N^6-Cyclopentyl-3′-substituted-xylofuranosyladenosines: A New Class of Non-Xanthine Adenosine A_1 Receptor Antagonists

Serge Van Calenbergh,[†] Jacobien K. von Frijtag Drabbe Künzel,[‡] Norbert M. Blaton,[§] Oswald M. Peeters,[§] Jef Rozenski,[∥] Arthur Van Aerschot,[∥] Andre De Bruyn,[∥] Denis De Keukeleire,[†] Adriaan P. IJzerman,[‡] and Piet Herdewijn*[,†,∥]

Laboratory for Medicinal Chemistry (FFW), University of Ghent, Harelbekestraat 72, B-9000 Gent, Belgium, Leiden/Amsterdam Center for Drug Research, Division of Medicinal Chemistry, P.O. Box 9502, 2300 RA Leiden, The Netherlands, Laboratory for Analytical Chemistry and Medicinal Physicochemistry, Faculty of Pharmaceutical Sciences, Catholic University of Leuven, Belgium, and Laboratory for Medicinal Chemistry, Rega Institute, Catholic University of Leuven, Belgium

Received March 17, 1997[⊗]

The present study explores the C-3′ site of the 3-deoxy-3-xylofuranosyl ring of nucleoside analogues with an adenine or N^6-cyclopentyladenine (CPA) base moiety and evaluates the effect on adenosine receptor affinity. Two series of sugar-modified adenosines, i.e., 3′-amido-3′-deoxyadenosines and 3′-amidated 3′-deoxyxylofuranosyladenines, were synthesized and tested for their affinity at A_1 and A_{2a} receptors in rat brain cortex and rat striatum, respectively. The modest affinity found in the "xylo series" prompted us to synthesize the corresponding N^6-cyclopentyl derivatives, which proved to be well accommodated by the A_1 receptors with potencies in the lower nanomolar range. This represents a new perspective in the purinergic field. The absence of a GTP-induced shift, i.e., the ratio between the affinities measured in the presence and absence of 1 mM GTP indicates an antagonistic behavior of this new class of CPA analogues.

Introduction

Although considerable efforts in the area of purinergic receptor related research have furnished many potent and selective ligands for adenosine receptors, critics claim that, with the exception of adenosine itself, none have been approved as drugs. Nevertheless, the potential role of adenosine receptors as a target for drug design was recently demonstrated most elegantly by Nyce and Metzger.[1] They developed a phosphorothioate 21-deoxynucleotide sequence complementary to the m-RNA that codes for adenosine A_1 receptor protein in rabbit airway smooth muscle tissue in order to block synthesis of the receptor. Rabbits treated with an aerosol solution of this antisense DNA developed less bronchoconstriction when challenged with adenosine or dust-mite allergen. These findings indicate that the adenosine A_1 receptor is an important mediator of airway obstruction and inflammation.

Adenosine receptors are subdivided in A_1, A_2, and the recently identified A_3 receptors,[2,3] which have been cloned from different species.[4] The A_2 class is further subdivided in A_{2a} and A_{2b}. The effect of numerous modifications of the adenosine scaffold on affinity and intrinsic activity has been investigated. In general, substitution at the N6 position of the adenine moiety of adenosine, e.g. N^6-cyclohexyladenosine (CHA) and N^6-cyclopentyladenosine (CPA), enhances the affinity for the A_1 receptor.[5] Bulky substituents at the 2-position of the adenine moiety, e.g. CGS 21680A (Figure 1), increase the A_{2a} receptor selectivity.[6] Ligands for the A_1 and A_{2a} receptors have also been found in the xanthine series (e.g., 1,3-dipropyl-8-cyclopentylxanthine (CPX) as antagonist for A_1)[7] and triazoloquinazoline series (e.g., CGS 15943,[8] an antagonist with moderate selectivity for A_{2a}). 2-Chloro-N^6-(3-iodobenzyl)-5′-(methylcarboxamoyl)adenosine (2Cl-IB-MECA) is an example of an A_3 receptor agonist.[9]

Except for a certain freedom of substitution at the 5′-position, e.g. by a 5′-uronamide moiety, A_1 and A_2 receptors are generally proposed to require an unchanged ribose moiety for adenosine agonist activity. The secondary hydroxyl groups of the ribose moiety are believed to be determinants for the intrinsic activity of adenosine receptor agonists. Most modifications at the 2′- and 3′- positions of the sugar ring or inversions of chiral centers at these positions were found to abolish adenosine receptor binding.[10] Removal of the 2′- and 3′-hydroxyl groups of N^6-substituted adenosine derivatives was shown to result in partial agonists,[11] or, in the case of the 2′,3′-dideoxy analogue of CHA, antagonist properties.[12] Such changes also affect affinity, whereby the drop in A_1 affinity by deletion of the 2′-hydroxyl moiety is more pronounced than the decrease caused by removal of the 3′-group.[11] Removal of the 2′-hydroxyl group of *R*-PIA (N^6-(*R*)-(1-phenyl-2-propyl)adenosine), for example, led to an 800-fold decrease in A_1 receptor affinity, while removal of its 3′-hydroxyl group only led to a 30-fold drop in affinity.[10,11] The A_1 affinity of 3′-deoxy-*R*-PIA is reflected in vivo, where significant behavioral (CNS) and cardiovascular effects were observed.[10] Likewise, 3′-deoxy-CPA exhibits submicromolar affinity for the A_1 receptor and can thus be considered as a relatively potent (partial) agonist for this receptor.[11]

In continuation of our synthetic work on ribose-modified adenosine analogues,[13−15] and in order to further explore the C-3′ site for modification, we synthesized a series of 3′-amido-3′-deoxyxylofuranosyl adenines (**2a**−**d** and **7a**−**l**) together with a number of 3′-

* To whom correspondence should be addressed.
[†] Laboratory for Medicinal Chemistry, University of Ghent.
[‡] Leiden/Amsterdam Center for Drug Research.
[§] Laboratory for Analytical Chemistry and Medicinal Physicochemistry, Catholic University of Leuven.
[∥] Laboratory for Medicinal Chemistry, Catholic University of Leuven.
[⊗] Abstract published in *Advance ACS Abstracts,* October 15, 1997.

