compound **26**, was poorly tolerated in receptor binding.[31,32] Only at A_1 receptors was there a measurable K_i value (29 μM). Deletion of both 2′- and 3′- hydroxyl groups, as in compound **27**, resulted in a 3-fold loss of potency at A_1 receptors (vs **26**) and an apparent slight gain in affinity at A_{2a} receptors.

The 2′-methoxy derivative of the A_1-selective agonist N^6-cyclohexyladenosine (CHA) has been reported by Wagner et al.[33] to have substantial *in vivo* activity, perhaps as a prodrug of CHA. We have evaluated methoxy derivatives of adenosine at the three subtypes and found the 3′-derivative **28a** to be nonselective and of very weak affinity and the 2′-derivative **28b** to be inactive. The inclusion of methyl groups in place of hydrogen in the ribose ring was examined in compounds **29a,b**. The 3′-methyl analogue **29a** bound weakly with A_1 selectivity, while the 4′-methyl analogue **29b** was virtually inactive.

Limited modification of the 5′-position of adenosine is tolerated at adenosine receptors. NECA, **31**, has long been known as a highly potent, nonselective agonist.[1] A cytotoxic aminosulfonate derivative **30**[34] was much less potent than NECA, with K_i values in the 1–10 μM range. 1-Deaza-NECA, **31**, as reported previously,[35] has substantial activity at A_1 receptors, and at A_{2a} and A_3 receptors, the potencies vs those of NECA are diminished by factors of 56- and 6-fold. Thus, at A_{2a} and A_3 receptors, the 1-deaza substitution is tolerated better in the 2-chloro series (cf. compounds **1** and **2**), while at A_1 receptors, the 1-deaza modification is tolerated better in the uronamide series. The addition of the 2-hexynyl group to NECA, resulting in the A_{2a} selective agonist compound **33** (HE-NECA), previously studied in platelets and on the coronary artery,[36] enhanced the A_3 potency. Thus, the order of selectivity of HE-NECA (with K_i values in nM) is A_{2a} (2.2) > A_3 (25.6) > A_1 (130).

Numerous modifications of the N^6-position of adenosine have been introduced and shown to result generally, but not exclusively, in A_1 selectivity.[1] Table 1b shows a comparison of affinities of a variety of N^6-substituted analogues. 6-Hydrazinopurine riboside, **34**, had K_i values in the 10^{-5} M range and was nearly nonselective for $A_1/A_{2a}/A_3$ receptors. 1-Deaza-6-(hydroxylamino)-purine riboside, **35**, also bound weakly but was 1 order of magnitude selective for A_1 and A_{2a} vs A_3 receptors. The affinity of adenosine, itself, for comparison with these compounds is difficult to evaluate, due to the presence of adenosine deaminase in the medium.

At A_3 receptors, N^6-benzyl substituents, as in **36**, have been shown to be favored. Several other known N^6-arylmethylene analogues were studied. Metrifudil, **37**, a potent hypotensive agent, which had entered human trials in the early 1970's,[37] was found to be 2.5-fold selective for rat A_{2a} vs A_1 receptors and 15-fold selective for rat A_{2a} vs A_3 receptors. The affinity of **37** was enhanced 12-fold and diminished 3-fold at A_{2a} and A_3 receptors, respectively, by the presence of the 2-methyl group on the benzyl ring. (−)-Kinetin riboside,[45] **38**, was also slightly selective for A_{2a} receptors, although 5-fold less potent than metrifudil. An N^6-bicyclic methylene analogue, **39**, was slightly selective for A_1 receptors.

N^6-Benzyl-NECA was the first A_3 selective agonist identified,[9] although it was only 14-fold selective verses either A_1 or A_{2a} receptors. The corresponding *N*-methyl analogue **40** had enhanced potency and selectivity.[8] A 4′-methyl analogue, **41**, displayed even greater selectiv-

Table 3. Displacement of the Antagonist Radioligand [^{3}H]CPX and the Degree of Shift of the Displacement Curve in the Presence of 1 mM GTP

	K_i value (μM) or % displacement at 10^{-4} M[a]		
compd	A_1 (−GTP)	A_1 (+GTP)	GTP Shift[b]
10a	40	nd	
12c	35	nd	
18	36	nd	
21	13	30	2.3
22	8.4	12	1.4
23	1.7	8.3	4.9
25	12	21	1.7
26	31	nd	
27	37	nd	
28b	12	nd	

[a] Average of two determinations. nd = not determined. [b] Ratio of K_i values in the presence and absence of GTP.

ity, although it was 38-fold less potent than **40** at A_3 receptors. Compound **41** was 100- and 89-fold selective for A_3 vs A_1 and A_{2a} receptors, respectively. Curiously, the affinity of **41** is in contrast to the inactivity of the simple 4′-methyladenosine derivative **29b**. The combination of the 5′-*N*-methyluronamide group with the N^6-furfuryl group of kinetin riboside resulted in an A_3-selective compound, **42**, of micromolar affinity.

A selective A_3 agonist that has been studied *in vivo* is IB-MECA, **43**.[10,11] The carbocyclic analogue of IB-MECA, **44**, was weakly binding and more potent at A_1 and A_3 vs A_{2a} receptors. IB-MECA, **43**, was 18 000-fold more potent than this carbocyclic analogue at A_3 receptors.

Since many of the adenosine derivatives diverge greatly in structure from adenosine itself, it was not to be assumed that all of the compounds found to bind to the receptors were agonists. Previously, removal of the 2′ and 3′-hydroxyl groups of N^6-substituted adenosine derivatives was shown to result in partial agonist or antagonist properties.[15,38] Therefore we tested selected analogues for A_1 agonist efficacy using a straight forward binding method. GTP shifts in the displacement curves for agonist verses antagonist have been shown to be indicative of agonist.[38] Thus, we examined the ability of selected analogues to displace the antagonist radioligand [^{3}H]CPX and the degree of shift of the displacement curve in the presence of 1 mM GTP, and the results are given in Table 3. For agonists a typical shift in the K_i value is >2-fold. Full agonists, such as (*R*)-PIA and CPA, under the same conditions give shifts of 5.5 and 6.0, respectively. For pure antagonists, no shift or only a very small shift is expected. For example, the value for the A_1 adenosine antagonist 9-methyladenine[14] is 1.2. Compound **22** appears to be in the antagonist range, which is consistent with its highly unnatural carbohydrate moiety. Compounds **21** and **25** are predicted to be partial agonists at A_1 receptors. The 2′-deoxy 2′-fluoro analogue, compound **23**, is likely a full agonist.

