Selective Ligands for Rat A_3 Adenosine Receptors: Structure–Activity Relationships of 1,3-Dialkylxanthine 7-Riboside Derivatives

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1,3-Dibutylxanthine 7-riboside has been found to be a partial agonist at A_3 adenosine receptors (van Galen et al. *Mol. Pharmacol.* **1994**, *45*, 1101–1111). 1,3-Dialkylxanthine 7-riboside analogues modified at the 1-, 3-, and 8-purine positions and at the ribose 5′-position were synthesized. The nucleoside analogues were examined for affinity in radioligand binding assays at rat brain A_3 adenosine receptors stably expressed in CHO cells, using the radioligand [[^{125}I]-4-amino-3-iodobenzyl]adenosine-5′-*N*-methyluronamide (AB-MECA). Affinity was assayed at rat brain A_1 and A_{2a} receptors using [^{3}H]PIA and [^{3}H]CGS 21680, respectively. The affinity of xanthine 7-ribosides at A_3 receptors depended on the 1,3-dialkyl substituents in the order: Pent ≥ Bu ≫ Hx > Pr ≈ Me. 1,3-Dipentylxanthine 7-riboside was slightly selective for A_3 receptors (2-fold vs A_1 and 10-fold vs A_{2a}). 8-Methoxy substitution was tolerated at A_3 receptors. 2-Thio vs 2-oxo substitution increased potency at all three subtypes and slightly increased A_3 vs A_1 selectivity. The 5′-uronamide modification, which was previously found to enhance A_3 selectivity in N^6-benzyladenosine derivatives, was also incorporated into the xanthine 7-ribosides, with similar results. The affinity of 1,3-dialkylxanthine 7-riboside 5′-uronamides at A_3 receptors depended on the *N*-alkyluronamide substituent in the order: MeNH > EtNH ≫ NH_2 ≫ Me_2N. Affinity of the 5′-uronamides at A_3 receptors was dependent on the 1,3-dialkyl substitution in the order: Bu > Pent > Hex. 1,3-Dibutylxanthine 7-riboside 5′-*N*-methylcarboxamide, with a K_i value of 229 nM at A_3 receptors, was 160-fold selective for rat A_3 vs A_1 receptors and >400-fold selective vs A_{2a} receptors. This derivative acted as a full agonist in the A_3 receptor-mediated inhibition of adenylate cyclase.

Introduction

The A_3 adenosine receptor is the most recent identified among the three major subtypes of adenosine receptors, A_1, A_2, and A_3.[1,2] It was cloned[1] using the polymerase chain reaction (PCR) from cDNA libraries from rat brain by sequence homology with other G-protein-coupled receptors and was identical to the sequence tgpcr cloned from rat testes.[3] Sheep[4] and human[5] brain A_3 receptors have also been cloned. Like A_1 receptors, A_3 receptors are coupled to both the inhibition of adenylate cyclase[1] and the stimulation of inositol phosphate metabolism (in antigen-exposed RBL-2H3 rat mast cells).[6,7] The adenosine receptor in the latter cell line, previously characterized by Ali et al.,[8] was insensitive to xanthines, as is the cloned rat brain A_3 receptor. In rat peritoneal mast cells, a component of enhancement of histamine release by adenosine also was reported to be insensitive to xanthines, suggesting the possible presence of A_3 receptors.[9]

Activation of A_3 receptors is also associated with hypotensive,[10] behavioral,[11] and cardioprotective[12] effects. Beaven et al.[7] have suggested that A_3 antagonists may have potential as antiinflammatory agents acting via mast cells. In human lung, A_3 receptors appear to be expressed mainly on eosinophils, suggesting a relevance to asthma.[34] We have proposed a role for A_3 receptors in the brain, based on the locomotor depressant response following administration of an A_3-selective agonist in mice.[11] The agonist used was N^6-(3-iodobenzyl)-5′-(*N*-methylcarbamoyl)adenosine (IB-MECA), which is 50-fold selective in binding assays for rat brain A_3 vs either A_1 or A_{2a} receptors.[13] Recently, chronically administered IB-MECA was found to be cerebroprotective in a model of global ischemia in gerbils[14] and against *N*-methyl-D-aspartate-induced seizures in mice.[15] The effects of A_3 receptor activation *in vivo* have been shown to be insensitive to xanthines such as XAC (8-[4-[[[[(2-aminoethyl)amino]carbonyl]methyl]oxy]phenyl]-1,3-dipropylxanthine).[10,11,14]

In an effort to define the structural requirements for A_3 receptor affinity, we have proposed a molecular model for ligand binding at this subtype,[16] which is consistent with known structure–activity relationships. This model features anchoring of the ribose moiety of adenosine to a His residue in the seventh transmembrane helix that is conserved among all adenosine receptor subtypes. Another His residue in the sixth transmembrane helix, also proposed to be involved in ligand recognition[39] and common to A_1 and A_2 adenosine receptors, is absent in A_3 receptors. Thus we proposed and verified that the affinity of xanthines at A_3 receptors could be enhanced by the presence of a ribose moiety. Xanthine-7-ribosides were previously found by IJzerman and colleagues to bind to A_1 receptors.[20] At rat brain A_3 receptors, we found 1,3-dibutylxanthine 7-riboside to bind with a K_i value of 6 μM, whereas the parent xanthine displayed a K_i value of 143 μM. As a hybrid between adenosine agonist and antagonist struc-

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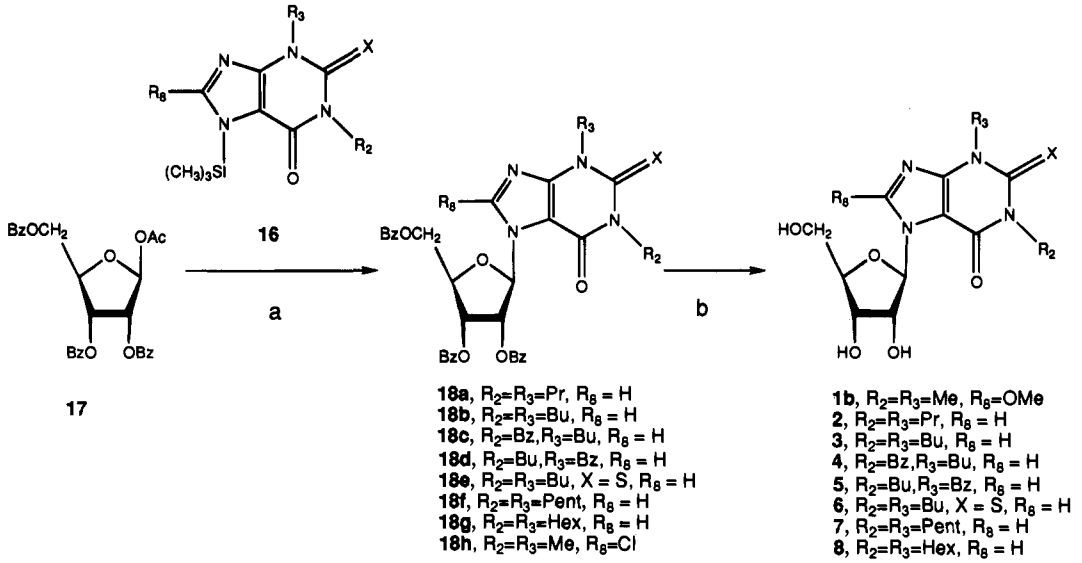


Figure 1. Synthesis of 1,3-dialkylxanthine 7-ribosides. X refers to oxygen, unless noted. Reagents: (a) potassium nonaflate, $SiHCl_3$, CH_3CN; (b) NH_3/MeOH.

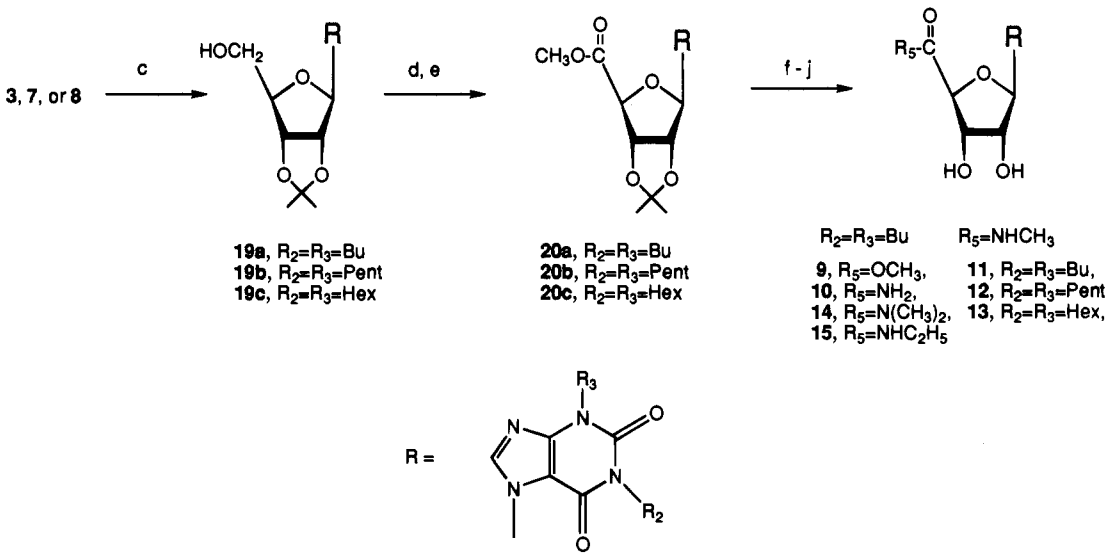


Figure 2. Synthesis of 1,3-dialkylxanthine-7-(5′-uronamidoribosides). X refers to oxygen, unless noted. Reagents: (c) *p*-TsOH, acetone; (d) $RuCl_3$, $NaIO_4$, $CHCl_3$–CH_3CN–H_2O (2:2:3); (e) EDAC, DMAP, MeOH; (f) 88% HCO_2H; (g) (i) $MeNH_2$, MeOH, 85 °C, (ii) 88% HCO_2H; (h) (i) NH_3, MeOH, 85 °C, (ii) 88% HCO_2H; (i) (i) $EtNH_2$, MeOH, 85 °C, (ii) 88% HCO_2H; (j) (i) Me_2NH, MeOH, 85 °C, (ii) 88% HCO_2H.

tures, it proved to be a partial agonist[16] in the A_3-mediated inhibition of adenylate cyclase, as was reported previously for xanthine 7-ribosides acting at A_1 receptors.[29] Since 1,3-dibutylxanthine 7-riboside was nonselective, we explored the structure–activity relationships in this series of unnatural nucleosides in an effort to identify A_3-selective agents.