S0022-2623(97)00176-3 CCC: $14.00

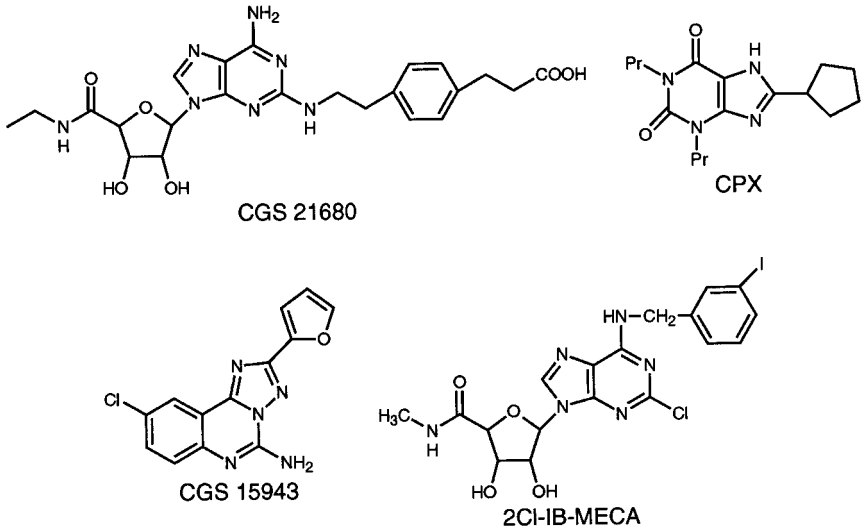
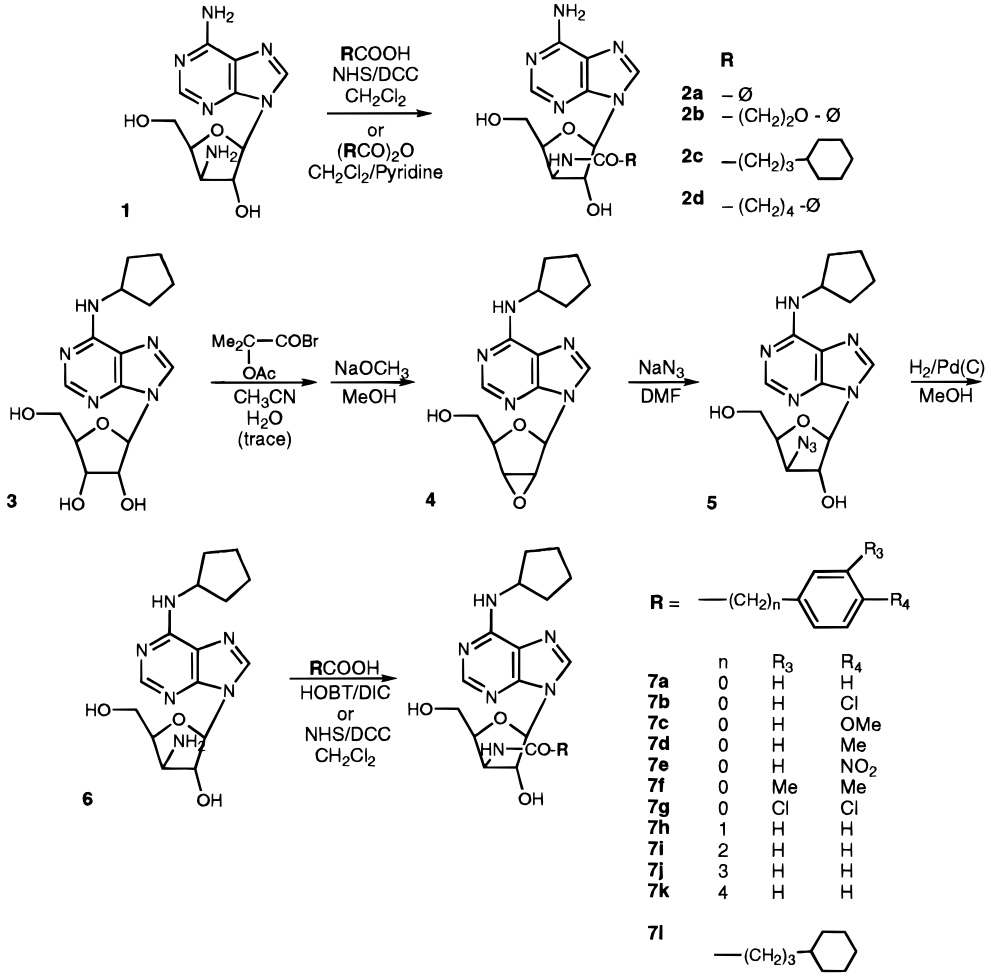


Figure 1. Structures of well-known adenosine receptor ligands and modulators.

Scheme 1



amido-3′-deoxyadenosines (formulas not shown). These compounds were tested in vitro for their affinity for the adenosine A_1 and A_{2a} receptors. The affinities found in the series of the xyloanalogues prompted us to prepare the compounds in which this favorable 3′-modification is combined with a N^6-cyclopentyl ring.

Chemistry

Compounds **2a**−**d** were prepared by amidation of amine **1**[16] with benzoic anhydride in the case of **2a**, or a suitable carboxylic acid together with *N*,*N*′-dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide (NHS) as coupling agents (Scheme 1). Protection of the free hydroxyl groups or 6-NH2 did not seem necessary, since only minor formation of the bis-acylated products was observed.