Compound **41**, which was A_3 selective, was tested in a functional assay at rat A_3 receptors. Compound **41** inhibited adenylate cyclase (Figure 1), using membranes from CHO cells stably transfected with rat A_3 receptors. We previously demonstrated that compounds with high affinity in binding were very active in this assay of A_3-mediated inhibition of adenylate cyclase.[39] Compound **41** appeared to be a full agonist, with an inhibition of forskolin-stimulated adenylate cyclase of 32.7% ± 3.2%

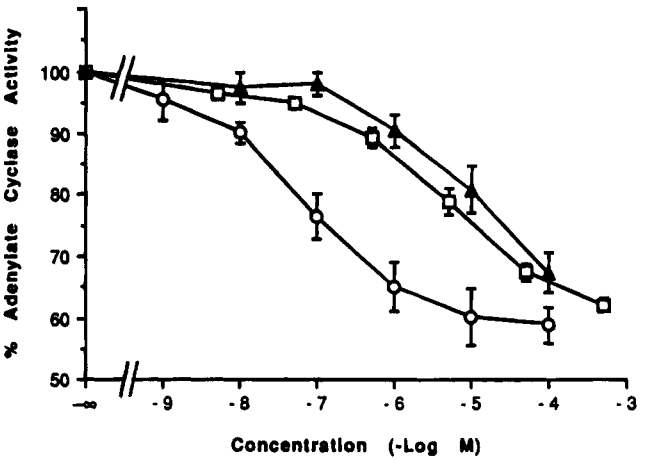


Figure 1. Inhibition of adenylate cyclase in membranes from CHO cells stably transfected with rat A_3 receptors. The assay was carried out as described in the Experimental Section in the presence of 1 mM forskolin. Each data point is shown as the mean ± SEM for four determinations. Adenosine derivatives were (number of separate experiments in parentheses) triangles, **41**, N^6-benzyl-4′-methyladenosine-5′-(*N*-methyluronamide); circles, 2-chloro-N^6-(3-iodobenzyl)adenosine-5′-(*N*-methyluronamide); and squares, NECA. IC_{50} values were Cl-IB-MECA, 66.8 ± 9.0 nM; NECA, 3 μM; and **41**, 10 μM.

at 10^{-4} M and an IC_{50} value of 10 μM (based on a maximal inhibition of 40%). Thus it was less potent than NECA, **31**, which had an IC_{50} value of 5.6 μM, but was more selective for A_3 receptors.

Discussion

The results of this study imply the existence of receptor binding sites for adenosine with very strict structural requirements. 1-Deaza modification of adenosine derivatives is well tolerated at A_1, A_{2a}, and A_3 receptors. The marked difference in affinity between 2-chloro- and 2-fluoroadenosine at rat A_3 receptor suggests preference for hydrophobic interaction near the 2-position of the purine ring. Substitution at the 8-position of adenosine resulted in agonists having decreased affinity for all the receptor subtypes.

Carbocyclic nucleosides were in general weakly A_{2a} selective ligands and showed poor affinity for A_3 receptors. Therefore it can be assumed that the 6′-oxygen of the ribose moiety is beneficial for binding to A_1 and A_3 receptors. Interestingly deletion of the 5′-methylene group of carbocyclic nucleosides (5′-noraristeromycin derivatives) resulted in enhanced affinity at A_1 and A_{2a} receptors. However, substitution at the 2-position of the purine ring of carbocyclic nucleosides did not enhance their affinity at A_{2a} receptors.

Replacement of the 6′-oxygen by sulfur was well tolerated at all the adenosine receptors. Adenine-β-D-arabinofuranoside, **20**, was weakly potent at all the receptor subtypes.[9] Curiously, the 2′-deoxyxylose modification combined with the 6′-thio modification resulted in enhanced binding at A_1 and A_{2a} receptors and a moderate affinity for A_3 receptors. In general 6′-thio and carbocyclic modifications of agonists were more suitable for increasing A_{2a} selectivity.

Various 2′-deoxy- and 2′,3′-dideoxyadenosine analogues were inactive in binding at rat A_3 receptors, but they showed considerable binding affinity at A_1 and A_{2a} receptors. Compounds **21** and **25** were putative partial agonists. 2-Chloro-2′-deoxy-1-deazaadenosine, **26**, was active, possibly as a partial agonist at A_1 receptors only. Recently Sipe et al.[40] reported that therapeutic use of

2-chloro-2′-deoxyadenosine, **25**, an antileukemic drug, slowed the progression of multiple sclerosis.

β-L-Adenosine, **17**, bounds appreciably A_1 receptors only.[9] However, β-L-5′-noraristeromycin, **18**, was an A_{2a} selective ligand. Surprisingly, when 6′-thio and 2′-deoxyxylo modifications were applied to the β-L-nucleoside enantiomer, the resultant nucleoside, **22**, behaved as an antagonist at A_1 receptors.

The 2-chloro 1-deaza modification was well tolerated at A_{2a} and A_3 receptors. Combination of the 1-deaza modification with a 5′-uronamide group leads to A_1 selectivity. Replacement of the 6-amino group by hydrazine or hydroxylamine was tolerated. Substitution at N^6 by benzyl, furfuryl, and benzopyryl groups was well tolerated at A_1, A_{2a}, and A_3 receptors. N^6-Substitution modification combined with 5′-uronamide derivatives increased A_3 selectivity. Substitution of 4′-hydrogen by a methyl group (compound **41**) maintained agonist activity at A_3 receptors and selectivity. This methyl group is designed to diminish metabolic hydrolysis of the amide group *in vivo* to provide a longer biological half-life. The 5′-uronamide N^6-benzyl-modified carbocyclic nucleoside **44** displaced binding at A_1 and A_3 receptors. It is to be noted that the inactivity of a singly modified derivative of adenosine, e.g., **29b**, does not preclude activity in multiple modified versions of the same, e.g., **41**.