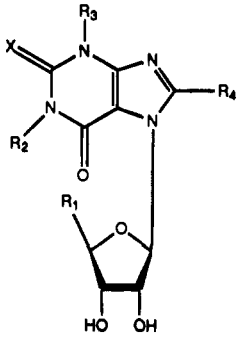
Results

Xanthine 7-ribosides modified with various alkyl substituents at 1- and 3-positions and with uronamide groups on the 5′-position substituent were synthesized (Figures 1 and 2) and tested in radioligand binding assays (Tables 1 and 2) at rat brain A_1, A_{2a}, and A_3 adenosine receptors. Affinity at A_3 receptors was measured in Chinese hamster ovary (CHO) cells stably expressing cloned rat brain A_3 receptors.[1] The radioligand used for binding to A_3 receptors was the recently reported [[^{125}I]-4-amino-3-iodobenzyl]adenosine-5′-*N*-methyluronamide (AB-MECA), which has a K_d value of 1.48 nM.[19] Affinity at A_1 receptors was measured in rat cortical membranes using [^{3}H]-(*R*)-N^6-(phenylisopropyl)-adenosine (PIA)[17] and at A_{2a} receptors in rat striatal membranes using [^{3}H]-2-[[[4-(2-carboxyethyl)phenyl]-ethyl]amino]-5′-(*N*-ethylcarbamoyl)adenosine (CGS 21680).[18]

The synthesis of theophylline-7-riboside, **1a**, and other xanthine glycosides has been described.[20–22] Silylated xanthines[25] were condensed with 1-acetyl-2,3,5-tri-*O*-benzoylribofuranoside using potassium nonaflate and trichlorosilane as Lewis acid catalyst (Figure 1). Unsymmetrical 1,3-disubstitution was accomplished by glycosylation of a mixture of 1-benzyl-3-butylxanthine and 3-benzyl-1-butylxanthine with acetyl 2,3,5-tri-*O*-benzoylribofuranoside followed by chromatographic separation and fractional crystallization of the isomers. Debenzoylation of **18a–g** with methanolic ammonia produced xanthine 7-ribosides **2–8**.

In order to synthesize 5′-modified xanthine nucleosides, the 2′- and 3′-hydroxyl groups were selectively

Table 1. Affinities of Xanthine Riboside Derivatives in Radioligand Binding Assays at Rat Brain A_1, A_{2a}, and A_3 Receptors and the Ratio of K_i Values, Indicating Selectivity for A_3 Receptors[a-d]



R_4 = H and X = O, unless noted.

compound	R_1	R_2	R_3	K_i (nM) or % inhibition[d] $K_i(A_1)$[a]	$K_i(A_{2a})$[b]	$K_i(A_3)$[c]	A_1/A_3	A_{2a}/A_3
1a[e]	$HOCH_2$	Me	Me	27000	2% (10^{-4})	89400	0.30	>1
1b[f]	$HOCH_2$	Me	Me	21 ± 3% (10^{-4})	4% (10^{-4})	74.0 ± 6.8	>1	>1
2[e]	$HOCH_2$	Pr	Pr	15900	32% (10^{-4})	81200	0.20	>1
3[e]	$HOCH_2$	Bu	Bu	4190	19500	6030	0.69	3.2
4	$HOCH_2$	Bz	Bu	1720 ± 30	4510 ± 1230	12400 ± 20	0.14	0.36
5	$HOCH_2$	Bu	Bz	2190 ± 390	8670 ± 1890	12900 ± 300	0.17	0.67
6[g]	$HOCH_2$	Bu	Bu	2250 ± 470	4250 ± 580	1400 ± 160	1.6	3.0
7	$HOCH_2$	pentyl	pentyl	8790 ± 1580	47300 ± 2200	4810 ± 1070	1.8	9.8
8	$HOCH_2$	hexyl	hexyl	9750 ± 400	7.8 ± 3.1% (10^{-5})	43000 ± 3400	0.23	
9	CH_3OCO	Bu	Bu	3720 ± 200	0% (3×10^{-6})	3230 ± 590	1.2	>1
10	H_2NCO	Bu	Bu	3060 ± 150	54900 ± 5300	15300 ± 700	0.20	3.6
11	MeNHCO	Bu	Bu	37300 ± 4600	19 ± 2% (10^{-4})	229 ± 27	160	>400
12	MeNHCO	pentyl	pentyl	11200 ± 1000	2% (10^{-4})	2630 ± 260	4.3	≫1
13	MeNHCO	hexyl	hexyl	30800 ± 4900	0% (10^{-4})	10300 ± 360	3.0	>10
14	Me_2NCO	Bu	Bu	9100 ± 2450	53500 ± 8700	228000 ± 9000	0.040	0.23
15	EtNHCO	Bu	Bu	6210 ± 1060	38100 ± 3500	602 ± 76	10	63

[a] Displacement of specific [^{3}H]PIA binding, unless noted, in rat brain membranes expressed as K_i ± SEM in nM (n = 3–5). [b] Displacement of specific [^{3}H]CGS 21680 binding, unless noted, in rat striatal membranes, expressed as K_i ± SEM in nM (n = 3–6). [c] Displacement of specific [^{125}I]AB-MECA binding, unless noted, in membranes of CHO cells stably transfected with the rat A_3-cDNA, expressed as K_i ± SEM in nM (n = 3–5). [d] A percent value indicates the percent displacement of radioligand at the concentration (M) given in parentheses. When one value is a percent, an exact ratio of K_i values cannot be determined. In such cases, a conservative estimate of the boundary of this ratio is given. [e] Values from van Galen et al.[16] A_3 affinity vs [^{125}I]APNEA. [f] R_4 = OCH_3. [g] X = S.

Table 2. Characterization of 1,3-Dialkylxanthine 7-Riboside Derivatives and Intermediates

compd	mp (°C)	formula	analysis
1b	213–214	$C_{13}H_{18}N_4O_7$[a]	C, H, N
3	139–140	$C_{18}H_{28}N_4O_6$	C, H, N
4	74–75	$C_{21}H_{26}N_4O_6$	C, H, N
5	119–122	$C_{21}H_{28}N_4O_6$	C, H, N
6	160.5–161.5	$C_{18}H_{28}N_4O_5S_1 \cdot 0.4H_2O$	C, H, N
7	123–123.5	$C_{20}H_{32}N_4O_6 \cdot 0.1(C_2H_5)_2O$	C, H, N
8	115–116	$C_{22}H_{36}N_4O_6$	C, H, N
9	178–179	$C_{19}H_{28}N_4O_7$	C, H, N
10	158.4	$C_{18}H_{28}N_5O_6 \cdot 0.3CH_3OH$	C, H, N
11	180–181	$C_{19}H_{29}N_5O_6 \cdot 0.48H_2O$	C, H, N
12	185	$C_{21}H_{33}N_5O_6$[a]	C, H, N
13	173–175	$C_{23}H_{37}N_5O_6$	C, H, N
14	154.4–154.9	$C_{20}H_{31}N_5O_6 \cdot 0.52C_6H_{14}$[a]	C, H, N
15	189.4–189.8	$C_{20}H_{31}N_5O_6 \cdot 0.4H_2O$	C, H, N
19a	syrup	$C_{21}H_{32}N_4O_6$	C, H, N
19b	syrup	$C_{25}H_{40}N_4O_6$	C, H, N
20a	72–73	$C_{22}H_{32}N_4O_7$	C, H, N

[a] High-resolution mass in FAB$^+$ mode (measured in ppm). Calcd for **1b**: $C_{13}H_{19}N_4O_7$ 343.1254, found 343.1252. Calcd for **12**: $C_{21}H_{34}N_5O_6$ 452.2509, found 452.2515. Calcd for **14**: $C_{20}H_{32}N_5O_6$ 438.2353, found 438.2354.

protected by isopropylidenation (Figure 2). Oxidation of the 5′-hydroxyl group was accomplished under mild conditions using ruthenium chloride in a procedure modified from ref 23. When 0.1 equiv of ruthenium chloride was used, as described in the literature, deglycosylation occurred, and the reaction could not be controlled. Use of only 0.01 equiv of ruthenium chloride suppressed the deglycosylation, and a longer reaction time was required. The 5′-carboxylic acid obtained was esterified as the methyl ester by a modification of the Hassner procedure.[24] The methyl ester was purified by silica gel column chromatography. Replacement of methyl ester group with several nucleophiles, such as methylamine, ammonia, dimethylamine, and ethylamine, and subsequent deisopropylidenation produced the 5′-modified xanthine 7-ribosides **9**–**11**, **13**–**15**. For the preparation of 8-substituted xanthine 7-ribosides, direct bromination of 1,3-dibutyl-7-[2,3-isopropylidene-5-(methylamido)-β-D-ribofuranosyl]xanthine or 1,3-dipentylxanthine riboside **7** or 2′,3′,5′-triacetyl-1,3-dipentylxanthine riboside was attempted. Use of bromine or *N*-bromosuccinimide (NBS) failed to provide the desired product. An alternate approach was the condensation of an 8-substituted-1,3-dibutylxanthine with the riboside sugar **17** under the standard condensation conditions. This reaction succeeded only with 8-substituted 1,3-dimethylxanthines and not with the corresponding 1,3-dibutyl- or 1,3-dipentylxanthines, likely as a result of steric hindrance by the 1-butyl or 1-pentyl group. Thus **17** was condensed with 8-chlorotheophylline to give **18h**, which was converted to the 8-methoxy derivative **1b** in NH_3/MeOH.

Theophylline 7-riboside, **1a**, and the corresponding 1,3-dipropyl and 1,3-dibutyl analogues, **2** and **3**, respectively, were shown by us previously to bind weakly to A_3 receptors. In this study we have more clearly defined the dependence of affinity of xanthine 7-ribosides at all

of the adenosine receptors on the size of the N_3 and N_1 alkyl substituents. Affinity at A_3 receptors was enhanced by 1,3-dialkyl substituents in the order: Pent ≥ Bu ≫ Hx > Pr ≈ Me. The rank order of affinity at A_1 receptors for 1,3-dialkyl substituents was Bu > Pent ≈ Hex > Pr > Me, and similarly, the order at A_{2a} receptors was Bu > Pent > Pr. In the ribose series, the 1,3-dipentyl analogue, **7**, had the most favorable ratio of A_3 receptor selectivity, although it was only slightly selective (2-fold vs A_1 and 10-fold vs A_{2a}).

Introduction of an aromatic group on the 1- or 3-substituent, as in the benzyl derivatives **4** and **5**, tended to increase the potency slightly at A_1 and A_{2a} receptors (2−4-fold) and decrease potency slightly at A_3 receptors (2-fold) relative to compound **3**. Thus, it appeared that in the ribose series, the presence of a benzyl group was somewhat disadvantageous for achieving selectivity for A_3 receptors.

Introduction of 8-substitution in theophylline 7-riboside in the form of a methoxy group (compound **1b**) diminished affinity at A_1 receptors but not at A_3 receptors. Thus, although a very weak competitor of binding, compound **1b** appeared to be slightly selective for A_3 receptors.

The presence of a 2-thio group vs a 2-oxo group in the pair of 1,3-dibutylxanthine 7-ribosides (cf. compounds **3** and **6**) increased potency at all three subtypes (4-fold at A_3 receptors) and slightly increased A_3 vs A_1 selectivity.

Introduction of an ester group at the 5′-position (compound **9** vs **3**) maintained the same affinity at A_1 receptors as the corresponding 5′-CH_2OH analogue and increased affinity at A_3 receptors by 2-fold. Thus, compound **9** was of equal affinity at A_1 and A_3 receptors, but was selective for A_3 vs A_{2a} receptors. Like the ester derivative, the 5′-primary carboxamide analogue **10** maintained roughly the same affinity at A_1 receptors as compound **3**. However, compound **10** displayed a decreased affinity at A_{2a} and A_3 receptors vs **3** by 2.8- and 2.5-fold, respectively.