N^6-Cyclopentyladenosine[5] (**3**) was converted to its 3′-azidoxylosyl analogue using the method of Moffatt and co-workers[17] as it was modified by Hansske and Rob-

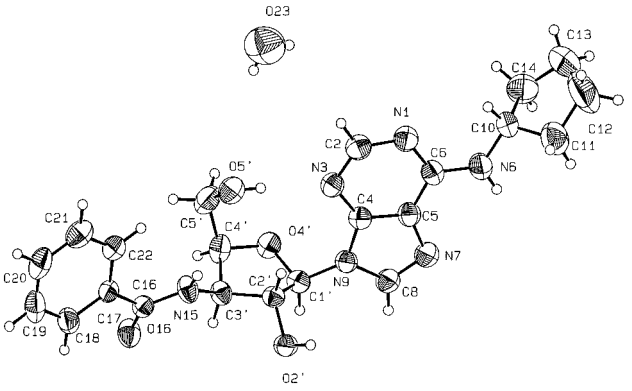


Figure 2. ORTEP view of compound **7b** as determined by X-ray crystallography.

ins.[18] Thus, **3** was first converted to its 2′,3′-anhydro analogue **4** by reaction with α-acetoxyisobutyryl bromide in "moist acetonitrile" followed by alkaline treatment. Epoxide opening of **4** with NaN_3 in hot DMF proceeded stereo- and regioselectively at the 3′-position to give the 3′-azido nucleoside **5** in good yield. Subsequent reduction of **5** to **6** proceeded smoothly by catalytic hydrogenation. Finally, amidation of **6** with suitable carboxylic acids yielded the desired **7a**−**l**. Hereto, the use of *N*,*N*′-diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole hydrate (HOBT) instead of the DCC−NHS combination was found more convenient with respect to workup and yield.

Structural Proof of Compound 7a by X-ray Analysis

The *N*-glycosidic torsion angle χ has a value of 53.8(3)° in the syn range. The syn conformation is stabilized by the intramolecular H-bond C(5′)−OH···N(3). The sugar pucker is ^{2}E with $P = 165.3(3)°$ and $\nu_{max} = 38.0(2)°$. The conformation about the exocyclic C-4′−C-5′ bond is +*sc* with $\gamma = 45.7(4)°$. The *N*-cyclopentyl ring adopts the envelope conformation. All oxygen and most of the nitrogen atoms are involved in a network of hydrogen bonds. An ORTEP view of the molecule with the atomic numbering scheme is shown in Figure 2.

Biological Evaluation

All modified adenosine and CPA analogues were tested in radioligand binding assays to determine their affinities toward adenosine A_1 and A_{2a} receptors in rat brain cortex and rat striatum, respectively (Table 1). Affinities of the parent 3′-deoxyadenosine and 3′-deoxy-CPA are included for reasons of comparison. The compounds were assayed for A_1 affinity using the tritiated antagonist [^{3}H]-1,3-dipropyl-8-cyclopentylxanthine (DPCPX). Displacement experiments were performed in the absence and presence of 1 mM GTP, allowing the determination of the GTP shift (i.e., the ratio of the apparent K_i values in the presence and absence of GTP, respectively). This shift is an in vitro parameter often indicative for intrinsic activity.[19] Since no radiolabeled antagonist is available for A_{2a} receptors, the tritiated agonist [^{3}H]CGS21680 was used. This prohibited the determination of a GTP shift on A_{2a} receptors, and all experiments on these receptors were done in the absence of GTP. Compounds **1** and **6** do not display affinity for adenosine receptors, probably because of protonation of the amino group.

Results and Discussion

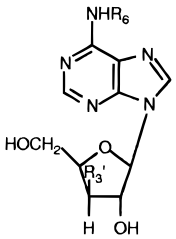
The affinity of the 3′-amido-3′-deoxyadenosines (mentioned in ref 15) for these receptors was low: only marginal (i.e., ⩽10%) displacement of radioligand is observed at 10 μM concentration (results not shown).

The 3′-amidated 3′-deoxyxylofuranosyl counterparts (**2a**−**d**) proved to be better tolerated at these receptors and displayed a K_i of 3−17 μM at A_1 and 2−12 μM at A_{2a} receptors. Here, we demonstrate the possibility to escape from the necessity of conserving the ribosyl configuration of adenosine for affinity.

Drastic (18−31-fold) improvement in potency toward A_1 receptors was obtained with the N^6-cycopentyl congeners, *i.e.* **7a**,**k**,**l**, suggesting the compatibility of our carbohydrate modification with this typical N^6-substituent. A series of structural analogues of the benzamido derivative (**7a**) provides a number of insights into structure−activity relationships with regard to adenosine receptor binding. Varying substituents in *para* position of the benzamido moiety shows the following trend on A_1 receptor affinity: NO_2 < H < OMe < Cl ⩽ Me. Adding a further chloro or methyl group in *meta* on the aromatic ring of **7b** and **7d**, respectively, to give **7g** and **7f**, further increases activity. Optimization of the spacer between the phenyl ring and the amido functionality reveals a length of three methylenes to be the most favorable. The 3′-azido intermediate **5** displays a relatively poor affinity for A_1 receptors, suggesting the importance of the amide moiety for effective binding at these receptors. For all analogues synthesized, the GTP shift for the A_1 receptor is nearly 1. The absence of a GTP-induced shift in binding vs radiolabeled DPCPX (1,3-dipropyl-8-cyclopentylxanthine) antagonist strongly suggests the 3′-amido xylosyl CPA analogues to be full antagonists for the A_1 receptor. This fact proves that by suitable sugar modification it is possible to turn a full (CPA) or partial agonist (3′-deoxy-CPA) into an antagonist. As expected, the effect of the N^6-cyclopentyl substituent is negligible at the A_{2a} receptors (for those compounds for which comparable data are available). With the exception of compound **5**, the selectivity for A_1 vs A_{2a} receptors was thus significantly improved (e.g., **7f**, the most potent A_1 ligand of this series was found to be 160 times selective vs A_{2a}).

The crystal structure of compound **7a** reveals the orientation of the ribose group relative to the adenine ring system. The compound appears to be in the so-called syn conformation stabilized by a hydrogen bond formed between N3 and the 5′-OH group (distance N3···H, 2.0 Å; angle N3···H−O, 176°). Generally it is assumed that the anti conformation (where the ribose group is turned away from the adenine ring) is essential for agonistic activity.[20] Although certainly not conclusive the syn/anti aspect may explain the antagonistic properties of this new series of compounds. Other studies have systematically addressed N^9-substitution other than ribose.[10,21,22] Taylor et al. synthesized ribose-modified analogues of adenosine.[10] Of relevance to the present study were compounds that did not display agonistic activity in vivo, but retained some affinity toward adenosine receptors as determined in radioligand binding studies. A 9-(2-tetrahydrofuranyl) substituent proved acceptable with modest adenosine A_1 receptor affinity (K_i value for N^6-(2-phenylethyl)-9-(2-tetrahydrofuran)adenine of 1.5 μM). Olsson and co-