Most of the compounds in this study are not substrates for adenosine deaminase. Those analogues having the N^6-alkyl, 5′-carboxamido, 2-chloro, 3- and 7-deaza, and 8-position modifications, and the carbocyclic "nor" analogues (e.g., **9**, **10a**, **12c**, and **16**),[24a] are expected to be stable to adenosine deaminase. It is possible that some of the compounds (**20**, **24**, **28**, and **29**) may be substrates for adenosine deaminase and that any residual deaminase present during the binding assay may raise the observed K_i value. Compound **7** is reported to be an adenosine deaminase substrate.[51] Compound **35** is an inhibitor of adenosine deaminase in the micromolar range.[48]

Conclusions

The most significant new compound, N^6-benzyl-4′-methyladenosine-5′-(*N*-methyluronamide), **41**, was identified as an A_3 selective agonist, and it displayed a K_i value of 604 nM at A_3 receptors and was 103- and 88-fold selective vs A_1 and A_{2a} receptors, respectively. Compounds **1**, **3**, and **25** were A_1 selective. Compounds **17**, **35**, and **39** were somewhat selective for A_1 receptors. Compounds **4**, **5**, **22**, **37**, **38**, and **39** were identified as slightly A_{2a} selective ligands. The moderately A_{2a} selective agonists were **9**, **11**, **18**, **19**, and **33**. On the basis of intermediate GTP shifts in binding versus an antagonist radioligand, 2-chloro-2′-deoxyadenosine, **25**, and 2-chloroadenine-9-(β-D-6′-thioarabinoside), **21**, are putative partial agonists at A_1 receptors, with K_i values of 7.4 and 5.4 μM, respectively. Compound **22** was identified as an A_1 antagonist from this search for new leads for ligand selectivity at adenosine receptors. We are synthesizing derivatives of **22** to enhance its potency as antagonists at adenosine receptors subtypes.

Although the corresponding simple 4′-methyladenosine derivative **29b** was inactive at adenosine receptors, compound **41**, containing two other modifications as well, was an A_3 selective, full agonist. Thus, this study emphasizes that inactivity or low binding affinity of an adenosine derivative does not preclude activity in optimally modified derivatives of the same ligand.

Experimental Section

All chemicals were purchased from Aldrich (Milwaukee, WI) unless otherwise noted. Compounds **28b** and **34** were the gift of the Drug Synthesis & Chemistry Branch, Developmental Therapeutics Program, Division of Cancer Treatment, NCI. Compounds **1**, **7**, **31**, and **38** were purchased from Sigma Chemicals, St. Louis, MO. Cylinders of ammonia and methylamine were obtained from Union Carbide and Matheson, respectively. Anhydrous methyl alcohol and *tert*-butyl alcohol were used from freshly opened bottles as received. Column chromatography was carried out with silica gel 60 from EM Science (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded in the solvent and field strength noted. Chemical shifts are reported relative to the solvent standard. Elemental analyses were performed by Midwest Microlab, Indianapolis, IN, and M-H-W Laboratories, Phoenix, AZ.

(±)-(1α,2β)-2-(2,6-Diamino-9*H*-purin-9-yl)cyclopentan-1-ol (12a). Compound **68** (220 mg, 0.87 mmol) in MeOH (30 mL) saturated with anhydrous NH_3 was heated in a sealed cylinder at 100 °C for 12 h. The solvent was removed under reduced pressure and the residue purified by column chromatography (CH_2Cl_2:MeOH, 9:1) to give **12a** as white crystals following recrystallization from MeOH (140 mg, 69.7%): mp 214–215 °C; ^1H NMR (DMSO-d_6) δ 1.5–2.2 (m, 6 H, 3 × CH_2 of cyclopentyl), 4.20 (m, 2 H, H-1 and H-2 of cyclopentyl), 5.79 (s, 2 H, NH_2), 6.69 (s, 2 H, NH_2), 7.74 (s, 1 H, H-8 of purine); ^{13}C NMR (DMSO-d_6) δ 19.90, 28.97, 31.99, 62.15, 74.93, 113.57, 136.30, 151.88, 156.04, 159.77.

(1*S*,2*R*,3*S*,4*R*)-4-[6-Amino-2-[(phenylethyl)amino]-9*H*-purin-9-yl]cyclopentane-1,2,3-triol (12c). To a suspension of **48** (300 mg, 1.05 mmol) in absolute EtOH (10 mL) was added phenylethylamine (300 mg, 2.45 mmol). This mixture was heated at 90 °C for 3 days. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography on silica gel (eluent CH_2Cl_2–MeOH) to give **12c** (272 mg, 70%) as a yellow solid: mp 200 °C dec; ^1H NMR (DMSO-d_6) δ 1.77–1.90 (m, 1 H, H-5′), 2.50–2.60 (m, 1 H, H-5′), 2.8 (m, 4 H, 2 × CH_2), 3.75 (m, 1 H, H-2′), 3.89 (m, 1 H, H-1′), 4.40–4.52 (m, 1 H, H-3′), 4.62–4.81 (m, 1 H, H-4′), 4.87 (d, 1 H, *J* = 3.6 Hz, OH), 5.01 (d, 1 H, *J* = 6.6 Hz, OH), 5.36 (d, 1 H, *J* = 4.8 Hz, OH), 7.22 (s, 2 H, NH_2), 7.48 (m, 5 H, Ph), 8.48 (s, 1 H, H-8).

(±)-(1α,2β,3β,5β)-3-[2-[[4-(1-Butyl)phenyl]amino]-4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]-5-(hydroxymethyl)-1,2-cyclopentanediol (15b). Into an ice-cooled solution of **64** (500 mg, 1.16 mmol) in dry MeOH (50 mL) was bubbled anydrous NH_3 until a saturated solution was obtained. The mixture was transfered to a sealed tube and heated at 125 °C for 55 h. After cooling to 0 °C, the sealed tube was opened and the volatiles were removed by evaporation *in vauo*. The residual solid was chromatographed on silica gel (CH_2Cl_2–MeOH, 9:1). The product-containing fractions were evaporated to dryness, and the residue was rechromatographed on 5 g of Norit-A (CH_2Cl_2–MeOH, 6:4) to give pure **15b** (454 mg, 95%): mp 210–213 °C; ^1H NMR (DMSO-d_6) δ 0.89 (t, 3 H, Me), 1.42 (m, 5 H, 2 × CH_2 and H-4′), 1.9 (m, 2 H, H-4′ and H-5′), 2.5 (m, 2 H, CH_2), 3.0–4.1 (m, 7 H, CH_2OH, H-1′, H-2′, H-3′, and 2 × OH), 5.0 (m, 1 H, OH), 6.4 (d, *J* = 3.8 Hz, 1 H, H-7), 7.0 (d, *J* = 8.5 Hz, 2 H, ArH). 7.4 (br, 3 H, H-8 and NH_2), 7.7 (d, *J* = 8.5 Hz, 2 H, ArH), 8.8 (br, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 13.76, 21.67, 30.06, 33.23, 34.13, 46.38, 55.15, 63.38, 77.14, 78.07, 100.38, 101.09, 118.43, 120.59, 128.56, 135.65, 136.89, 147.41, 148.82, 158.35.