The 5′-uronamide modification, which was previously found to enhance A_3 selectivity among N^6-benzyladenosine derivatives, was incorporated into xanthine 7-ribosides with similar results. The affinity of 5′-uronamides at A_3 receptors depended on the *N*-alkyluronamide substituent in the order MeNH > EtNH ≫ NH_2 ≫ Me_2N (all 1,3-dibutylxanthine analogues, compounds **10**, **11**, **13**−**15**). 1,3-Dibutylxanthine 7-riboside 5′-*N*-methylcarboxamide, **11**, with a K_i value of 229 nM at A_3 receptors, was 160-fold selective for A_3 vs A_1 receptors and >400-fold selective vs A_{2a} receptors. The presence of an *N*-methyl group vs a primary carboxamide, **10**, caused a 67-fold increase in affinity at A_3 receptors, and at both A_1 receptors and A_{2a} receptors affinity diminished. Multiple substitution of the 5′-carboxamide group, as in the *N*,*N*-dimethyl analogue, **14**, was not favorable for A_3 selectivity. Relative to compound **11**, the dimethyl derivative had slightly increased affinity at A_1 and A_{2a} receptors, and the affinity at A_3 receptors was decreased by 1000-fold. The *N*-ethyl analogue, **15**, was slightly less potent than compound **11** at A_3 receptors, but less selective. Thus, a monomethyl substitution in the 5′-uronamide series appears to be optimal.

The effect of decreased A_3 potency as a result of increasing the size of the purine 1- and 3-alkyl groups from butyl to hexyl, noted above for the 7-riboside series, was similar in the 5′-uronamide series. A_3 affinity of the 5′-uronamides was dependent on the 1,3-dialkyl substitution in the order Bu > Pent > Hex, while A_1 affinity varied only slightly.

Since compound **11** was very A_3-selective, the affinity of this derivative at non-adenosine receptors was examined in a battery of radioreceptor binding assays (NovaScreen, Division of Oceanix Biosciences, Hanover, MD).[36] At a concentration of 10^{-5} M, the displacement of radioligand from cholinergic (M_1, M_2, and M_3), dopamine (D_1 and D_2), serotonin (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_2, and 5-HT_3), central benzodiazepine, amino acid ($GABA_A$; $GABA_B$; *N*-methyl-D-aspartate; kainate; quisqualate; glycine, strychnine sensitive and insensitive; MK-801), PCP, sigma, and cholecystokinin (central and peripheral) receptors was insignificant (0 ± 20%). At 10^{-5} M compound **11** displaced the binding of [^{3}H]serotonin by 44%. The displacement of binding of radioligand from second messenger sites (forskolin and inositol triphosphate) and serotonin uptake sites and the percent inhibition of monoamine oxidase (A and B) were insignificant. The observation that high affinity was not observed at any of these sites emphasizes the selectivity of compound **11** for A_3 receptors.[37] The lipophilicity of compound **11** was examined. It partitioned strongly in the octanol layer (log P > 2) in an extraction from aqueous phosphate buffer (pH 7.0, 50 mM).

The effects of compound **11** on A_3-mediated inhibition of adenylate cyclase were also examined (Figure 3) using membranes from CHO cells stably transfected with rat A_3 receptors. We previously demonstrated that the corresponding riboside derivative, compound **3**, inhibited adenylate cyclase with less than full efficacy, compared to full agonists such as NECA (5′-(*N*-ethylcarbamoyl)adenosine); thus the dose−response curve for **3** was shallow and did not reach the maximal effect (Figure 3A).[16] Compound **11**, however, appeared to be a full agonist, with a maximal 36.3 ± 5.6% inhibition of forskolin-stimulated adenylate cyclase at 10^{-4} M. Compound **11**, with a IC_{50} value estimated at ~18 μM, was less potent than NECA which had an IC_{50} value of 5.55 ± 1.83 μM. This is consistent with the 2-fold higher affinity of NECA at rat A_3 receptors (113 nM). The discrepancy between IC_{50} values in the functional assay and the K_i values in binding assay, i.e., the latter is lower by a factor of 40 or more, is typical of the effects of other adenosine agonists (N^6-benzyladenosin-5′-uronamides) at A_3 receptor-mediated inhibition of adenylate cyclase.[38] To rule out the possible partial agonist properties of compound **11**, we examined the adenylate cyclase effects of a potent and selective A_3 agonist (Figure 3B), 2-chloro-N^6-(3-iodobenzyl)adenosine-5′-*N*-methyluronamide,[38] alone and in the presence of compound **11** (40 μM). The maximal inhibitory effect was reached, and there was no significant right-shift of the curve, thus no antagonistic properties of **11** could be detected. Therefore compound **11** was a full agonist.

Discussion

We have found a general parallel between the structure−activity relationships (SAR) for adenosine derivatives as A_3 agonists[13] and xanthine 7-ribosides, particu-

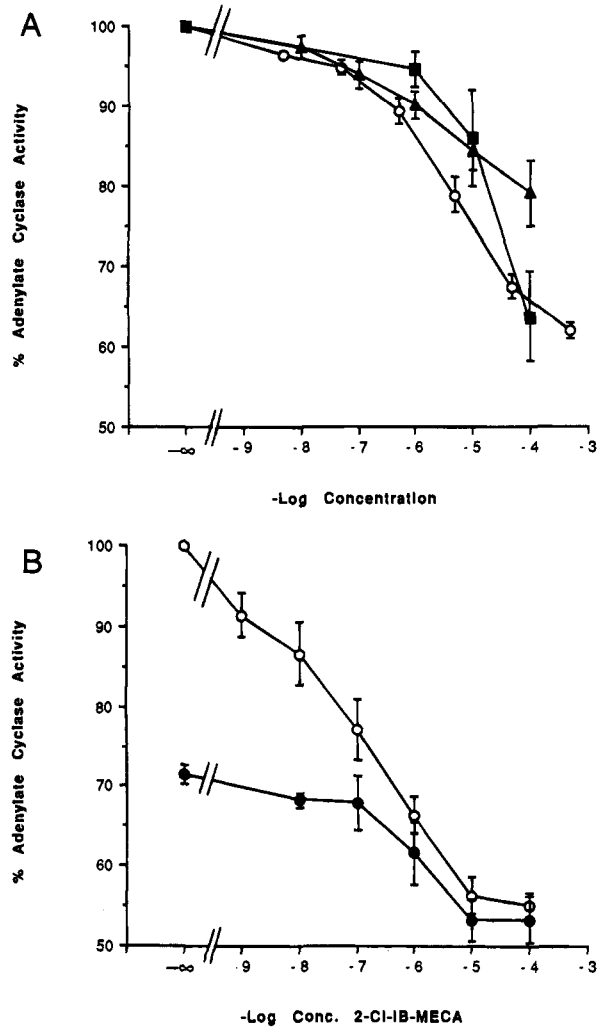


Figure 3. Inhibition of adenylate cyclase in membranes from CHO cell stably transfected with rat A_3 receptors. The assay was carried out as described in Materials and Methods in the presence of 1 μM forskolin. Each data point is shown as mean ± SEM for three determinations. (A) Concentration-dependent effects on adenylate cyclase by a NECA (IC_{50} value 5.55 ± 1.83 μM, maximal inhibitory effect 37.9 ± 1.0% at 5 × 10^{-4} M, circles), compound **3** (triangles), and compound **11** (squares). (B) Concentration-dependent inhibition of adenylate cyclase by the potent and selective A_3 agonist 2-Cl-IB-MECA (2-chloro-N^6-(3-iodobenzyl)adenosine-5′-*N*-methyluronamide) in the absence (IC_{50} value 140 ± 55 nM, maximal inhibitory effect 45 ± 1.6% at 10^{-4} M, open circles) and presence (filled circles) of compound **11** (40 μM). Compound **11** (40 μM) inhibited basal adenylate cyclase activity by 28.6 ± 1.2% of control.

larly in the ribose moiety. The substituent effects at the 5′-position, i.e., for uronamide derivatives, are nearly identical. This parallel in SAR is supportive of our A_3 receptor model which features the ribose moiety of the ligand, either adenosine or xanthine ribosides, coordinated by hydrogen bonding to the same amino acid residue, His of the seventh transmembrane helix.

Xanthine ribosides were originally tested as ligands at adenosine receptors in an effort to develop a conformational model of binding.[20,21] The 7-ribosides have affinity for the receptor, whereas the 9-ribosides do not bind.[26,27] For purposes of comparing SAR of xanthine and adenosine derivatives, one may consider the case in which the purine rings overlap in a "flipped" orientation,[28] i.e., the xanthine N-7 occupies the same position as the adenosine N-9, xanthine N-3 corresponds roughly to C-6 of adenosine, etc. Thus, the position corresponding to the critical N^6-substituent on adenosine analogues would correspond approximately to the xanthine 3-substituent in the xanthine 7-ribosides, minus the α-carbon which might occupy the space of the N^6-NH. A 3-benzyl group, as in compound **4**, somewhat enhanced affinity at A_1 receptors, in parallel to the modest enhancement of affinity at A_1 receptors of N^6-phenyladenosine derivatives. Thus, some of the data in this study are compatible with the hypothesis of a "flipped" overlap of purines.

However, there were possible differences between the two classes of nucleosides in structural determinants of affinity on the purine ring. At the purine 8-position, substitution is tolerated in A_3 receptor binding (8-methoxy) for xanthine 7-ribosides but not for adenosine derivatives, as in 8-bromoadenosine.[16] Similarly, it was recently reported that 8-alkylamino substitution of theophylline 7-riboside is tolerated at A_1 receptors.[35]

The effects on binding at A_1 and A_{2a} receptors of *syn* vs *anti* conformations about the glycosidic bond of nucleosides have been deduced from the affinity of the xanthine 7-ribosides.[20,21] As was shown by NMR and molecular modeling, the xanthine 7-ribosides have a much stronger energetic preference for the *anti* conformation than do adenosine derivatives, suggesting that this is the conformation favored at the receptors. An examination of NMR chemical shift (δ) values for the xanthine 7-ribosides in this study shows that both the ribose and the ribos-5′-uronamide derivatives have an upfield shift of the C2′-H resonance (for compound **11** at 4.45 ppm in DMSO-d_6) relative to adenosine, indicative of the *anti* conformation.[20] Further support for the *anti* conformation of adenosine binding to the receptors is based on the absence of affinity at adenosine receptors of 8-bromoadenosine, which is restricted energetically to a *syn* conformation. Since the same observations, i.e. activity of xanthine 7-ribosides and inactivity of 8-bromoadenosine,[16] apply to A_3 receptors, it is likely that the glycosidic conformation of adenosine binding at A_3 receptors is similar to that at A_1 receptors, i.e., in a non-*syn* conformation. It is also possible that the orientation is not purely *anti*,[35] since certain 8-substitution of the xanthine 7-ribosides is tolerated.

Xanthine 7-ribosides were initially described as adenosine antagonists,[20] but Borea et al.[29] have suggested that theophylline 7-riboside is a partial agonist at A_1 receptors, based on diminished shifts in binding in the presence of guanine nucleotides. Borea and co-workers also developed more fully a thermodynamic approach to measuring adenosine partial agonism,[30] noting that many adenosine derivatives display a correlation between lower affinity and partial agonism. It is unknown whether the interconnection between intrinsic activity and affinity exists for this series of xanthine ribosides, although for compounds **3** and **11** this generalization applies. We have reported[16a] that 1,3-dibutylxanthine 7-riboside, **3**, is a partial agonist in the inhibition of adenylate cyclase via A_3 adenosine receptors, consistent with its hybrid agonist/antagonist structure. However, the corresponding 5′-*N*-methyluronamide, compound **11**, which is 26-fold more potent than **3** in the A_3 binding assay, is a full agonist. A partial agonist may have therapeutic applications, based on the case of glycine receptors.[31] The indication that compound **3** is a partial agonist may be useful in studying receptor regulation,[32]

which is mainly unexplored for the A_3 receptor. Also, the exploration of partial agonists may lead to the development of antagonists,[32] which are lacking for rat A_3 receptors.