Table 1. Affinities [K_i Values (Standard Errors of the Mean) in the Presence and Absence of GTP] and GTP Shifts of the (N^6-Substituted) 3′-Deoxyadenosine Analogues



compd	R_6	$R_{3'}$	K_i (μM) A_1 − GTP	K_i (μM) A_1 + GTP	GTP shift	K_i (μM) A_{2a}
	H	H	7.12 ± 3.62	15.2 ± 2.0	2.1 ± 1.4	−[a]
2a	H	NHCO-Ph	10.9 ± 2.8	11.1 ± 0.4	1.1 ± 0.3	2.47 ± 0.52
2b	H	NHCO-$(CH_2)_2$O-Ph	16.9 ± 1.6	12.6 ± 2.0	0.74 ± 0.05	11.8 ± 3.0
2c	H	NHCO−$(CH_2)_3C_6H_{11}$	3.59 ± 0.10	2.68 ± 0.04	0.75 ± 0.03	1.77 ± 0.48
2d	H	NHCO-$(CH_2)_4$-Ph	7.84 ± 0.37	5.74 ± 0.58	0.73 ± 0.04	4.66 ± 1.35
	cyclopentyl	H	0.11 ± 0.03	0.47 ± 0.04	4.3 ± 1.2	18.6 ± 6.8
5	cyclopentyl	N_3	8.47 ± 3.48	11.2 ± 1.5	1.4 ± 0.3	2.41 ± 0.52
7a	cyclopentyl	NHCO-Ph	0.40 ± 0.13	0.31 ± 0.05	0.80 ± 0.13	2.76 ± 1.19
7b	cyclopentyl	NHCO-Ph-*p*Cl	0.11 ± 0.09	0.081 ± 0.033	0.87 ± 0.29	0.58 ± 0.13
7c	cyclopentyl	NHCO-Ph-*p*OMe	0.20 ± 0.13	0.13 ± 0.02	0.77 ± 0.30	0.77−2.45
7d	cyclopentyl	NHCO-Ph-*p*Me	0.083 ± 0.015	0.068 ± 0.010	0.84 ± 0.19	0.79−2.52
7e	cyclopentyl	NHCO-Ph-*p*NO_2	0.82 ± 0.31	0.74 ± 0.22	0.91 ± 0.08	6.85 ± 2.39
7f	cyclopentyl	NHCO-Ph-3,4-diMe	0.0236 ± 0.0025	0.0174 ± 0.0042	0.73 ± 0.11	3.68 ± 1.50
7g	cyclopentyl	NH-CO-Ph-3,4-diCl	0.0325 ± 0.0031	0.0237 ± 0.0014	0.73 ± 0.09	2.02 ± 0.98
7h	cyclopentyl	NHCO-CH_2-Ph	0.85 ± 0.29	0.77 ± 0.24	0.95 ± 0.31	(50%)[b]
7i	cyclopentyl	NHCO-$(CH_2)_2$-Ph	0.37 ± 0.12	0.35 ± 0.12	0.99 ± 0.36	7.94 ± 4.48
7j	cyclopentyl	NHCO-$(CH_2)_3$-Ph	0.13 ± 0.08	0.10 ± 0.02	0.94 ± 0.38	0.65 ± 0.16
7k	cyclopentyl	NHCO-$(CH_2)_4$-Ph	0.24 ± 0.03	0.20 ± 0.03	0.83 ± 0.16	4.23 ± 0.94
7l	cyclopentyl	NHCO-$(CH_2)_3$-C_6H_{11}	0.19 ± 0.11	0.15 ± 0.09	0.80 ± 0.03	(74%)[b]

[a] −, not determined because the addition of deoxycoformycin, necessary to prevent degradation of this compound by adenosine deaminase, disturbed the binding assay. This was not the case for the A_1 receptor assay. [b] Percentage radioligand bound to the receptor in the presence of 10^{-5} M ligand.

workers explored methyl, ethyl, 2-hydroxyethyl, cyclopentyl, phenyl, and 2-tetrahydrofuranyl substituents at N-9.[21] In this study N^6-cyclopentyl-9-ethyladenine was most potent with a K_i value of 440 nM. More recently, Jacobson and colleagues investigated the relationship between adenosine A_3 receptor affinity and N^9-substitution.[22] For comparison adenosine A_1 receptor affinities were also included in this study, showing that again a 2-tetrahydrofuran substituent yielded moderate affinity for this receptor subtype. From the present study we conclude that N^6-cyclopentylxylofuranosyladenines bearing a substituent of considerably larger size at the 3′-position can be accommodated as well, and may even lead to derivatives with enhanced potencies in the lower nanomolar range.

Conclusion

Full adenosine A_1 receptor agonists such as CPA and other N^6-substituted adenosine analogues have previously been shown to become partial agonists upon deletion of the 3-hydroxyl moiety. The present study further explored the C-3′ site for modification. The most interesting and unexpected finding was that the 3′-amidated xylofuranosyl analogues of CPA displayed potent affinities for the A_1 adenosine receptor. The so-called GTP shifts indicate these analogues to be full antagonists for this receptor type. These findings represent a new perspective in the purinergic field and may provide new non-xanthine leads with improved antagonist activity for use as cardiotonics, cognition enhancers, or antiasthmatics. Determination of in vivo activity of most potent congeners is in progress.

Experimental Section

(1) Radioligand Binding Studies. Adenosine A_1 receptor affinities were determined on rat cortical membranes with [^{3}H]-1,3-dipropyl-8-cyclopentylxanthine (DPCPX) as radioligand according to a protocol published previously.[23] Measurements with [^{3}H]DPCPX were performed in the presence and absence of 1 mM GTP.

Adenosine A_{2a} receptor affinities were determined on rat striatal membranes with [^{3}H]CGS 21680 as radioligand according to Jarvis et al.[24] All data reflect three or four independent experiments, performed in duplicate. Data analysis (K_i values) was done with the software program PRISM (GraphPad, San Diego, CA).