N^6-(Benzodioxanylmethyl)adenosine Hemihydrate (39). 6-Chloropurine riboside (200 mg, 0.70 mmol) was refluxed in 10 mL of ethanol with 162 mg (0.77 mmol) of racemic benzdioxan-2-methylamine and 2 g (2.1 mmol) of triethylamine solution (5.3 g of triethylamine in 50 g of ethanol) for 18 h. After 48 h at −20 °C, a white crystalline product was formed that was collected and dried. Further workup afforded a second crop of the product: total yield 180 mg (62%); mp 176–178 °C; MS (CI) MH^+ = 416.

1-[6-(Benzylamino)-9*H*-purin-9-yl]-1-deoxy-*N*,4-dimethyl-β-D-ribofuranosiduronamide (41). The diacetyl

nucleoside **52** (195 mg, 0.474 mmol) was selectively deacylated by treatment with a methanolic solution of NH_3 at 0 °C for 10 min. The solution was evaporated to dryness, and to the residue was added a 1:1 solution of *t*-BuOH and benzylamine (4 mL). This solution was heated at 70 °C for 16 h and concentrated under reduced pressure (0.1 Torr, 40 °C). Chromatography of the residue on silica gel (gradient 30:1−10:1 CH_2Cl_2:MeOH) gave 159 mg (84%) of *N*-benzyladenine nucleoside **41** as a white solid: $[\alpha]^{23}_D$ −25.7° (*c* 1.02, CH_3OH); ^1H NMR (500 MHz, CD_3OD, prior H−D exchange) δ 8.29 (s, 1 H), 8.13 (s, 1 H), 7.35 (d, 2 H, *J* = 7.0 Hz), 7.28 (t, 2 H, *J* = 7.5 Hz), 7.21 (t, 1 H, *J* = 7.5 Hz), 5.97 (d, 1 H, *J* = 8.5 Hz), 4.83 (dd, 1H, *J* = 8.5, 5.0 Hz), 4.78 (br s, 2 H), 4.30 (d, 1 H, *J* = 5.0 Hz), 2.82 (s, 3 H), 1.50 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.98, 154.73, 152.48, 148.33, 140.77, 138.78, 128.13, 127.10, 126.81, 120.10, 88.16, 87.74, 73.75, 71.75, 43.62, 24.90, 18.79.

1-[6-(Furfurylamino)-9*H*-purin-9-yl]-1-deoxy-*N*-methyl-β-D-ribo-furanosiduronamide (42). To a solution of 2′,3′-isopropylidene-1-(6-chloro-9*H*-purin-9-yl)-1-deoxy-*N*-methyl-β-D-ribofuranosiduronamide[8] (50 mg, 0.16 mmol) in absolute EtOH (5 mL) was added furfurylamine (20 mg, 0.21 mmol). This mixture was heated at 90 °C for 20 h. After cooling to room temperature, solvent was removed by rotary evaporation and the residue was dissolved in 0.5 N HCl and heated at 60 °C for 1 h. After cooling to 0 °C in an ice bath, the reaction mixture was neutralized with concentrated NH_4OH and evaporated to dryness. The residue was purified by preparative thin-layer chromatography on silica gel to give **42** (21 mg, 40%) as white solid: ^1H NMR (DMSO- d_6) δ 3.32 (d, *J* = 4.3 Hz, 3 H, Me), 4.12 (m, 1 H, H-3′), 4.33 (s, 1 H, H-4′), 4.60 (dd, *J* = 4.6, *J* = 4.3 Hz, 1 H, H-2′), 4.70 (br s, 2 H, N^6-*CH*$_2$-), 5.53 (d, *J* = 6.4 Hz, 1 H, OH-2′), 5.56 (d, *J* = 7.4 Hz, 1 H, H-1′), 5.71 (d, *J* = 4.1 Hz, 1 H, OH-3′), 5.60 (d, *J* = 7.4 Hz, 1 H, H-1′), 7.3 (m, 3 H), 8.42 (s, 1 H, H-8), 8.56 (br s, 1 H, *H*-N^6), 8.55 (br s, 1 H, N*H*-Me).

(±)-9-[2α,3α-Dihydroxy-4β-(*N*-methylcarbamoyl)cyclopent-1β-yl)]-N^6-(3-iodobenzyl)adenine (44). To a solution of **57** (100 mg, 0.32 mmol) in absolute EtOH (10 mL) was added 3-iodobenzylamine hydrochloride (90 mg, 0.34 mmol), and the resulting mixture was heated at 90 °C for 24 h, under a nitrogen atmosphere. The solvent was removed by evaporation *in vacuo*, and the residue was purified by column chromatography on silica gel (eluent CH_2Cl_2−MeOH, 10:0.5) to give **44** (140 mg, 85%) as colorless foam: ^1H NMR (DMSO-d_6) δ 2.71 (s, 2 H, CH_2), 3.31 (m, 1 H, H-1′), 3.42 (d, *J* = 4.3 Hz, 3 H, Me), 4.32 (m, 1 H, H-3′), 4.35 (s, 1 H, H-4′), 4.70 (s, 2 H, *CH*$_2$-Ph), 4.74 (dd, *J* = 4.0, *J* = 4.3 Hz, 1 H, H-2′), 5.45 (d, *J* = 6.4 Hz, 1 H, OH-2′), 5.60 (d, *J* = 4.1 Hz, 1 H, OH-3′), 5.60 (d, *J* = 7.4 Hz, 1 H, H-1′), 7.13 (t, *J* = 7.1 Hz, 1 H), 7.40 (d, *J* = 7.7 Hz, 1 H), 7.60 (d, *J* = 7.6 Hz, 1 H), 8.21 (s, 1 H, H-8), 8.50 (br s, 1 HN^6), 8.60 (br s, 1 H, N*H*-Me).