There are also common features between the structure–activity relationships for dialkylxanthines[25] binding to A_3 receptors and xanthine 7-ribosides. The 1,3-dibutyl analogues in both cases contain the optimal chain length (for neutral molecules). A major difference is that for the xanthines, selectivity at the rat A_3 receptor was not achieved.[25] At A_1 receptors, the xanthines are generally more potent than the corresponding xanthine 7-ribosides,[20] while at rat A_3 receptors the converse is true. At other species, however, notably sheep[4] and human[5] A_3 receptors, certain xanthines, particularly those bearing negative charges, bind with high affinity.

We have identified compound **11** (*N*-methyl-(1,3-di-*n*-butylxanthin-7-yl)-β-D-ribofuronamide) as a very selective ligand for A_3 receptors. Although it is not as potent as the adenosine derivative, IB-MECA (5′-*N*-methyl-N^6-(3-iodobenzyl)adenosine), reported recently,[11,13] it is more selective and will add to the useful tools available for studying this newly cloned subtype. The *in vivo* properties of the A_3-selective xanthine 7-ribosides should also be explored, since we have recently proposed a therapeutic capacity of A_3 agonists in neuroprotection,[14,15] and others laboratories have proposed that A_3 antagonists be investigated for antiinflammatory properties.[7] The lipophilicity of **11** suggests that it may cross the blood–brain barrier more readily than other adenosine agonists.[40]

Experimental Section

Chemistry. New compounds were characterized (and resonances assigned) by 300 MHz proton nuclear magnetic resonance mass spectroscopy using a Varian GEMINI-300 FT-NMR spectrometer. Unless noted, chemical shifts are expressed as ppm downfield from tetramethylsilane. Synthetic intermediates were characterized by chemical ionization mass spectrometry (NH_3) and adenosine derivatives by fast atom bombardment mass spectrometry (positive ions in a noba or m-bullet matrix) on a JEOL SX102 mass spectrometer. In the EI mode accurate mass was determined using a VG7070F mass spectrometer. C, H, and N analyses were carried out by Atlantic Microlabs (Norcross, GA), and ±0.4% was acceptable. Analytical TLC plates and silica gel (230–400 mesh) were purchased from VWR (Bridgeport, NJ). A sample of theophylline-7-riboside was kindly provided by Dr. Ad IJzerman (University of Leiden, Netherlands). Xanthines were synthesized by known methods.[25]

8-Methoxytheophylline 7-β-D-Ribofuranoside (1b). A mixture of 8-chlorotheophylline (276 mg, 1.29 mmol) and *N,O*-bis(trimethylsilyl)acetamide (1 mL) in dry dichloromethane (6 mL) was stirred for 40 min at room temperature under nitrogen. Solvent was removed by rotary evaporation *in vacuo* with exclusion of moisture. The residue was suspended in dry acetonitrile (9 mL). Acetyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside (**17**, 500 mg, 1.0 mmol), potassium nonaflate (1.0 g, 2.96 mmol), and trichlorosilane (0.38 mL, 2.8 mmol) were added, and the reaction mixture was refluxed for 4 h under nitrogen. Aqueous saturated sodium bicarbonate (30 mL) and dichloromethane (30 mL) were added. After stirring for 15 min, two layers were separated and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layer and extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. The residue was crystallized from ethyl acetate–hexanes to give **18h** (424 mg). Purification of the filtrate on silica gel column chromatography (hexanes–ethyl acetate, 3:1 → 1:1) yielded additional compound **18h** (59.1 mg, 76%) as a solid: mp shrinks at 179–180 °C and decomposed at 258 °C; ^{1}H NMR ($CDCl_3$) δ 3.38 (s, 3 H, N-CH_3), 3.57 (s, 3 H, N-CH_3), 4.72–4.77 (m, 2 H), 4.90 (m, 1 H), 6.17 (m, 2 H, H-5′), 6.36 (d, J = 4.6 Hz, 1 H, H-1′), 7.25–8.11 (m, 15 H, Ar).

A mixture of **18h** (212 mg, 0.33 mmol) and NH_3/MeOH (20 mL) was stirred for 4 days at room temperature. After the reaction mixture was concentrated to dryness, the residue was purified on silica gel column chromatography (chloroform–methanol, 20:1) to give **1b** (33 mg, 29%) as a soft solid: ^{1}H NMR (DMSO-d_6) δ 3.21 (s, 3 H, NCH_3), 3.43 (s, 3 H, NCH_3), 3.45 (m, 1 H, H-5′a), 3.60 (dd, J = 11.7 and 5.2 Hz, 1 H, H-5′b), 3.79 (m, 1 H), 4.02 (m, 1 H), 4.11 (s, 4 H, OCH_3), 4.59 (t, J = 5.9 Hz, 1 H), 4.78 (t, J = 5.4 Hz, 1 H, exchangeable with D_2O, 5′-OH), 5.08 (d, J = 4.8 Hz, 1 H, exchangeable with D_2O, OH), 5.25 (d, J = 6.4 Hz, 1 H, exchangeable with D_2O, OH), 5.89 (d, J = 6.5 Hz, 1 H, H-1′).

1,3-Di-*n*-butylxanthine 7-β-D-Ribofuranoside (3). A mixture of 1,3-di-*n*-butylxanthine (3 g, 11.35 mmol), ammonium sulfate (5 mg), and hexamethyldisilazane (HMDS, 20 mL) was stirred in reflux for 1 h under nitrogen. HMDS was removed by rotary evaporation *in vacuo* with exclusion of moisture. The brown syrup was dissolved in dry acetonitrile (70 mL). Acetyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside (**17**, 5.73 g, 11.36 mmol), potassium nonaflate (15.35 g, 45.39 mmol), and trichlorosilane (4.29 mL, 42.5 mmol) were added to the solution, and the reaction mixture was refluxed for 3 h under nitrogen. Aqueous saturated sodium bicarbonate (30 mL) and chloroform (30 mL) were added. After stirring for 30 min, two layers were separated and the aqueous layer was extracted with chloroform (300 mL). The combined organic layer and extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. Purification on silica gel column chromatography (chloroform–methanol, 250:1 → 100:1) yielded compound **18b** as pale yellow foam: ^{1}H NMR ($CDCl_3$) δ 0.92–0.98 (m, 6 H, 2 × CH_3), 1.71–1.44 (m, 4 H, 2 × CH_2), 1.53–1.61 (m, 2 H, CH_2), 1.68–1.76 (m, 2 H, CH_2), 3.98 (t, J = 7.6 Hz, 2 H, NCH_2), 4.09 (t, J = 7.5 Hz, 2 H, NCH_2), 4.71–4.82 (m, 2 H), 4.87 (dd, J = 11.5 and 2.7 Hz, 1 H), 5.98–6.05 (m, 2 H, H-5′), 6.68 (d, J = 4.9 Hz, 1 H, H-1′), 7.34–7.62, 7.91–8.11 (m, 16 H, Ar and H-8).

A mixture of compound **18b** and methanolic ammonia (saturated at 0 °C, 80 mL) was stirred for 2.5 days at room temperature. The volatiles were removed, and the residue was purified on silica gel column chromatography (chloroform–methanol, 20:1) to give compound **3** (3.5 g, 78.1%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 0.89 (pseudo t, J = 7.4 and 7.3 Hz, 6 H, 2 × CH_3), 1.23–1.35 (m, 4 H, 2 × CH_2), 1.47–1.57 (m, 2 H, CH_2), 1.59–1.69 (m, 2 H, CH_2), 3.54 (dd, J = 12.1 and 3.7 Hz, 1 H), 3.68 (dd, J = 12.1 and 3.7 Hz, 1 H), 3.84–3.94 (m, 2 H), 3.99 (t, J = 7.2 Hz, 2 H, NCH_2), 4.08 (t, J = 4.9 Hz, 1 H, NCH_2), 4.33 (t, J = 4.8 Hz, 1 H), 5.05 (t, 1 H, exchangeable with D_2O, 5′-OH), 5.15 (d, 1 H, exchangeable with D_2O, OH), 5.50 (d, 1 H, exchangeable with D_2O, OH), 6.10 (d, J = 4.8 Hz, 1 H, H-1′), 8.45 (s, 1 H, H-8).

1-Benzyl-3-butylxanthine 7-β-D-Ribofuranoside (4) and 3-Benzyl-1-butylxanthine 7-β-D-Ribofuranoside (5). A mixture of 1-benzyl-3-butylxanthine and 3-benzyl-1-butylxanthine (3.89 g, 13.04 mmol), ammonium sulfate (5 mg), and HMDS (20 mL) was silylated by reflux for 1 h under nitrogen. HMDS was removed by rotary evaporation *in vacuo* with exclusion of moisture. The brown syrup was dissolved in dry acetonitrile (70 mL). Acetyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside (**17**, 5.73 g, 11.36 mmol), potassium nonaflate (15.35 g, 45.39 mmol), and trichlorosilane (4.29 mL, 42.5 mmol) were added to the solution, and the reaction mixture was refluxed for 3.5 h under nitrogen. After similar workup for compound **18b**, the residue was purified on silica gel column chromatography (chloroform–methanol, 250:1 → 100:1) to give **18d** [R_f = 0.76 (chloroform–methanol, 100:1)] and **18c** [R_f = 0.70 (chloroform–methanol, 100:1)] as a syrup. Compound **18d**: ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3 H, CH_3), 1.36 (m, 2 H, CH_2), 1.55 (m, 2 H, CH_2), 3.97 (t, J = 7.6 Hz, 2 H, N-CH_2), 4.73 (dd, J = 11.5 and 4.3 Hz, 1 H, H-5′a), 4.79 (m, 1 H, H-4′), 4.86 (dd, J = 11.5 and 2.7 Hz, 1 H, H-5′b), 5.26 (s, 2 H, NCH_2-Ph), 6.01 (m, 2 H, H-2′, -3′), 6.68 (d, J = 4.7 Hz, 1 H, H-1′),

7.27–7.62, 7.93–8.11 (m, 16 H, Ar and H-8). Compound **18c**: ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3 H, CH_3), 1.36 (m, 2 H, CH_2), 1.72 (m, 2 H, CH_2), 4.07(t, J = 7.5 Hz, 2 H, NCH_2), 4.71–4.90 (m, 3 H, H-4′, -5′), 5.26 (s, 2 H, NCH_2Ph), 6.01 (m, 2 H, H-2′, -3′), 6.71 (d, J = 4.7 Hz, 1 H, H-1′), 7.20–7.62, 7.92–8.11 (m, 16 H, Ar and H-8).