(2) Structure Determination of 7a by X-ray Crystallography. $C_{22}H_{26}N_6O_4 \cdot {}^1/_2H_2O$, M_r = 447.50, orthorhombic, $P2_12_12_1$; a = 6.6666(5) Å, b = 15.2695(5) Å, c = 21.9515(8) Å, V = 2234.6(2) Å^3, Z = 4, D_c = 1.330 mg m^{-3}; graphite monochromated Cu Kα radiation, λ = 1.541 78 Å; 2000 observed reflections [$I > 2\sigma(I)$], 2209 independent reflections [R(int) = 0.0128]; μ = 0.788 mm^{-1}, F(000) = 948, T = 293(2) K, final R = 0.0335[$I > 2\sigma(I)$], $\Delta\rho_{max}$ = 0.124 e Å^{-3}, $\Delta\rho_{min}$ = −0.136 e Å^{-3}; structure solution using SIR92,[25] structure refinement using SHELXL93.[26]

(3) Synthesis. General. Melting points were determined in capillary tubes with an Electrothermal (IA 9000 series) digital melting point apparatus and are uncorrected. For compounds **2b**, **2d**, **6**, **7f**, and **7g**, determination of melting points was impossible since decomposition occurred prior to melting. Ultraviolet spectra were recorded in MeOH with a Schimadzu 2100 UV/vis spectrophotometer. ^{1}H NMR spectra at 19° were obtained with a Bruker WH 360 spectrometer. The solvent signal of DMSO-d_6 (2.50 ppm) was used as secondary reference. All signals assigned to amino and hydroxyl groups were exchangeable with D_2O. ^{13}C NMR spectra were measured on a Varian Gemini 200 MHz spectrometer with the solvent signal of DMSO-d_6 (39.70 ppm) as secondary reference.

Liquid secondary-ion mass spectra (LSIMS) were obtained using a Kratos concept ^{1}H mass spectrometer (Kratos, Manchester, UK).

Elemental analyses were performed at the university of Konstanz, Germany, and are within ±0.4% of theoretical values unless otherwise specified.

Precoated Merck silica gel F_{254} plates were used for TLC, and spots were examined with UV light at 254 nm and sulfuric acid−anisaldehyde spray. Column chromatography was performed on SÜD-Chemie silica gel (0.2−0.05 mm).

Anhydrous solvents were obtained as follows: pyridine was refluxed overnight in the presence of KOH and distilled; CH_2Cl_2 was obtained by distillation after reflux overnight with CaH_2; MeOH was obtained by distillation after refluxing overnight on CaH_2; water was removed from absolute DMF by storing on Linde type 4 Å molecular sieves, followed by distillation under reduced pressure.

9-(3-Benzamido-3-deoxy-β-D-xylofuranosyl)adenine (2a). To a cooled (0 °C) suspension of 420 mg (1.58 mmol) of amine **1**[16,27] in 30 mL of dry CH_2Cl_2−pyridine (3:1) was added 433 mg (1.91 mmol) of benzoic anhydride. After the mixture was stirred for 3 h at room temperature, the reaction was quenched with 5 mL of H_2O. The mixture was evaporated to dryness and purified by column chromatography (EtOAc−MeOH, 98:2 and then 95:5) to obtain 287 mg (49%) of the title compound as a white solid: mp 236 °C; ^{1}H NMR (DMSO-d_6) δ 3.54 (m, H-5B′), 3.67 (m, $J_{5A',5B'} = -12.2$ Hz, H-5A′), 4.32 (app q, H-4′), 4.63 (app q, H-3′), 4.78 (app q, $J_{2',3'} = 4.7$ Hz, H-2′), 5.27 (t, $J = 5.9$ Hz, 5′-OH), 5.86 (d, $J = 4.0$ Hz, 2′-OH), 6.00 (d, $J = 4.9$ Hz, H-1′), 7.48 (br s, NH_2), 7.54 (t, arom H-3,5), 7.59 (t, arom H-4), 7.87 (d, arom H-2,6), 8.07 (s, H-2), 8.40 (s, H-8), 9.34 (d, $J = 8.1$ Hz, 3′-NH); ^{13}C NMR (DMSO-d_6) δ 57.28 (C-3′), 60.48 (C-5′), 77.82 (C-2′), 80.42 (C-4′), 89.93 (C-1′), 119.75 (C-5), 127.27, 128.67 (2 C_o, 2 C_m), 131.65 (C_p), 134.55 (C_{ipso}), 140.84 (C-8), 148.47 (C-4), 152.34 (C-2), 156.47 (C-6), 166.94 (CO); MS (LSIMS, thioglycerol) m/z 393 (M + Na)$^+$, 371 (M + H)$^+$, 178 (s_1),[28] 164 (s2), 136 (B + 2H)$^+$, 105 (C_6H_5CO)$^+$. Anal. ($C_{17}H_{18}N_6O_4 \cdot C_2H_5OH$) C, H, N.

9-[3-Deoxy-3-(3-phenoxypropionamido)-β-D-xylofuranosyl]adenine (2b). To a cooled (−20 °C), stirred suspension of 565 mg (2.13 mmol) of **1** and 353 mg (2.13 mmol), of 3-phenoxypropionic acid in 20 mL of dry DMF were added NHS (245 mg, 2.13 mmol) and DCC (439 mg, 2.13 mmol) and stirring was continued for 24 h at room temperature. The reaction mixture was filtered and the filtrate evaporated. The obtained residue was purified by column chromatography (CH_2Cl_2, then CH_2Cl_2−MeOH, 95:5 and finally 90:10) to yield a white solid, which after crystallization from EtOH gave 280 mg (32%) of the pure title compound: ^{1}H NMR (DMSO-d_6) δ 2.68 (m, $COCH_2$), 3.54 (m, 2 dd after D_2O exchange, H-5′), 4.17−4.26 (m, 3 H, H-4′, Ph-OCH_2), 4.45 (app q, t after D_2O exchange, $J = 5.9$ Hz, H-2′, coupling constant measured after D_2O exhange), 4.68 (app q, t after D_2O exchange, $J = 6.5$ Hz, H-3′), 5.43 (dd, $J = 4.4$, 7.5 Hz, 5′-OH), 5.78 (d, $J = 5.6$ Hz, H-1′), 5.90 (d, $J = 5.4$ Hz, 2′-OH), 6.90 (m, arom H-2,4,6), 7.27 (t, arom H-3,5), 7.47 (br s, NH_2), 8.15 (s, H-2), 8.33 (s, H-8), 8.82 (d, 3′-NH, $J = 8.0$ Hz); ^{13}C NMR (DMSO-d_6) δ 36.03 (CH_2-CO), 56.36 (C-3′), 60.89 (C-5′), 64.42 (Ph-O-CH_2), 76.95 (C-2′), 80.17 (C-4′), 89.46 (C-1′), 114.87 (2 C_o), 121.19 (C_p), 130.06 (2 C_m), 141.22 (C-8), 148.98 (C-4), 152.73 (C-2), 156.53 (C-6), 158.79 (C_{ipso}), 171.07 (CO); MS (LSIMS, thioglycerol) m/z 415 (M + H)$^+$, 149 (PhO$(CH_2)_2$CO)$^+$, 136 (B + 2H)$^+$. Anal. ($C_{19}H_{22}N_6O_5 \cdot C_2H_5OH$) C, H, N.