(1*R*,4*S*)-4-(2,6-Dichloro-9*H*-purin-9-yl)cyclopent-2-en-1-ol (46). To a solution of 2,6-dichloropurine (2 g, 10.64 mmol) in dry DMSO (25 mL) was added sodium hydride (60% suspension in mineral oil, 0.42 g, 10.64 mmol). The reaction mixture was stirred at the room temperature for 30 min followed by the addition of tetrakis(triphenylphosphine)-palladium (0.5 g, 0.22 mmol), triphenylphosphine (0.25 g, 0.95 mmol), and a solution of (+)-**45**[20] (1.66 g, 11.70 mmol) in dry THF (25 mL). This mixture was stirred at 50 °C for 20 h. The volatiles were removed by rotary evaporation *in vacuo* at 50 °C. The residue was slurried in CH_2Cl_2 (50 mL) and filtered to remove insoluble solids. The filtrate that resulted was washed with brine (2 × 50 mL), dried ($MgSO_4$), and evaporated to dryness. The residual oil was purified by flash chromatography on silica gel by eluting first with AcOEt to remove the nonpolar impurities and then with AcOEt−MeOH (9:1). The product containing fractions were evaporated to dryness to give **46** (3.55 g, 89%) as a colorless foam: ^1H NMR (DMSO-d_6) δ 1.62−2.7 (m, 2 H, H-5′), 3.26 (m, 3 H, OH), 3.65 (m, 1 H, H-1′), 4.58 (m, 3 H, H-2′, H-3′, H-4′), 8.34 (m, 1 H, H-8).

(1*S*,2*R*,3*S*,4*R*)-4-(6-Amino-2-chloro-9*H*-purin-9-yl)cyclopentane-1,2,3-triol (48). To a solution of **46** (1 g, 3.70 mmol) in THF−H_2O (10:1, 50 mL) was added a 60% aqueous solution of *N*-methylmorpholine *N*-oxide (1.2 mL, 1.14 mmol) and then osmium tetraoxide (30 mg). The reaction mixture was stirred at room temperature for 24 h. The solvent was removed by rotary evaporation, and the residue was coevaporated with EtOH (3 × 50 mL) to give a gummy material. This residue was dissolved in MeOH presaturated with anhydrous ammonia (50 mL) and stirred in a sealed tube at room temperature for 5 days. Volatiles were removed by rotary evaporation, and the residue was subjected to column chromatography on silica gel (eluent MeOH−CH_2Cl_2, 9:1) to give **48** (800 mg, 80%) as a white solid: mp 180 °C dec; ^1H NMR (DMSO-d_6) δ 1.77−190 (m, 1 H, H-5′), 2.50 (m, 1 H, H-5′) 3.75 (m, 1 H, H-2′), 3.89 (m, 1 H, H-1′), 4.40−4.52 (m, 1 H, H-3′), 4.62−4.81 (m, 1 H, H-4′), 4.87 (d, 1 H, *J* = 3.6 Hz, OH), 5.01 (d, 1 H, *J* = 6.6 Hz, OH), 5.36 (d, 1 H, *J* = 4.8 Hz, OH), 7.22 (s, 2 H, NH_2), 8.11 (s, 1 H, H-8).

Methyl 2,3-*O*-Isopropylidene-*N*,4-dimethyl-β-D-ribofuranosiduronamide (50). A solution of methyl ester **49**[21] (502 mg, 2.04 mmol) in MeOH (30 mL) was saturated with gaseous methylamine and stirred until TLC (2:1 hexane: EtOAc) showed the reaction was complete. The solution was concentrated and the residue chromatographed on silica gel (1.5:1 hexane:EtOAc) to give 502 mg (100%) of **50** as a clear oil: $[\alpha]^{23}_D$ −45.0° (*c* 1.05, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 6.56 (br s, 1 H), 5.10 (d, 1 H, *J* = 5.9 Hz), 4.93 (s, 1 H), 4.51 (d, 1 H, *J* = 5.9 Hz), 3.39 (s, 3 H), 2.79 (d, 3 H, *J* = 5.0 Hz), 1.47 (s, 3 H), 1.44 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.55, 112.53, 110.25, 89.33, 85.15, 82.35, 55.96, 26.16, 25.98, 24.76, 20.96.

Methyl 2,3-*O*-Diacetyl-*N*,4-dimethyl-β-D-ribofuranosiduronamide (51). To a solution of acetonide **50** (502 mg, 2.04 mmol) in MeOH (60 mL) was added concentrated HCl (0.1 mL). The solution was stirred for 18 h and then concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient EtOAc−30% MeOH in EtOAc) to give 105 mg (21%) of starting acetonide and 310 mg of diols as a mixture of glycosides which were acetylated with Ac_2O (0.48 mL) and pyridine (0.85 mL) in CH_2Cl_2 (30 mL) containing a catalytic amount of DMAP. Toluene (10 mL) was added, and the solution was concentrated to dryness. The residue was chromatographed on silica gel (1:1 hexane:EtOAc) to give 380 mg (64%) of β-**51** and 40 mg (7%) of α-**51** (81% and 8.5% yields, respectively, based on recovered acetonide). β-**51**: oil; $[\alpha]^{23}_D$ −27.5° (*c* 1.2, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 6.77 (br s, 1 H), 5.54 (d, 1 H, *J* = 4.8 Hz), 5.19 (dd, 1 H, *J* = 3.2, 4.8 Hz), 5.01 (d, 1 H, *J* = 3.2 Hz), 3.48 (s, 3 H), 2.82 (d, 3 H, *J* = 5.0 Hz), 2.10 (s, 3 H), 2.05 (s, 3 H), 1.46 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.26, 169.19 (2), 106.54, 85.69, 74.71, 73.75, 56.87, 26.11, 20.56 (2), 20.45. Anal. Calcd for $C_{12}H_{19}NO_7$: C, 49.82; H, 6.62. Found: C, 49.75; H, 6.52. α-**51**: mp 112−113 °C (CH_2Cl_2/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 6.71 (br s, 1 H), 5.64 (d, 1 H, *J* = 6.3 Hz), 5.12 (d, 1 H, *J* = 4.8 Hz), 4.94 (dd, 1 H, *J* = 6.3, 4.8 Hz), 3.42 (s, 3 H), 2.81 (d, 3 H, *J* = 5.0 Hz), 2.16 (s, 3 H), 2.08 (s, 3 H), 1.48 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.92, 169.81, 169.58, 101.35, 85.59, 72.08, 70.78, 55.83, 26.08, 21.14, 20.65, 20.45.