A mixture of compound **18d** and methanolic ammonia (saturated at 0 °C, 50 mL) was stirred for 4 days at room temperature. The volatiles were removed, and the residue was purified on silica gel column chromatography (chloroform–methanol, 20:1) to give compound **5** (1.65 g, 34%) as a colorless syrup which was crystallized from ether/methanol: ^{1}H NMR (DMSO-d_6) δ 0.89 (pseudo t, J = 7.4 and 7.2 Hz, 3 H, CH_3), 1.31 (m, 2 H, CH_2), 1.53 (m, 2 H, CH_2), 3.55 (dt, J = 12.5 and 4.7 Hz, 1 H, H-5′a), 3.69 (dt, J = 12.0 and 4.7 Hz, 1 H, H-5′b), 3.89 (m, 1 H, H-4′), 3.91 (t, J = 7.2 Hz, 2 H, NCH_2), 4.09 (q, J = 4.9 Hz, 1 H, H-3′), 4.34 (q, J = 5.0 Hz, 1 H, H-2′), 5.04 (t, J = 5.3 Hz, 1 H, exchangeable with D_2O, 5′-OH), 5.14 (d, J = 5.3 Hz, 1 H, exchangeable with D_2O, OH), 5.18 (s, 2 H, NCH_2-Ph), 5.48 (d, J = 5.8 Hz, 1 H, exchangeable with D_2O, OH), 6.12 (d, J = 4.6 Hz, 1 H, H-1′), 7.24–7.36 (m, 5 H, Bn), 8.48 (s, 1 H, H-8).

A mixture of compound **18c** and **18d** in methanolic ammonia (saturated at 0 °C, 30 mL) was stirred for 3 days at room temperature. The volatiles were removed, and the residue was purified on silica gel column chromatography (chloroform–methanol, 24:1) to give a mixture of compound **4** and **5** (0.75 g, 15%) which was crystallized from ether/methanol. Part of the solid was recrystallized from ethyl acetate with heating and cooling for 5 h. The resulting white, cotton-like solid was filtered and dried *in vacuo* to give **4**: ^{1}H NMR (DMSO-d_6) δ 0.89 (pseudo t, J = 7.4 and 7.2 Hz, 3 H, CH_3), 1.30 (m, 2 H, CH_2), 1.63 (m, 2 H, CH_2), 3.55 (dt, J = 11.8 and 4.6 Hz, 1 H, H-5′a), 3.68 (dt, J = 12.0 and 4.0 Hz, 1 H, H-5′b), 3.91 (q, J = 4.0 Hz, 1 H, H-4′), 4.00 (t, J = 7.3 Hz, 1 H, NCH_2), 4.09 (q, J = 4.9 Hz, 1 H, H-3′), 4.34 (q, J = 5.0 Hz, 1 H, H-2′), 5.04 (t, J = 5.3 Hz, 1 H, exchangeable with D_2O, 5′-OH), 5.07 (s, 2 H, NCH_2Ph), 5.14 (d, J = 5.3 Hz, 1 H, exchangeable with D_2O, OH), 5.48 (d, J = 5.8 Hz, 1 H, exchangeable with D_2O, OH), 6.12 (d, J = 4.6 Hz, 1 H, H-1′), 7.23–7.30 (m, 5 H, Bn), 8.50 (s, 1 H, H-8).

1,3-Di-*n*-butyl-2-thioxanthine 7-β-D-Ribofuranoside (6). A solution of 1,3-di-*n*-butyl-2-thioxanthine (0.325 g, 1.16 mmol) and *N,O*-bis(trimethylsilyl)acetamide (0.96 mL, 2.8 mmol) in dry methylene chloride (6 mL) was stirred for 30 min at room temperature under nitrogen. After the reaction mixture was concentrated to dryness *in vacuo*, the residue was dissolved in dry acetonitrile (10 mL). Acetyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside (**17**, 0.5 g, 0.99 mmol), potassium nonaflate (1 g, 2.96 mmol), and trichlorosilane (0.38 mL, 2.8 mmol) were added to the solution, and the reaction mixture was refluxed for 18 h under nitrogen. After similar workup for compound **3**, the residue was purified on silica gel column chromatography (hexanes–ethyl acetate, 3:1) to yield compound **18e** (0.58 g, 82.4%) as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 0.91–1.00 (m, 6 H, 2 × CH_3), 1.41 (sixtett, 4 H, 2 × CH_2), 1.63–1.76 (m, 2 H, CH_2), 1.79–1.84 (m, 2 H, CH_2), 4.54 (pseudo t, J = 7.9 and 7.6 Hz, 2 H, NCH_2), 4.64 (pseudo t, J = 8.2 and 7.6 Hz, 2 H, NCH_2), 4.74 (dd, J = 11.4 and 3.7 Hz, 1 H), 4.81 (m, 1 H), 4.88 (dd, J = 11.4 and 2.5 Hz, 1 H), 5.99 (m, 2 H), 6.70 (d, J = 4.4 Hz, 1 H, H-1′), 7.34–7.63, 7.94–8.11 (m, 16 H, Ar and H-8).

A mixture of compound **18e** (555 mg, 0.78 mmol) and methanolic ammonia (saturated at 0 °C, 45 mL) was stirred for 22 h at room temperature. The volatiles were removed, and the residue was purified on silica gel column chromatography (chloroform–methanol, 20:1) to give compound **6** (276 mg, 85.3%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 0.93 (t, J = 7.3 Hz, 6 H, 2 × CH_3), 1.31–1.42 (m, 4 H, 2 × CH_2), 1.60–1.69 (m, 2 H, CH_2), 1.72–1.79 (m, 2 H, CH_2), 3.57 (dd, J = 12.1 and 3.5 Hz, 1 H, H-5′a), 3.71 (dd, J = 12.1 and 3.5 Hz, 1 H, H-5′b), 3.94 (m, 1 H, H-4′), 4.10 (t, J = 4.9 Hz, 1 H, H-3′), 4.33 (t, J = 4.6 Hz, 1 H, H-2′), 4.47 (pseudo t, J = 8.3 and 7.2 Hz, 2 H, NCH_2), 4.57 (pseudo t, J = 7.8 and 7.5 Hz, 2 H, NCH_2), 5.09 (br s, 1 H, exchangeable with D_2O, OH), 5.15 (br s, 1 H, exchangeable with D_2O, OH), 5.52 (br s, 1 H, exchangeable with D_2O, OH), 6.14 (d, J = 4.0 Hz, 1 H, H-1′), 8.63 (s, 1 H, H-8).

1,3-Di-*n*-pentylxanthine 7-β-D-Ribofuranoside (7). A solution of 1,3-di-*n*-pentylxanthine (0.377 g, 1.29 mmol) and *N,O*-bis(trimethylsilyl)acetamide (0.96 mL, 2.8 mmol) in dry methylene chloride (5 mL) was stirred for 30 min at room temperature under nitrogen. After the reaction mixture was concentrated to dryness *in vacuo*, the residue was dissolved in dry acetonitrile (10 mL). Acetyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside (**17**, 0.5 g, 0.99 mmol), potassium nonaflate (1 g, 2.96 mmol), and trichlorosilane (0.38 mL, 2.8 mmol) were added to the solution, and the reaction mixture was refluxed for 20 h under nitrogen. After similar workup for compound **3**, the residue was purified on silica gel column chromatography (hexanes–ethyl acetate, 3:1) to yield compound **18f** (0.599 g, 82.1%) as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 0.87 (m, 6 H, 2 × CH_3), 1.25–1.35 (m, 8 H, 4 × CH_2), 1.57–1.60 (m, 2 H, CH_2), 1.72–1.77 (m, 2 H, CH_2), 3.96 (pseudo t, J = 7.9 and 7.5 Hz, 2 H, N-CH_2), 4.08 (pseudo t, J = 8.2 and 7.1 Hz, 2 H, NCH_2), 4.72 (dd, J = 11.8 and 4.6 Hz, 1 H), 4.79 (m, 1 H), 4.86 (dd, J = 11.4 and 2.5 Hz, 1 H), 6.02 (m, 2 H), 6.69 (d, J = 4.7 Hz, 1 H, H-1′), 7.34–7.62, 7.91–8.11 (m, 16 H, Ar and H-8).

A mixture of compound **18f** (570 mg, 0.77 mmol) and methanolic ammonia (saturated at 0 °C, 15 mL) was stirred for 67 h at room temperature. The volatiles were removed, and the residue was purified on silica gel column chromatography (chloroform–methanol, 20:1) to give compound **7** (280 mg, 85.4%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 0.83–0.88 (m, 6 H, 2 × CH_3), 1.23–1.32 (m, 8 H, 4 × CH_2), 1.49–1.59 (m, 2 H, CH_2), 1.61–1.71 (m, 2 H, CH_2), 3.51–3.56 (m, 1 H, H-5′a), 3.66–3.71 (m, 1 H, H-5′b), 3.86 (pseudo t, J = 7.5 and 7.2, 1 H, N-CH_2), 3.91 (m, 1 H, H-4′), 3.98 (t, J = 7.2 Hz, 1 H, N-CH_2), 4.09 (q J = 4.9 Hz, 1 H, H-3′), 4.34 (q, J = 5.1 Hz, 1 H, H-2′), 5.04 (pseudo t, J = 5.2 and 5.0 Hz, 1 H, exchangeable with D_2O, 5′-OH), 5.14 (d, J = 5.4 Hz, 1 H, exchangeable with D_2O, OH), 5.46 (d, J = 6.1 Hz, 1 H, exchangeable with D_2O, OH), 6.11 (d, J = 4.7 Hz, 1 H, H-1′), 8.46 (s, 1 H, H-8).

1,3-Di-*n*-hexylxanthine 7-β-D-Ribofuranoside (8). A solution of 1,3-di-*n*-hexylxanthine (0.428 g, 1.34 mmol) and *N,O*-bis(trimethylsilyl)acetamide (0.99 mL, 2.97 mmol) in dry methylene chloride (5 mL) was stirred for 40 min at room temperature under nitrogen. After the reaction mixture was concentrated to dryness *in vacuo*, the residue was dissolved in dry acetonitrile (10 mL). Acetyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside (**17**, 0.5 g, 0.99 mmol), potassium nonaflate (1 g, 2.96 mmol), and trichlorosilane (0.38 mL, 2.8 mmol) were added to the solution, and the reaction mixture was refluxed for 14 h under nitrogen. After similar workup for compound **3**, the residue was purified on silica gel column chromatography (hexanes–ethyl acetate, 3:1) to yield compound **18g** (0.526 g, 69.4%) as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 0.77–0.87 (m, 6 H, 2 × CH_3), 1.22–1.40 (m, 12 H, 6 × CH_2), 1.54–1.59 (m, 2 H, CH_2), 1.69–1.74 (m, 2 H, CH_2), 3.96 (t, J = 7.6 Hz, 2 H, NCH_2), 4.08 (t, J = 7.6 Hz, 2 H, NCH_2), 4.74 (dd, J = 11.6 and 4.3 Hz, 1 H, H-5′a), 4.80 (m, 1 H, H-4′), 4.86 (dd, J = 11.6 and 2.5 Hz, 1 H, H-5′b), 6.02 (m, 2 H), 6.68 (d, J = 4.8 Hz, 1 H, H-1′), 7.34–7.62, 7.91–8.11 (m, 16 H, Ar and H-8).