9-[3-Deoxy-3-(4-cyclohexylbutyramido)-β-D-xylofuranosyl]adenine (2c). This compound was prepared as described for **2b**, using 425 mg (1.6 mmol) of the amine **1**, 272 mg (1.6 mmol) of 4-cyclohexanebutyric acid, 184 mg (1.6 mmol) of NHS, and 330 mg (1.6 mmol) of DCC. The title compound was obtained as a white solid: 265 mg (40% yield); mp 107 °C dec; ^{1}H NMR (DMSO-d_6) δ 0.80 (dd, 2H), 1.13 (m, 6H), 1.5−1.7 (m, 7H), 2.17 (m, 2H) (($CH_2)_3C_6H_{11}$)), 3.50 (m, H-5′), 4.20 (m, H-4′), 4.39 (app q, t after D_2O exchange, $J = 5.9$ Hz, H-3′), 4.60 (app q, t after D_2O exchange, $J = 5.3$ Hz, H-2′), 5.32 (app t, 5′-OH), 5.77 (d, $J = 5.3$ Hz, H-1′), 5.88 (d, 2′-OH), 7.45 (br s, NH_2), 8.17 (s, H-2), 8.34 (s, H-8), 8.62 (d, $J = 8.4$ Hz, 3′-NH); ^{13}C NMR (DMSO-d_6) δ 22.81, 25.88, 26.26, 32.88, 35.78, 36.46, 36.81 (($CH_2)_3-C_6H_{11}$), 55.91 (C-3′), 60.44 (C-5′), 76.91 (C-2′), 79.89 (C-4′), 89.27 (C-1′), 119.5 (C-5), 140.74 (C-8), 148.49 (C-4), 152.28 (C-2), 156.28 (C-6), 172.91 (CO); MS (LSIMS, thioglycerol) m/z 419 (M + H)$^+$, 284 (M − B)$^+$, 136 (B + 2H)$^+$. Anal. ($C_{20}H_{30}N_6O_4 \cdot C_2H_5OH$) C, H, N.

9-[3-Deoxy-3-(5-phenylvaleramido)-β-D-xylofuranosyl]-adenine (2d). This compound was prepared as described for **2b**, using 425 mg (1.6 mmol) of the amine **1**, 285 mg (1.6 mmol) of 5-phenylvaleric acid, 184 mg (1.6 mmol) of NHS, and 330 mg (1.6 mmol) of DCC. The title compound was obtained as a white solid: 210 mg (32% yield); ^{1}H NMR (DMSO-d_6) δ 1.57 (m, 4 H), 2.25 (m, 2 H), 2.58 (m, 2 H) (4 CH_2 of valeramide), 3.45 (m, dd after D_2O exchange, $J_{5B',4'} = 4.5$ Hz, $J_{5B',5A'} = -12.4$ Hz, H-5B′), 3.56 (m, dd after D_2O exchange, $J_{5A',4'} = 3.2$ Hz, H-5A′), 4.20 (m, H-4′), 4.41 (app q, t after D_2O exchange, $J = 6.4$ Hz, H-3′), 4.63 (app q, t after D_2O exchange, $J = 5.7$ Hz, H-2′), 5.37 (dd, $J = 5.4$, 7.2 Hz, 5′-OH), 5.78 (d, H-1′, $J = 5.4$ Hz), 5.88 (d, 2′-OH, $J = 5.1$ Hz), 7.16 (t, arom H-4), 7.18 (d, arom H-2,6), 7.26 (t, arom H-3,5), 7.47 (br s, NH_2), 8.17 (s, H-2), 8.35 (s, H-8), 8.63 (d, $J = 8.0$ Hz, 3′-NH); ^{13}C NMR (DMSO-d_6) δ 25.52, 31.06, 35.38, 35.76 (4 CH_2 of valeramide), 56.29 (C-3′), 60.95 (C-5′), 77.18 (C-2′), 80.21 (C-4′), 89.55 (C-1′), 119.92 (C-5), 126.26 (C_p), 128.84 (2 C_o, 2 C_m), 141.23 (C-8), 142.61 (C_{ipso}), 148.99 (C-4), 152.80 (C-2), 156.58 (C-6), 173.54 (CO); MS (LSIMS, thioglycerol) m/z 449 (M + Na)$^+$, 427 (M + H)$^+$, 178 (s_1), 164 (s_2), 136 (B + 2H)$^+$. Anal. ($C_{21}H_{26}N_6O_4 \cdot C_2H_5$-OH) C, H, N.