2,3-*O*-Diacetyl-1-(6-chloro-9*H*-purin-9-yl)-1-deoxy-*N*,4-dimethyl-β-D-ribofuranosiduronamide (52). A suspension of 6-chloropurine (590 mg, 3.82 mmol) in hexamethyldisilazane (6 mL) was heated to 100 °C until dissolution was complete, *ca.* 1 h. Toluene (2 mL) was added, and the solution was concentrated under an inert atmosphere. To remove final traces of HMDS, toluene (2 × 4 mL) was again added and the solution was concentrated in a similar manner. To the silylated 6-chloropurine in dry CH_3CN (3 mL) was added 307 mg (1.05 mmol) of β-**51** (dried by azeotropic distillation with toluene under reduced pressure) in dry CH_3CN (5 mL) and trimethylsilyl trifluoromethanesulfonate (0.75 mL). This solution was heated to reflux for 12 h. The two initial nucleoside products detected by TLC gave way to a single thermodynamic product during this time. The reaction mixture was cooled, the reaction quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL), and the mixture partitioned between CH_2Cl_2 (40 mL) and H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Column chromatography on silica gel (1:2 CH_2Cl_2: EtOAc) gave 270 mg (63%) of 6-Cl-purine nucleoside **52** as a faint yellow foam: $[\alpha]^{23}_D$ 2.48° (*c* 1.45, CH_2Cl_2); ^1H NMR (300

MHz, $CDCl_3$) δ 8.68 (s, 1 H), 8.27 (s, 1 H), 7.61 (br q, 1 H, J = 4.9 Hz), 6.15 (d, 1 H, J = 7.5 Hz), 6.00 (dd, 1 H, J = 7.5, 5.0 Hz), 5.82 (d, 1 H, J = 5.0 Hz), 2.77 (d, 3 H, J = 4.9 Hz), 2.13 (s, 3 H), 1.88 (s, 3 H), 1.49 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.13, 168.78 (2), 151.80, 151.56, 150.96, 144.67, 133.39, 86.80, 86.07, 73.03, 71.15, 25.99, 20.20, 19.96, 19.75.

(±)-9-[2α,3α-Dihydroxy-4β-(*N*-methylcarbamoyl)cyclopent-1β-yl)]-6-chloropurine (57). To a solution of compound **54** (1 g, 7.04 mmol, prepared according to the procedure reported by Cermak and Vince[47]) in dry MeOH (20 mL) was bubbled anhydrous methylamine for 10 min. The resulting solution was heated at 90 °C in a sealed tube for 20 h. After cooling to room temperature, solvent was removed by rotary evaporation *in vacuo* and the residue was used in the next step without further characterization. To this residue were added 5-amino-4,6-dichloropyrimidine (1.00 g, 6.13 mmol), triethylamine (2 mL), and *n*-BuOH (20 mL). The resulting mixture was heated at 100 °C, under an N_2 atmosphere, for 24 h. Volatiles were evaporated *in vacuo*, and the residue was dissolved in methyl diethoxyacetate (10 mL). This mixture was heated at 100 °C for 2 h and then evaporated to dryness. The residue was dissolved in 1 N HCl (10 mL) and stirred at room temperature for 3 h. The ice-cold reaction mixture was neutralized with concentrated NH_4OH and evaporated to dryness. The residue was subjected to column chromatography on silica gel (eluent CH_2Cl_2–MeOH, 9.5:0.5) to give **57** (1.3 g, 59% yield based upon **54**) as a yellow foam: ^1H NMR (DMSO-d_6) δ 2.75 (s, 2 H, CH_2), 3.33 (m, 1 H, H-1′), 3.40 (d, J = 4.3 Hz, 3 H, Me), 4.22 (m, 1 H, H-3′), 4.33 (s, 1 H, H-4′), 4.75 (dd, J = 4.0, J = 4.3 Hz, 1 H, H-2′), 5.45 (d, J = 6.4 Hz, 1 H, OH-2′), 5.60 (d, J = 4.1 Hz, 1 H, OH-3′), 5.60 (d, J = 7.4 Hz, 1 H, H-1′), 8.21 (s, 1 H, H-8), 8.50 (br s, 2 H, HN[6]), 8.60 (br s, 1 H, N*H*-Me).

5-Allyl-2-[[4-(1-butyl)phenyl]amino]-4,6-dihydroxypyrimidine (58). *N*-[4-(1-Butyl)phenyl]guanidine nitrate[55] (16 g, 62.99 mmol) was added to cold NaOEt in EtOH (250 mL prepared by dissolving 25 g of Na in 250 mL of absolute EtOH). This mixture was stirred at 5 °C for 10 min before diethyl allylmalonate (12.59 g, 62.95 mmol; Aldrich Chemical Co.) was added. The reaction mixture was then refluxed for 3 h. Concentrated HCl (40 mL) was added to the cold reaction mixture, which was allowed to stand for several hours. The crude product and inorganic salts precipitated. After filtration and washing the crude mixture with water and recrystallization of this material using EtOH, 12.5 g (66%) of pure **58** was obtained: mp 211–212 °C; ^1H NMR (DMSO-d_6) δ 0.81 (t, 3 H, CH_3), 1.39 (m, 4 H, 2 × CH_2), 2.44 (t, 2 H, CH_2), 2.90 (d of t, 2 H, CH_2), 3.03 (br, 1 H, OH), 4.86 (m, 2 H, CH_2), 5.61 (m, 1 H, CH), 7.09 (d, 2 H of C_6H_5), 7.62 (d, 2 H of C_6H_5), 8.57 (s, 1 H, side chain NH), 10.50 (br, 1 H, ring OH/NH); ^{13}C NMR (DMSO-d_6) δ 13.77, 21.73, 26.39, 33.32, 34.25, 90.75, 113.66, 119.89, 128.51, 136.20, 136.80, 149.58, 165.08.

5-Allyl-2-[[4-(1-butyl)phenyl]amino]-4,6-dichloropyridimidine (60). To a suspension of dried **58** (10 g, 33.44 mmol) in dry acetonitrile (150 mL) was added tetraethylammonium chloride (dried over P_2O_5) (2 g, 17.09 mmol) followed by *N,N*-diethylaniline (2.5 mL) and phosphorus oxychloride (30 mL). The reaction mixture was kept in an oil bath preheated at 70 °C for 2 h. An additional amount of phosphorus oxychloride (20 mL), containing *N,N*-diethylaniline (1.5 mL), was added, and the temperature was raised to 100 °C. After 2 h, the volatiles were evaporated under reduced pressure and the residue was dissolved in $CHCl_3$ (100 mL). The organic solution was added to ice H_2O, and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (3 × 50 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (2 × 50 mL) and then H_2O (2 × 50 mL). The $CHCl_3$ solution was dried over $MgSO_4$ and filtered, and the filtrates were evaporated on a rotary evaporator to yield crude **60**. Recrystallization of this material using MeOH afforded 7.72 g (69%) of pure **60**: mp 70–72 °C; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3 H, CH_3), 1.25 (m, 4 H, 2 × H_2), 2.48 (m, 2 H, CH_2), 3.97 (m, 2 H, CH_2), 5.03 (m, 2 H, CH_2), 6.00 (m, 1 H, CH_2), 7.36 (m, 5 H, C_6H_5 and NH); ^{13}C NMR ($CDCl_3$) δ 13.89, 22.23, 33.23, 33.61, 34.96, 116.71, 119.58, 128.79, 132.42, 135.67, 138.22, 156.91, 161.78.