A mixture of compound **18g** (520 mg, 0.68 mmol) and methanolic ammonia (saturated at 0 °C, 15 mL) was stirred for 4 days at room temperature. The volatiles were removed, and the residue was purified on silica gel column chromatography (chloroform-methanol, 20:1) to give compound **8** (240 mg, 80%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 0.85 (m, 6 H, 2 × CH_3), 1.27 (m, 12 H, 6 × CH_2), 1.53 (m, 2 H, CH_2), 1.64 (m, 2 H, CH_2), 3.56 (dt, 1J = 11.8 and 4.7 Hz, 1 H, H-5′a), 3.68 (dt, J = 11.7 and 4.4 Hz, 1 H, H-5′b), 3.86 (pseudo t, J = 7.8 and 6.9, 1 H, N-CH_2), 3.91 (m, 1 H, H-4′), 3.98 (pseudo t, J = 7.5 and 7.1 Hz, 1 H, NCH_2), 4.08 (q, J = 5.0 Hz, 1 H, H-3′), 4.34 (q, J = 5.1 Hz, 1 H, H-2′), 5.05 (pseudo t, J = 5.4 and 5.3 Hz, 1 H, exchangeable with D_2O, 5′-OH), 5.15 (d, J = 5.5 Hz, 1 H, exchangeable with D_2O, OH), 5.48 (d, J = 5.8 Hz, 1 H, exchangeable with D_2O, OH), 6.11 (d, J = 4.7 Hz, 1 H, H-1′), 8.47 (s, 1 H, H-8).

Methyl 1,3-Di-*n*-butylxanthine 7-β-D-Ribofuronate (9).

A solution of compound **20a** (30 mg, 0.065 mmol) in 88% formic acid (3 mL) was stirred for 3 h at room temperature, and the solvent was removed by rotary evaporation. The residue was purified by preparative TLC (chloroform–methanol, 10:1) to yield compound **9** (14.8 mg, 57%) as a colorless solid: ^{1}H NMR (DMSO-d_6) δ 0.90 and 0.91 (2 × t, J = 7.5 Hz, 2 × 3 H, 2 × CH_3), 1.23–1.35 (m, 4 H, 2 × CH_2), 1.47–1.57 (m, 2 H, CH_2), 1.60–1.70 (m, 2 H, CH_2), 3.72 (s, 3 H, OCH_3), 3.87 (t, J = 7.3 Hz, 2 H, NCH_2), 4.00 (t, J = 7.2 Hz, 2 H, NCH_2), 4.29 (m, 1 H), 4.49 (m, 2 H), 5.73 (d, J = 6.1 Hz, exchangeable with D_2O, 1 H, OH), 5.81 (d, J = 4.7 Hz, exchangeable with D_2O, 1 H, OH), 6.29 (d, J = 5.4 Hz, 1 H, H-1′), 8.46 (s, 1 H, H-8).

1,3-Di-*n*-butylxanthine 7-β-D-Ribofuronamide (10). A mixture of compound **20a** (87 mg, 0.19 mmol) and methanolic ammonia (10 mL, saturated at 0 °C) was stirred for 18 h at 85 °C in a sealed bottle. After cooling, the volatiles were removed by rotary evaporation, and the residue was purified by preparative TLC (chloroform–methanol, 20:1) to give 1,3-di-*n*-butylxanthine 7-(2,3-*O*-isopropylidene)-β-D-ribofuronamide (67.5 mg, 80.2%) as a syrup: ^{1}H NMR ($CDCl_3$) δ 0.93–0.99 (m, 6 H, 2 × CH_3), 1.32–1.47 (m, 7 H, 2 × CH_2 and isopropylidene), 1.55–1.66 (m, 5 H, CH_2 and isopropylidene), 1.69–1.79 (m, 2 H, CH_2), 4.00 (pseudo t, J = 7.8 and 7.3 Hz, 2 H, NCH_2), 4.12 (pseudo t, J = 7.5 and 7.3 Hz, 2 H, NCH_2), 4.59 (d, J = 3.6 Hz, 1 H), 5.15 (dd, J = 7.1 and 3.9 Hz, 1 H), 5.28 (dd, J = 7.1 and 3.6 Hz, 1 H), 5.35 and 6.86 (2 × br s, 2 × 1 H, NH_2′), 5.93 (d, J = 3.9 Hz, 1 H, H-1′), 7.74 (s, 1 H, H-8). Anal. Calcd for $C_{21}H_{31}N_5O_6$·0.2$(C_2H_5)_2O$: C, 56.39; H, 7.16; N, 15.08. Found: C, 56.63; H, 7.22; N, 15.13.

Deisopropylidenation was carried out, as described for compound **9**, with 56 mg of the protected compound. Following crystallization from ether–methanol, compound **10** (20 mg, 40%) was obtained as a slightly yellow solid. ^{1}H NMR (DMSO-d_6) δ 0.88–0.92 (m, 6 H, 2 × CH_3), 1.23–1.37 (m, 4 H, 2 × CH_2), 1.47–1.57 (m, 2 H, CH_2), 1.60–1.70 (m, 2 H, CH_2), 3.87 (pseudo t, J = 7.5 and 7.2 Hz, 2 H, NCH_2), 4.00 (pseudo t, J = 7.3 and 7.2 Hz, 2 H, NCH_2), 4.14–4.15 (m, 1 H, H-3′), 4.29 (d, J = 3.7 Hz, 1 H, H-4′), 4.40–4.43 (m, 1 H, H-2′), 5.58 (d, J = 5.0 Hz, exchangeable with D_2O, 1 H, OH), 5.62 (d, J = 6.1 Hz, exchangeable with D_2O, 1 H, OH), 6.19 (d, J = 5.8 Hz, 1 H, H-1′), 7.43 and 7.62 (2 × br s, exchangeable with D_2O, 2 × 1 H, NH_2), 8.67 (s, 1 H, H-8).

***N*-Methyl 1,3-Di-*n*-butylxanthine 7-β-D-Ribofuronamide (11).** To a solution of compound **20a** (50 mg, 0.11 mmol) in methanol (10 mL) was bubbled methylamine for 5 min at −78 °C (1/3 increase in volume). The reaction mixture was heated for 17 h at 85 °C in a sealed tube. After evaporation of the solvent, the slightly yellow residue was purified by preparative TLC (chloroform–methanol, 20:1) to yield *N*-methyl 1,3-di-*n*-butylxanthine 7-(2,3-*O*-isopropylidene)-β-D-ribofuronamide (23.1 mg, 46.3%) as a foam: ^{1}H NMR ($CDCl_3$) δ 0.96 and 0.97 (2 × t, J = 7.3 Hz, 2 × 3 H, 2 × CH_3), 1.34–1.44 (m, 7 H, 2 × CH_2 and isopropylidene), 1.51–1.69 (m, 5 H, CH_2 and isopropylidene), 1.72–1.79 (m, 2 H, CH_2), 2.79 (d, J = 4.9 Hz, 3 H, $NHCH_3$), 4.01 (t, J = 7.5 Hz, 2 H, N-CH_2), 4.12 (pseudo t, J = 7.6 and 7.3 Hz, 2 H, NCH_2), 4.60 (d, J = 3.0 Hz, 1 H), 5.14 (dd, J = 6.9 and 4.0 Hz, 1 H), 5.21 (dd, J = 6.9 and 3.1 Hz, 1 H), 5.91 (d, J = 4.0 Hz, 1 H, H-1′), 6.92 (m, 1 H, NH), 7.72 (s, 1 H, H-8).

A mixture of the isopropylidene compound (20 mg, 0.043 mmol) and 88% formic acid (3 mL) reacted for 6 h at room temperature. After the reaction mixture was concentrated to dryness, the residue was coevaporated with toluene (2 × 5 mL) and triturated with ether to give compound **11** (12.7 mg, 69.5%) as a colorless solid: ^{1}H NMR (DMSO-d_6) δ 0.88–0.92 (m, 6 H, 2 × CH_3), 1.26–1.35 (m, 4 H, 2 × CH_2), 1.48–1.58 (m, 2 H, CH_2), 1.61–1.70 (m, 2 H, CH_2), 2.64 (d, J = 4.3 Hz, 3 H, $NHCH_3$), 3.88 (t, J = 7.4 Hz, 2 H, NCH_2), 4.01 (pseudo t, J = 7.3 and 7.1 Hz, 2 H, NCH_2), 4.16–4.19 (m, 1 H), 4.30 (d, J = 3.6 Hz, 1 H), 4.44–4.47 (m, 1 H), 5.60 (2 × d, J = 6.5 and 5.5 Hz, exchangeable with D_2O, 2 × 1 H, 2 × OH), 6.19 (d, J = 5.4 Hz, 1 H, H-1′), 8.11 (q, J = 4.3 Hz, exchangeable with D_2O, 1 H, NH), 8.65 (s, 1 H, H-8); UV spectrum (MeOH) λ_{max} 276 nm, ϵ = 10 100.

***N*-Methyl 1,3-Di-*n*-pentylxanthine 7-β-D-Ribofuronamide (12).** A solution of compound **20b** (65.4 mg, 0.13 mmol) and 2 M methylamine/tetrahydrofuran (2 mL) was heated for 18 h at 85 °C in a sealed tube. After evaporation of the solvent, the slightly yellow residue was purified by preparative TLC (chloroform–methanol, 20:1) to yield *N*-methyl 1,3-di-*n*-pentylxanthine 7-(2,3-*O*-isopropylidene)-β-D-ribofuronamide (52 mg, 80%) as a foam: ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 6.5 Hz, 6 H, 2 × CH_3), 1.25–1.36 (m, 11 H, 4 × CH_2 and isopropylidene), 1.56–1.61 (m, 5 H, CH_2 and isopropylidene), 1.71–1.78 (m, 2 H, CH_2), 2.79 (d, J = 5.0 Hz, 3 H, $NHCH_3$), 4.00 (t, J = 7.7 Hz, 2 H, NCH_2), 4.11 (pseudo t, J = 8.0 and 7.2 Hz, 2 H, NCH_2), 4.61 (d, J = 3.1 Hz, 1 H), 5.14 (dd, J = 6.7 and 4.0 Hz, 1 H), 5.21 (dd, J = 6.8 and 3.2 Hz, 1 H), 5.91 (d, J = 3.7 Hz, 1 H, H-1′), 6.93 (br d, J = 4.0 Hz, 1 H, NH), 7.73 (s, 1 H, H-8).

A mixture of the isopropylidene compound (46 mg, 0.094 mmol) and 88% formic acid (5 mL) reacted for 2.5 h at room temperature. After the reaction mixture was concentrated to dryness, the residue was purified on preparative TLC (chloroform–methanol, 10:1) to give compound **12** (32.6 mg, 78%) as a colorless solid: ^{1}H NMR (DMSO-d_6) δ 0.86 (pseudo t, J = 7.1 and 6.2 Hz, 6 H, 2 × CH_3), 1.24–1.29 (m, 8 H, 4 × CH_2), 1.50–1.63 (m, 2 H, CH_2), 1.65–1.72 (m, 2 H, CH_2), 2.64 (d, J = 4.7 Hz, 3 H, $NHCH_3$), 3.87 (t, J = 7.3 Hz, 2 H, NCH_2), 4.00 (pseudo t, J = 7.3 and 7.2 Hz, 2 H, N-CH_2), 4.16–4.18 (m, 1 H), 4.31 (d, J = 3.6 Hz, 1 H), 4.38–4.54 (m, 1 H), 5.60 (2 × d, J = 5.8 and 5.1 Hz, exchangeable with D_2O, 2 × 1 H, 2 × OH), 6.20 (d, J = 5.7 Hz, 1 H, H-1′), 8.11 (q, J = 4.5 Hz, exchangeable with D_2O, 1 H, NH), 8.65 (s, 1 H, H-8).