9-(2,3-Anhydro-β-D-ribofuranosyl)-N^6-cyclopentyladenine (4). To a suspension of 5.71 g (17.03 mmol) of N^6-cyclopentyladenosine **(3)** in 150 mL of dry acetonitrile, containing 15 mL of CH_3CN-H_2O (100:1), was added 9.9 mL (68 mmol) of α-acetoxyisobutyryl bromide, and the mixture was stirred at room temperature for 3 h. The clear solution was diluted with 150 mL of saturated aqueous $NaHCO_3$ solution and extracted twice with 200 mL of EtOAc. The combined organic layers were washed with water, dried ($MgSO_4$), and evaporated. The residue was dissolved in 0.4 N methanolic sodium methoxide and kept overnight at room temperature. It was then neutralized with acetic acid−water (1:9) and evaporated on Celite. Purification by column chromatography yielded 3.82 g (71% yield) of **4** as a white foam: ^{1}H NMR (DMSO-d_6) δ 1.55 (br s, 4H), 1.70 (br s, 2H), 1.90 (br s, 2H) (cyclopentyl), 3.54 (m, H-5′), 4.17 (app t, $J_{4'-5A',5B'} = 5.2$ Hz, H-4′), 4.22 (d, $J_{3',2'} = 2.6$, H-3′), 4.44 (d, H-2′), 4.52 (br s, cyclopentyl C*H*NH), 5.05 (t, $J = 5.1$ Hz, 5′-OH), 6.20 (s, H-1′), 7.75 (br d, $J = 7$ Hz, NH), 8.22 (br s, H-2), 8.33 (s, H-8); MS (LSIMS, thioglycerol) m/z 340 (M + Na)$^+$, 318 (M + H)$^+$, 249 (M + H − cyclopentyl), 232 (s_2), 204 (B + 2H)$^+$, 136 (B − cyclopentyl + 2H)$^+$.

9-(3-Azido-3-deoxy-β-D-xylofuranosyl)-N^6-cyclopentyladenine (5). A mixture of 3.82 g of the epoxide **4** and 3.91 g (60 mmol) of NaN_3 in 60 mL of DMF was stirred for 3 days at 80 °C. The solvent was evaporated; the residue was adsorbed on Celite and purified by column chromatography (EtOAc, then EtOAc−MeOH, 95:5 and finally 90:10), yielding 2.42 g (42%) of **5** as a white solid: mp 113 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.50 (br s, 4H), 1.70 (br s, 2H), 1.93 (br s, 2H) (cyclopentyl), 3.60−3.74 (m, H-5′), 4.28−4.39 (m, 2H, H-3′,4′), 4.52 (br s, cyclopentyl C*H*-NH), 4.80 (app q, $J_{2',3'} = 5.4$ Hz, H-2′), 5.41 (t, $J = 5.6$ Hz, 5′-OH), 5.84 (d, $J = 5.3$ Hz, H-1′), 6.20 (d, $J = 5.2$ Hz, 2′-OH), 7.80 (d, NH), 8.20 (br s, H-2), 8.30 (s, H-8); MS (LSIMS, thioglycerol) m/z 361 (M + H)$^+$, 318 (M − N_3)$^+$, 246 (s_1), 232 (s_2), 204 (B + 2H)$^+$, 136 (B − cyclopentyl + 2H)$^+$. Anal. ($C_{15}H_{20}N_8O_3$) C, H; N: calcd, 31.10; found, 28.85.

9-(3-Amino-3-deoxy-β-D-xylofuranosyl)-N^6-cyclopentyladenine (6). A solution of 2.42 g (6.7 mmol) of **5** in 30 mL of MeOH was hydrogenated at room temperature and 1100 psi of pressure in the presence of 10% Pd/C (0.5 g). The mixture was filtered over a Celite pad and evaporated to yield 2.21 g (95%) of **6** as a white solid, which was sufficiently pure for the next step: ^{1}H NMR (DMSO-d_6) δ 1.5−2.0 (m, 8H, cyclopentyl), 3.54 (app t, $J = 6.3$ Hz, H-2′), 3.70 (m, H-3′, H-5A′), 4.19 (app dt, H-4′), 4.50 (br s, cyclopentyl C*H*-NH), 5.0 (br s, 3H, 5′-OH, 3′-NH_2), 5.78 (d, $J = 5.2$ Hz, H-1′), 5.90 (br s, 2′-OH), 7.66 (br d, $J = 6$ Hz, N*H*-cyclopentyl), 8.20 (br s, H-2),

8.39 (s, H-8); MS (FAB, thioglycerol) *m/z* 336 $(M + 2H)^+$, 204 $(B + 2H)^+$, 136 $(B - \text{cyclopentyl} + 2H)^+$.

9-(3-Benzamido-3-deoxy-β-D-xylofuranosyl)-N^6-cyclopentyladenine (7a). To a solution of 600 mg (1.72 mmol) of **6** in 60 mL of dry CH_2Cl_2−pyridine (5:1) cooled at 0 °C was added 428 mg (1.89 mmol) of benzoic anhydride. After the mixture was stirred for 3 h at room temperature, the reaction was quenched with 5 mL of H_2O. The mixture was evaporated to dryness and the residue purified by column chromatography (CH_2Cl_2, then CH_2Cl_2−MeOH, 95:5 and finally 90:10) to obtain the crude title compound. Crystallization from acetone and petroleum ether gave 500 mg (65%) of pure **7a**: mp 161 °C; ^{1}H NMR (DMSO-d_6) δ 1.5−1.8 (m, 6H), 1.92 (br s, 2H, cyclopentyl), 3.55 (m, H-5B′), 3.67 (app dt, $J_{5A',5B'} = -12.3$ Hz, H-5A′), 4.32 (m, H-4′), 4.52 (br s, cyclopentyl C*H*-NH), 4.62 (m, H-3′), 4.77 (m, H-2′), 5.27 (br s, 5′-OH), 5.86 (d, $J = 4.3$ Hz, H-1′), 6.00 (d, $J = 4.8$ Hz, 2′-OH), 7.60 (m, arom H-3,4,5), 7.85 (d, arom H-2,6), 7.91 (br s, N*H*-cyclopentyl), 8.12 (br s, H-2), 8.39 (s, H-8), 9.39 (d, 3′-NH, $J = 6.7$ Hz); ^{13}C NMR (DMSO-d_6) δ 23.60, 32.13, 51.6 (cyclopentyl), 57.32 (C-3′), 60.48 (C-5′), 77.95 (C-2′), 80.49 (C-4′), 90.07 (C-1′), 120.1 (C-5), 127.28, 128.70 (2 C_o, 2 C_m), 131.66 (C_p), 134.58 (C_{ipso}), 140.54 (C-8), 147.5 (C-4), 152.25 (C-2), 154.64 (C-6), 166.92 (CO); MS (LSIMS, thioglycerol) *m/z* 461 $(M + Na)^+$, 439 $(M + H)^+$, 246 (s_1), 232 (s_2), 204 $(B + 2H)^+$, 136 $(B - \text{cyclopentyl} + 2H)^+$, 105 $(PhCO)^+$. Anal. ($C_{22}H_{26}N_6O_4 \cdot 1/2H_2O$) C, H, N.