[2-[[4-(1-Butyl)phenyl]amino]-4,6-dichloropyrimidin-5-yl]acetaldehyde (61). To a suspension of **60** (37.12 g, 110.81 mmol) in MeOH (300 mL), acetone (200 mL), and H_2O (200 mL) were added OsO_4 (230 mg) and $NaIO_4$ (94.8 g, 443.21 mmol). After mechanically stirring for 48 h, the reaction mixture was evaporated to remove the organic solvent. The suspension was diluted with H_2O (500 mL) and extracted several times with EtOAc. The EtOAc layer was separated, dried over $MgSO_4$, and evaporated to dryness. The crude product was recrystallized from a small amount of MeOH to give **61** (29.83 g, 79%) as white needles: ^1H NMR (DMSO-d_6) δ 0.91 (t, 3 H, CH_3), 1.40 (m, 4 H, 2 × CH_2), 1.99 (t, 2 H, CH_2), 3.90 (s, 2 H, CH_2CHO), 7.16 (d, J = 8.5 Hz, 2 H, ArH), 7.4 (d, J = 8.5 Hz, 2 H, ArH), 9.7 (s, 1 H, NH), 10.25 (s, 1 H, C*H*O); ^{13}C NMR (DMSO-d_6) δ 13.87, 21.71, 33.20, 34.24, 43.58, 112.65, 119.66, 128.38, 136.36, 137.01, 158.81, 161.37, 197.79.

2-[[4-(1-Butyl)phenyl]amino]-4,6-dichloro-5-(2,2-dimethoxyethyl)pyrimidine (62). To a solution of **61** (29.25 g, 86.79 mmol) in dry MeOH (250 mL) was added pyridinium *p*-toluensulfonate (2.18 g, 8.67 mmol) and NH_4Cl (460 mg, 8.68 mmol, freshly dried over P_2O_5), and this solution was refluxed for 4 h. After cooling to room temperature, the reaction mixture was treated with Norit-A and filtered through a pad of Celite, and the filtrate was evaporated to dryness. The residue was dissolved in AcOEt–hexane (2:8) and filtered through a plug of Florisil (150 g). Removal of the solvent and chromatography on Florisil (AcOEt–hexane, 2:8) gave **62** (29.71 g, 89%) as a yellow oil, which crystallized slowly at room temperature and was recrystallized from hexane to give pure **62** as colorless needles: mp 52–55 °C; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, Me), 1.3 (m, 4 H, 2 × CH_2), 2.5 (t, 2 H, CH_2), 3.0 (d, 2 H, CH_2), 3.3 (s, 6 H, OMe), 4.5 (t, 1 H, $(MeO)_2CH$), 7.1 (d, J = 8.5 Hz, 2 H, ArH), 7.2 (s, 1 H, NH), 7.4 (d, J = 8.5 Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$) δ 13.83, 22.39, 33.55, 33.72, 35.12, 54.14, 103.38, 116.93, 119.74, 129.01, 135.73, 138.43, 157.02, 162.43.

(±)-(1α,2β,3β,5β)-3-[2-[[4-(1-Butyl)phenyl]amino]-4-chloro-7*H*-pyrrolo[2,3-*d*]pryimidin-7-yl]-5-(hydroxymethyl)-1,2-cyclopentanediol (64). A mixture of (±)-4α-amino-2β,3β-dihydroxy-1α-cyclopentanemethanol (obtained by the acidic hydrolysis of 3.5 g (11.18 mmol) of its tetraacetate derivative[54]), **62** (3.0 g, 8.9 mmol), and Et_3N (20 mL) in 1-BuOH (100 mL) was heated under reflx for 38 h. The reaction mixture was evaporated to dryness to give crude **63**. A small amount of **63** was purified by column chromatography (CH_2Cl_2–MeOH, 95:5): ^1H NMR (DMSO-d_6) δ 0.89 (t, 3 H, Me), 1.42 (m, 5 H, 2 × CH_2 and H-4), 2.0 (m, 2 H, H-4 and H-5), 2.5 (t, 2 H, CH_2), 2.8 (d, 1 H, H-3), 3.3 (s, 6 H, 2 × OMe), 3.4–4.0 (m, 6 H, $(MeO)_2CHCH_2$-, CH_2OH, H-1, and H-2), 4.2–5.2 (m, 4 H, $(MeO)_2CH$ amd 3 × OH), 6.5 (d, 1 H, NH), 7.0 (d, J = 8.5 Hz, 2 H, ArH), 7.6 (d, J = 8.5 Hz, 2 H, ArH), 9.2 (s, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 12.57, 20.53, 30.50, 32.18, 33.35, 45.51, 51.57, 52.82, 53.20, 62.41, 75.74, 77.09, 99.09, 103.53, 117.34, 126.93, 133.59, 137.17, 156.38, 161.22.

The crude **63** from the above step was dissolved in 1,4-dioxane (200 mL), and 2 N HCl (20 mL) was added to this. After stirring for 20 h at room temperature, the reaction mixture was neutrallized with concentrated NH_4OH followed by evaporation to dryness. The residue was purified by medium pressure chromatography (CH_2Cl_2–MeOH, 95:5) to give **64** (1.6 g, 42% based upon **62**) as a yellow foam, which crystallized from CH_2Cl_2: mp 172–175 °C; ^1H NMR (DMSO-d_6) δ 0.89 (t, 3 H, Me), 1.41 (m, 5 H, 2 × CH_2 and H-4′), 2.0 (m, 2 H, H-4′ and H-5′), 2.5 (m, 2 H, CH_2), 3.1 (d, 1 H, H-3′), 3.2–4.0 (m, 6 H, CH_2OH, H-1′, H-2′, and 2 × OH), 5.1 (d, 1 H, OH), 6.36 (d, J = 3.8 Hz, 1 H, H-7), 7.0 (d, J = 8.5 Hz, 2 H, ArH), 7.38 (d, J = 3.5 Hz, 1 H, H-8), 7.7 (d, J = 8.5 Hz, 2 H, ArH), 9.5 (br, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 13.97, 21.88, 29.74, 33.53, 34.40, 45.72, 55.31, 63.44, 77.14, 78.23, 98.00, 110.14, 118.48, 127.25, 128.45, 135.00, 138.58, 150.61, 152.88, 154.83.