***N*-Methyl 1,3-Di-*n*-hexylxanthine 7-β-D-Ribofuronamide (13).** A mixture of compound **20c** (62 mg, 0.12 mmol) and 2 M methylamine/tetrahydrofuran (2 mL) was heated for 16 h at 85 °C in a sealed tube. After evaporation of the volatiles, the slightly yellow residue was purified by preparative TLC (chloroform–methanol, 20:1) to yield *N*-methyl 1,3-di-*n*-hexylxanthine 7-(2,3-*O*-isopropylidene)-β-D-ribofuronamide (45.4 mg, 73%) as thick oil: ^{1}H NMR ($CDCl_3$) δ 0.86–0.91 (pseudo t, J = 6.8 and 6.2 Hz, 6 H, 2 × CH_3), 1.25–1.36 (m, 15 H, 6 × CH_2 and isopropylidene), 1.60 (m, 5 H, CH_2 and isopropylidene), 1.70–1.77 (m, 2 H, CH_2), 2.79 (d, J = 4.8 Hz, 3 H, $NHCH_3$), 3.99 (t, J = 7.8 Hz, 2 H, NCH_2), 4.11 (pseudo t, J = 7.9 and 7.2 Hz, 2 H, NCH_2), 4.60 (d, J = 3.5 Hz, 1 H, H-4′), 5.14 (dd, J = 7.1 and 3.9 Hz, 1 H, H-3′), 5.20 (dd, J = 6.9 and 3.1 Hz, 1 H, H-2′), 5.91 (d, J = 3.7 Hz, 1 H, H-1′), 6.92 (br d, J = 4.3 Hz, 1 H, NH), 7.72 (s, 1 H, H-8).

A mixture of the isopropylidene compound (42.5 mg, 0.082 mmol) and 88% formic acid (2 mL) reacted for 6 h at room temperature. After the reaction mixture was concentrated to dryness, the residue was evaporated to dryness and dried *in vacuo* to give compound **13** (35 mg, 89%) as a colorless solid: ^{1}H NMR (DMSO-d_6) δ 0.84 (m, 6 H, 2 × CH_3), 1.28 (m, 12 H, 6 × CH_2), 1.54 (m, 2 H, CH_2), 1.65 (m, 2 H, CH_2), 2.64 (d, J = 4.4 Hz, 3 H, $NHCH_3$), 3.87 (pseudo t, J = 7.8 and 6.6 Hz, 2 H, NCH_2), 4.00 (pseudo t, J = 7.2 and 6.9 Hz, 2 H, NCH_2), 4.18 (m, 1 H, H-3′), 4.30 (d, J = 3.5 Hz, 1 H, H-4′), 4.46 (m, 1 H, H-2′), 5.60 (m, exchangeable with D_2O, 2 H, 2 × OH), 6.19 (d, J = 5.5 Hz, 1 H, H-1′), 8.11 (br d, J = 4.4 Hz, exchangeable with D_2O, 1 H, NH), 8.65 (s, 1 H, H-8).

***N,N*-Dimethyl 1,3-Di-*n*-butylxanthine 7-β-D-Ribofuronamide (14).** A solution of compound **20a** (77 mg, 0.166 mmol) and 25% dimethylamine/methanol (10 mL, dissolved at −78 °C) was heated for 15 h at 75 °C in a sealed tube. After evaporation of the volatiles, the residue was purified by preparative TLC (chloroform–methanol, 20:1) to yield *N,N*-dimethyl 1,3-di-*n*-butylxanthine-7-(2,3-*O*-isopropylidene)-β-D-ribofuronamide (50 mg, 63.2%) as a thick syrup. ^{1}H NMR ($CDCl_3$) δ 0.92–0.98 (m, 6 H, 2 × CH_3), 1.33–1.46 (m, 7 H, 2 × CH_2 and isopropylidene), 1.58–1.68 (m, 5 H, CH_2 and isopropylidene), 1.71–1.78 (m, 2 H, CH_2), 2.93 and 3.11 [2 × s, 2 × 3 H, $N(CH_3)_2$], 4.01 (t, J = 7.8 Hz, 2 H, NCH_2), 4.09 (t, J = 7.6 Hz, 2 H, NCH_2), 5.07 (s, 1 H), 5.15 (d, J = 6.3 Hz, 1 H), 5.33 (m, 1 H), 6.69 (s, 1 H, H-1′), 8.01 (s, 1 H, H-8).

Similar deisopropylidenation for compound **9** with 40 mg of protected compound and purification on preparative TLC (chloroform–methanol, 10:1) yielded compound **14** (30 mg, 82%) as a colorless solid. ^{1}H NMR (DMSO-d_6) δ 0.88–0.92 (m, 6 H, 2 × CH_3), 1.24–1.37 (m, 4 H, 2 × CH_2), 1.48–1.57 (m, 2 H, CH_2), 1.60–1.70 (m, 2 H, CH_2), 2.89 and 3.05 [2 × s,

2 × 3 H, N(CH_3)$_2$], 3.87 (pseudo t, J = 7.5 and 7.1 Hz, 2 H, NCH_2), 4.00 (pseudo t, J = 7.2 and 6.9 Hz, 2 H, NCH_2), 4.22 (dd, J = 8.7 and 4.2 Hz, 1 H), 4.29–4.34 (m, 1 H), 4.90 (d, J = 3.9 Hz, 1 H), 5.65 and 5.69 (2 × d, J = 5.5 and 6.0 Hz, exchangeable with D_2O, 2 H, 2 × OH), 6.32 (d, J = 4.7 Hz, 1 H, H-1′), 8.75 (s, 1 H, H-8).

***N*-Ethyl 1,3-Di-*n*-butylxanthine 7-β-D-Ribofuronamide (15).** A mixture of compound **20a** (70 mg, 0.15 mmol) and 25% ethylamine/methanol (10 mL, dissolved at −78 °C) was heated for 18 h at 85 °C in a sealed tube. After evaporation of the solvent, the slightly yellow residue was purified by preparative TLC (chloroform–methanol, 20:1) to yield *N*-ethyl 1,3-di-*n*-butylxanthine 7-(2,3-*O*-isopropylidene)-β-D-ribofuronamide (55.7 mg, 77.4%) as a syrup: ^{1}H NMR ($CDCl_3$) δ 0.93–0.99 (m, 6 H, 2 × CH_3), 1.11 (t, J = 7.3 Hz, 3 H, NHCH$_2$CH_3), 1.33–1.41 (m, 7 H, 2 × CH_2 and isopropylidene), 1.58–1.70 (m, 5 H, CH_2 and isopropylidene), 1.72–1.77 (m, 2 H, CH_2), 3.24–3.32 (m, 2 H, NHCH_2CH$_3$), 4.00 (pseudo t, J = 7.9 and 7.8 Hz, 2 H, N-CH_2), 4.12 (pseudo t, J = 7.5 and 7.3 Hz, 2 H, NCH_2), 4.58 (d, J = 3.5 Hz, 1 H), 5.13 (dd, J = 6.7 and 3.8 Hz, 1 H), 5.18 (dd, J = 6.7 and 3.1 Hz, 1 H), 5.91 (d, J = 4.2 Hz, 1 H, H-1′), 6.96 (m, 1 H, NH), 7.73 (s, 1 H, H-8). Anal. Calcd for $C_{23}H_{35}N_5O_6$·0.5(C_2H_5)$_2$O: C, 58.35; H, 7.84; N, 13.61. Found C, 58.06; H, 7.57; N, 13.54.

Similar deisopropylidenation for compound **9** with 55 mg of protected compound and crystalization with ether–methanol yielded compound **15** (25.1 mg, 73.8%) as a colorless solid: ^{1}H NMR (DMSO-d_6) δ 0.88–0.93 (m, 6 H, 2 × CH_3), 1.05 (t, J = 7.4 Hz, 3 H, NHCH$_2$CH_3), 1.24–1.35 (m, 4 H, 2 × CH_2), 1.48–1.58 (m, 2 H, CH_2), 1.61–1.71 (m, 2 H, CH_2), 3.09–3.19 (m, 2 H, NHCH_2CH$_3$), 3.88 (pseudo t, J = 7.5 and 7.2 Hz, 2 H, NCH_2), 4.01 (t, J = 7.2 Hz, 2 H, NCH_2), 4.14–4.19 (m, 1 H), 4.29 (d, J = 3.5 Hz, 1 H), 4.43–4.48 (m, 1 H), 5.57 and 5.59 (2 × d, J = 6.4 and 5.5 Hz, exchangeable with D_2O, 2 H, 2 × OH), 6.17 (d, J = 5.5 Hz, 1 H, H-1′), 8.18 (t, J = 5.4 Hz, exchangeable with D_2O, 1 H, NH), 8.64 (s, 1 H, H-8).

1,3-Di-*n*-butylxanthine 7-(2,3-*O*-Isopropylidene)-β-D-ribofuranoside (19a). A mixture of compound **3** (1.56 g, 3.94 mmol), *p*-toluenesulfonic acid (1.3 g, 1.58 mmol), and dry acetone (25 mL) was stirred for 7 h at room temperature and refrigerated for 2 days. After stirring for 1 h at room temperature, the reaction mixture was neutralized by triethylamine, and the solvent was removed by rotary evaporation. The residue was purified by silica gel column chromatography (chloroform–methanol, 100:0 → 50:1) to give compound **19a** (1.7 g, 98.9%) as a thick syrup: ^{1}H NMR (DMSO-d_6) δ 0.89 (t, J = 7.3 Hz, 6 H, 2 × CH_3), 1.21–1.35 (m, 7 H, 2 × CH_2 and isopropylidene), 1.47–1.56 (m, 5 H, CH_2 and isopropylidene), 1.59–1.69 (m, 2 H, CH_2), 3.49–3.57 (m, 2 H, H-5′), 3.86 (pseudo t, J = 7.6 and 7.2 Hz, 2 H, NCH_2), 3.99 (pseudo t, J = 7.3 and 7.2 Hz, 2 H, NCH_2), 4.17 (dd, J = 8.1 and 4.9 Hz, 1 H), 4.88 (dd, J = 6.4 and 3.1 Hz, 1 H), 5.07 (t, J = 5.2 Hz, exchangeable with D_2O, 1 H, 5′-OH), 5.15 (dd, J = 6.4 and 3.5 Hz, 1 H), 6.29 (d, J = 3.0 Hz, 1 H, H-1′), 8.40 (s, 1 H, H-8).

1,3-Di-*n*-pentylxanthine 7-(2,3-*O*-Isopropylidene)-β-D-ribofuranoside (19b). A solution of compound **7** (145.2 mg, 0.34 mmol) and (1*R*)-(−)-camphorsulfonic acid (80 mg, 0.34 mmol) in dry acetone (5 mL) was stirred for 21 h at room temperature. The solvent was removed by rotary evaporation, and the residue was purified by silica gel column chromatography (chloroform–methanol, 20:1) to give compound **19b** (147.2 mg, 92.5%) as a thick syrup: ^{1}H NMR ($CDCl_3$) δ 0.90 (pseudo t, J = 7.1 and 6.4 Hz, 6 H, 2 × CH_3), 1.34–1.38 (m, 11 H, 4 × CH_2 and isopropylidene), 1.59–1.69 (m, 5 H, CH_2 and isopropylidene), 1.70–1.78 (m, 2 H, CH_2), 3.79–4.03 (m, 5 H, H-4′, 5′ and NCH_2), 4.11 (pseudo t, J = 7.6 and 7.3 Hz, 2 H, NCH_2), 4.34 (br s, 1 H), 5.12 (dd, J = 7.2 and 4.7 Hz, 1 H, H-2′), 5.21 (dd, J = 10.1 and 3.0 Hz, 1 H, H-3′), 5.75 (d, J = 5.0 Hz, 1 H, H-1′), 7.79 (s, 1 H, H-8).