(±)-(1α,2β)-2-(2-Amino-6-chloro-9*H*-purin-9-yl)cyclopentan-1-ol (68). A solution of 18.64 g (114 mmol) of 2-amino-4,6-dichloropyrimidine and 11.50 g (114 mmol) of (±)-*trans*-2-aminocyclopentanol[57] in BuOH was heated at reflux under Ar. Following the reflux period, the solvent was removed by distillation under reduced pressure and the residue treated

with H_2O. The resulting beige solid was collected by filtration and washed well with H_2O followed by $CHCl_3$. The solid that remained was dried at 60 °C under vacuum to give 18.13 g (70%) of (±)-(1α,2β)-2-[(2-amino-6-chloropyrimidin-4-yl)amino]-cyclopentan-1-ol, **65**, as a tan solid, which was suficiently pure for the following step. An analytical sample was prepared by recrystallization from MeCN: mp 171–173 °C.

A solution of 3.42 g (26.85 mmol) of 4-chloroaniline in 95% EtOH (25 mL) was treated with concentrated H_2SO_4 (2.75 mL). The solution was cooled to 27 °C and treated dropwise with 1-butyl nitrite (3.2 g). The solution was then warmed carefully to 35–40 °C for 10 min and then chilled in ice. The crystals of diazonium salt that separated were collected and washed with a minimum amount of cold EtOH and used immediately in the next step.

The diazonium salt prepared in the last step was dissolved in MeOH (30 mL) and the resulting solution treated with **65** (3.0 g, 13.12 mmol). Yellow crystals began to separate immediately. After 20 min, a solution of anhydrous AcONa (2.2 g) in H_2O (20 mL) was added and the reaction mixture then stirred for 90 min. The thick yellow paste was collected and washed well with hot MeOH. The bright yellow sample (4.10 g, 85%) of (±)-(1α,2β)-2-[[2-amino-6-chloro-5-[(4-chlorophenyl)azo]pyrimidin-4-yl]amino]cyclopentan-1-ol, **66**, was dried under high vacuum and found to be suffiently pure to use in the next step.

A solution of **66** (1.6 g, 4.37 mmol) and Zn (2.5 g) in a mixture of AcOH (1 mL), EtOH (60 mL), and H_2O (20 mL) was refluxed under N_2 until the yellow color disappeared. After filtration, the solvent was evaporated under reduced pressure to give a residue of (±)-(1α,2β)-2-[(2,5-diamino-6-chloropyrimidin-4-yl)amino]cyclopentan-1-ol, **67**, which was placed in a mixture of cooled DMF (20 mL) and trimethyl orthoformate (50 mL) containing concentrated HCl (0.5 mL). This mixture was then stirred at room temperature overnight and the solvent mixture evaporated under reduced pressure. The residue was stirred in 0.5 N HCl (50 mL) for 3 h. After adjusting the pH to 9, the mixture was evaporated to dryness under reduced pressure to provide a residue that was purified by column chromatography (CH_2Cl_2:MeOH, 10:1) to give **68** as white crystals following recrystallization from MeOH (770 mg, 68.8%): mp 197–198 °C; ^1H NMR (DMSO-d_6) δ 1.5–2.2 (m, 6 H, 3 × CH_2 of cyclopentyl), 4.45 (m, 2 H, H-1 and H-2 of cyclopentyl), 6.88 (s, 2 H, NH_2), 8.21 (s, 1 H, H-8 of purine); ^{13}C NMR (DMSO-d_6) δ 19.64, 28.53, 31.78, 62.55, 74.71, 123.78, 142.15, 149.27, 154.23, 159.45.

Cell Culture and Radioligand Binding. CHO cells stably expressing the A_3 receptor[9,19] were grown in F-12 medium containing 10% FBS and penicillin/streptomycin (100 U/mL and 100 μg/mL, respectively) at 37 °C in a 5% CO_2 atmosphere, and membrane homogenates were prepared as reported.[9]

Binding of [^{125}I]-N^6-(4-amino-3-iodobenzyl)adenosine-5′-(*N*-methyluronamide) ([^{125}I]AB-MECA) to the CHO cells membranes was performed essentially as described.[16,19] Assays were performed in 50/10/1 buffer in glass tubes and contained 100 μL of the membrane suspension, 50 μL of [^{125}I]AB-MECA (final concentration 0.3 nM), and 50 μL of inhibitor. Inhibitors were routinely dissolved in DMSO and then diluted with buffer; final DMSO concentrations never exceeded 1%. Incubations were carried out in duplicate for 1 h at 37 °C and terminated by rapid filtration over Whatman GF/B filters, using a Brandell cell harvester (Brandell, Gaithersburg, MD). Tubes were washed three times with 3 mL of buffer. Radioactivity was determined in a Beckman γ-5500B counter. Nonspecific binding was determined in the presence of 40 μM (*R*)-PIA. K_i values were calculated according to the Cheng–Prusoff equation,[41] assuming a K_d for [^{125}I]AB-MECA of 1.55 nM.[16]

Binding of [^{3}H]PIA (Amersham, Arlington Heights, IL) to A_1 receptors from rat brain membranes and [^{3}H]CGS 21680 (DuPont NEN, Boston, MA) to A_2 receptors from rat striatal membranes was performed as described previously.[17,18] Adenosine deaminase (3 U/mL) was present during the preparation of brain membranes, in which an incubation at 30 °C for 30 min is carried out, and during the incubation with radioligand. At least six different concentrations spanning 3 orders of magnitude, adjusted appropriately for the IC_{50} of each compound, were used. IC_{50} values, computer-generated using a nonlinear regression formula on the InPlot program (GraphPAD, San Diego, CA), were converted to apparent K_i values using K_d values of 1.0 and 14 nM for [^{3}H]PIA and [^{3}H]CGS 21680 binding, respectively, and the Cheng–Prusoff equation.[41]

GTP shifts in the displacement of the binding of [^{3}H]-8-cyclopentyl-1,3-dipropylxanthine (CPX; DuPont NEN) were determined as described.[38] Adenylate cyclase measurements in A_3-transfected CHO cells were carried out as described.[9]

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