1,3-Di-*n*-hexylxanthine 7-(2,3-*O*-Isopropylidene)-β-D-ribofuranoside (19c). A solution of compound **8** (0.17 g, 0.37 mmol) and (1*R*)-(−)-camphorsulfonic acid (0.088 g, 0.378 mmol) in dry acetone (5 mL) was stirred for 20 h at room temperature. The solvent was removed by rotary evaporation, and the residue was purified by silica gel column chromatography (chloroform–methanol, 20:1) to give compound **19c** (0.132 g, 70%) as a thick syrup: ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 6 H, 2 × CH_3), 1.26–1.38 (m, 15 H, 6 × CH_2 and isopropylidene), 1.61–1.69 (m, 5 H, CH_2 and isopropylidene), 1.72–1.76 (m, 2 H, CH_2), 3.83–4.02 (m, 5 H, H-4′, 5′ and NCH_2), 4.11 (pseudo t, J = 7.7 and 7.3 Hz, 2 H, NCH_2), 4.34 (br s, 1 H), 5.10 (dd, J = 6.8 and 4.9 Hz, 1 H), 5.22 (dd, J = 6.9 and 3.2 Hz, 1 H), 5.74 (d, J = 4.8 Hz, 1 H, H-1′), 7.78 (s, 1 H, H-8).

Methyl 1,3-Di-*n*-butylxanthine 7-(2,3-*O*-Isopropylidene)-β-D-ribofuronate (20a). A solution of sodium periodate (1.61 g, 7.53 mmol) in water (15 mL) was added to a solution of compound **19a** (0.8 g, 1.83 mmol) in chloroform–acetonitrile (1:1, 20 mL) at room temperature and followed by ruthenium(III) chloride (3.8 mg, 0.018 mmol). The reaction mixture was vigorously stirred for 6 days at room temperature. After the two layers were separated, the aqueous layer was extracted with chloroform (2 × 50 mL) and the combined organic layer was washed with saline, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness to yield crude 1,3-di-*n*-butylxanthine 7-(2,3-*O*-isopropylidene)-β-D-ribofuronic acid (0.74 g) as a foam.

To a solution of this acid (dried *in vacuo* for 3 h) in methanol (15 mL) were added (dimethylamino)pyridine (DMAP, 0.02 g, 0.16 mmol) and then EDAC (0.79 g, 4.13 mmol), and the reaction mixture was stirred for 17 h at room temperature. After removal of solvent, the residue was dissolved in ethyl acetate (70 mL), washed with water (2 × 30 mL) and saline (40 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 1:1) to give compound **20a** (0.36 g, 47.2%) as a colorless solid, and unreacted compound **19a** (0.24 g) was recovered: ^{1}H NMR ($CDCl_3$) δ 0.92–0.99 (m, 6 H, 2 × CH_3), 1.32–1.47 (m, 7 H, 2 × CH_2 and isopropylidene), 1.55–1.69 (m, 5 H, CH_2 and isopropylidene), 1.71–1.79 (m, 2 H, CH_2), 3.77 (s, 3 H, OCH_3), 3.95 (t, J = 7.8 Hz, 2 H, NCH_2), 4.10 (pseudo t, J = 7.6 and 7.3 Hz, 2 H, NCH_2), 4.80 (s, 1 H), 5.17 (d, J = 6.2 Hz, 1 H), 5.46 (d, J = 6.2 Hz, 1 H), 6.26 (s, 1 H, H-1′), 7.88 (s, 1 H, H-8).

Methyl 1,3-Di-*n*-pentylxanthine 7-(2,3-*O*-Isopropylidene)-β-D-ribofuronate (20b). A mixture of compound **19b** (136.7 mg, 0.29 mmol), sodium periodate (258 mg, 1.21 mmol), and ruthenium(III) chloride (0.8 mg, 0.0039 mmol) in chloroform–acetonitrile–water (2:2:3, 7 mL) was vigorously stirred for 86 h at room temperature. Similar workup as compound **20a** yielded crude 1,3-di-*n*-hexylxanthine 7-(2,3-*O*-isopropylidene)-β-D-ribofuronic acid (109 mg) as a thick syrup.

To a solution of acid in methanol (10 mL) were added DMAP (2.8 mg, 0.023 mmol) and then EDAC (109 mg, 0.57 mmol), and the reaction mixture was stirred for 25 h at room temperature. After removal of solvent, the residue was dissolved in ethyl acetate (50 mL), washed with water (2 × 20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography (hexanes–ethyl acetate, 1:1) to give compound **20b** (85 mg, 76%) as a foam, and unreacted compound **19b** (40 mg) was recovered. **20b**: ^{1}H NMR (DMSO-d_6) δ 0.88 (m, 6 H, 2 × CH_3), 1.26–1.46 (m, 11 H, 4 × CH_2 and isopropylidene), 1.49–1.67 (m, 5 H, CH_2 and isopropylidene), 1.70–1.80 (m, 2 H, CH_2), 3.77 (s, 3 H, OCH_3), 3.94 (t, J = 7.6 Hz, 2 H, NCH_2), 4.09 (t, J = 7.5Hz, 2 H, NCH_2), 4.80 (s, 1 H), 5.16 (d, J = 6.1 Hz, 1 H), 5.45 (d, J = 6.5 Hz, 1 H), 6.25 (s, 1 H, H-1′), 7.87 (s, 1 H, H-8).

Methyl 1,3-Di-*n*-hexylxanthine 7-(2,3-*O*-Isopropylidene)-β-D-ribofuronate (20c). A mixture of compound **19c** (113 mg, 0.23 mmol), sodium periodate (201 mg, 0.94 mmol), and ruthenium(III) chloride (1.23 mg, 0.006 mmol) in chloroform–acetonitrile–water (2:2:3, 7 mL) was vigorously stirred for 25 h at room temperature. Similar workup as compound **20a** yielded crude 1,3-di-*n*-hexylxanthine 7-(2,3-*O*-isopropylidene)-β-D-ribofuronic acid (115 mg) as a thick syrup.

To a solution of acid in methanol (2.3 mL) were added DMAP (2.8 mg, 0.023 mmol) and then EDAC (109 mg, 0.57 mmol), and the reaction mixture was stirred for 24 h at room temperature. After removal of solvent, the residue was dissolved in chloroform (50 mL), washed with water (2 × 20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by

silica gel column chromatography (hexanes–ethyl acetate, 1:1) to give compound **20c** (65.1 mg, 55%) as a colorless solid, and unreacted compound **19c** (26.6 mg) was recovered. ^{1}H NMR (DMSO-d_6) δ 0.88 (pseudo t, J = 6.6 and 6.4 Hz, 6 H, 2 × CH_3), 1.22–1.49 (m, 15 H, 6 × CH_2 and isopropylidene), 1.54–1.65 (m, 5 H, CH_2 and isopropylidene), 1.69–1.77 (m, 2 H, CH_2), 3.88 (s, 3 H, OCH_3), 3.94 (pseudo t, J = 8.0 and 7.6 Hz, 2 H, NCH_2), 4.09 (pseudo t, J = 7.8 and 7.6 Hz, 2 H, NCH_2), 4.80 (s, 1 H), 5.17 (d, J = 6.0 Hz, 1 H), 5.46 (d, J = 6.5 Hz, 1 H), 6.26 (d, J = 2.2 Hz, 1 H, H-1′), 7.87 (s, 1 H, H-8).

Biological Methods. Receptor Binding. Materials. F-12 (Ham's) medium, fetal bovine serum (FBS) and penicillin/streptomycin were from Gibco BRL (Gaithersburg, MD). [^{125}I]AB-MECA was prepared as described.[19] [^{3}H]R-PIA was from Amersham (Arlington Heights, IL), and [^{3}H]CGS 21680 was from DuPont NEN (Boston, MA). Adenosine deaminase (ADA) was from Boehringer Mannheim (Indianapolis, IN). Composition of lysis buffer: 10 mM Tris/5 mM EDTA, pH 7.4 at 5 °C. 50/10/1 buffer: 50 mM Tris; 10 mM $MgCl_2$; 1 mM EDTA, pH 8.26 at 5 °C. All other materials were from standard local sources and of the highest grade commercially available.

Cell Culture and Radioligand Binding. CHO cells stably expressing the A_3 receptor[1] were grown in F-12 medium containing 10% FBS and penicillin/streptomycin (100 units/mL and 100 μg/mL. respectively) at 37 °C in a 5% CO_2 atmosphere, and membrane homogenates were prepared as reported.[16,19]

Binding of [[^{125}I]-4-amino-3-iodobenzyl]adenosine-5′-*N*-methyluronamide ([^{125}I]AB-MECA) to the CHO cells membranes was performed essentially as described.[13,19] 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 were then diluted with buffer; final DMSO concentrations never exceeded 1%. Incubations were carried out in duplicate for 1 h at 37 °C and were 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 gamma 5500B γ-counter. Nonspecific binding was determined in the presence of 40 μM R-PIA. K_i values were calculated according to Cheng–Prusoff,[33] assuming a K_d for [^{125}I]AB-MECA of 1.48 nM.[19]

Binding of [^{3}H]PIA to A_1 receptors from rat brain membranes and of [^{3}H]CGS 21680 to A_{2a} receptors from rat striatal membranes was performed as described previously.[17,18] Adenosine deaminase (3 units/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.[33]

Adenylate cyclase was assayed in membranes from CHO cells stably expressing the rat A_3 receptor, prepared as above, using a previously reported method.[16] The method involved addition of [α-^{32}P]ATP to membranes in the presence of forskolin to stimulate adenylate cyclase and papaverine as a phosphodiesterase inhibitor. The reaction was terminated by addition of a stop solution containing 20 000 cpm/mL [^{3}H]cyclic AMP. The total radiolabeled cyclic AMP was isolated on columns of Dowex 50 ion-exchange resin and alumina. Maximal inhibition of adenylate cyclase activity corresponded to 40–50% of total activity under conditions of stimulation (typically by 6–8-fold) in the presence of 1 μM forskolin. IC_{50} values were calculated using InPlot (GraphPad, San Diego, CA).

Abbreviations: 2-Cl-IB-MECA, 2-chloro-N^6-(3-iodobenzyl)-adenosine-5′-*N*-methyluronamide; CGS 21680, 2-[[[4-(2-carboxyethyl)phenyl]ethyl]amino]-5′-*N*-(ethylcarbamoyl)adenosine; DMAP, 4-(dimethylamino)pyridine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; EDAC, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; [^{125}I]AB-MECA, N^6-(4-amino-3-iodobenzyl)adenosine-5′-*N*-methyluronamide; HMDS, hexamethyldisilazane; NECA, 5′-(*N*-ethylcarbamoyl)adenosine; PCR, polymerase chain reaction; PIA, (*R*)-N^6-(phenylisopropyl)adenosine; Tris, tris(hydroxymethyl)aminomethane.

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