9-[3-Deoxy-3-(5-phenylvaleramido)-β-D-xylofuranosyl]-N^6-cyclopentyladenine (7k). To a cooled (−20 °C) suspension of 606 mg (1.74 mmol) of **6** and 306 mg (1.72 mmol) of 5-phenylvaleric acid in 40 mL of dry DMF were added 532 mg (2.58 mmol) of DCC and 296 mg (2.58 mmol) of NHS. The mixture was allowed to come to room temperature and stirred for 24 h, after which it was filtered. The filtrate was evaporated and the residue purified by column chromatography (CH_2Cl_2, then CH_2Cl_2−MeOH, 95:5 and finally 90:10) to obtain 370 mg (42%) of **7i** as a white solid: mp 81 °C; ^{1}H NMR (DMSO-d_6) δ 1.5−2.6 (m, 16H, cyclopentyl, 4 CH_2 of valeramide), 3.42 (dd after D_2O exchange, $J_{5B',4'} = 4.6$ Hz, H-5B′), 3.56 (dd after D_2O exchange, $J_{5A',4'} = 3.0$ Hz, $J_{5A',5B'} = -12.5$ Hz, H-5A′), 4.20 (app q, H-4′), 4.39 (app q, t after D_2O exchange, $J = 6.4$ Hz, H-3′), 4.48 (cyclopentyl C*H*-NH), 4.60 (app q, t after D_2O exchange, $J = 5.7$ Hz, H-2′), 5.42 (dd, 5′-OH), 5.76 (d, $J = 5.4$ Hz, H-1′), 5.88 (d, 2′-OH), 7.18 (m, 3H, arom H-2,4,6), 7.28 (t, 2H, arom H-3,5), 7.9 (d, N*H*-cyclopentyl), 8.24 (br s, H-8), 8.35 (s, H-2), 8.62 (d, NH−CO); ^{13}C NMR (DMSO-d_6) δ 23.98, 32.55, 52.09 (cyclopentyl), 25.51, 31.03, 35.36, 35.76 (4 CH_2 of valeramide), 56.29 (C-3′), 60.92 (C-5′), 77.20 (C-2′), 80.21 (C-4′), 89.61 (C-1′), 120.19 (C-5), 126.23 (C_p), 128.82 (2 C_o, 2 C_m), 140.81 (C-8), 142.59 (C_{ipso}), 148.2 (C-4), 152.73 (C-2), 154.88 (C-6), 173.47 (CO); MS (LSIMS, thioglycerol) *m/z* 495 $(M + H)^+$, 246 (s_1), 232 (s_2), 204 $(B + 2H)^+$, 136 $(B - \text{cyclopentyl} + 2H)^+$. Anal. ($C_{26}H_{34}N_6O_4$) H, N; C: calcd, 63.12; found, 62.52.

General Procedure for the Synthesis of the Remaining Derivatives 7. An amount of 200 mg (0.6 mmol) of **6**, 90 mg (0.67 mmol) of HOBT, and 0.6 mmol of the respective carboxylic acid were dissolved in 10 mL of CH_2Cl_2. The mixture was cooled at 0 °C, and 100 μL (0.64 mmol) of DIC was added. After the mixture was stirred for 2 h, it was evaporated, and the residue purified on silica gel eluted with CH_2Cl_2−MeOH (98:2 and then 95:5). The desired compounds were obtained as amorphous white powders in 75−90% yield. Analytical samples were obtained after crystallization from MeOH (**7b**−**g**) or a second purification on silica gel (**7h**−**k**).

9-[3-(4-Chlorobenzamido)-3-deoxy-3-β-D-xylofuranosyl]-N^6-cyclopentyladenine (7b): mp 249−250.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.5−1.8 (m, 6H), 1.92 (br s, 2H) (cyclopentyl), 3.52 (m, H-5B′), 3.68 (m, H-5A′), 4.32 (app q, H-4′), 4.51 (br s, cyclopentyl C*H*-NH), 4.61 (app q, H-3′), 4.78 (app q, H-2′), 5.30 (br s, 5′-OH), 5.86 (d, $J = 4.7$ Hz, H-1′), 6.00 (d, $J = 4.8$ Hz, 2′-OH), 7.64 (d, arom H-3,5), 7.90 (m, arom H-2,6, N*H*-cyclopentyl), 8.15 (br s, H-2), 8.38 (s, H-8); ^{13}C NMR (DMSO-d_6) δ 23.69, 32.21 (cyclopentyl), 57.37 (C-3′), 60.58 (C-5′), 77.71 (C-2′), 80.42 (C-4′), 89.98 (C-1′), 128.90, 129.34 (2 C_o, 2 C_m), 133.36, 136.53 (C_{ipso}, C_p), 140.59 (C-8), 152.40 (C-2), 154.73 (C-6), 165.99 (CO); MS (LSIMS, thioglycerol) *m/z* 473 $(M + H)^+$, 246 (s_1), 232 (s_2), 204 $(B + 2H)^+$, 139 (COC_6H_4-*p*-Cl)$^+$, 136 $(B - \text{cyclopentyl} + 2H)^+$. Anal. ($C_{22}H_{25}N_6O_4Cl$) C, H, N.

9-[3-Deoxy-3-(4-methoxybenzamido)-β-D-xylofuranosyl]-N^6-cyclopentyladenine (7c): mp 240−241.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.5−1.8 (m, 6H), 1.92 (br s, 2H) (cyclopentyl), 3.52 (m, H-5B′), 3.66 (m, H-5A′), 3.82 (s, OCH_3), 4.30 (app q, H-4′), 4.52 (br s, cyclopentyl C*H*-NH), 4.60 (app q, H-3′), 4.78 (app q, H-2′), 5.25 (br s, 5′-OH), 5.85 (d, $J = 4.5$ Hz, H-1′), 5.99 (d, $J = 4.9$ Hz, 2′-OH), 7.10 (d, arom H-3,5), 7.87 (d, arom H-2,6), 7.90 (br s, N*H*-cyclopentyl), 8.20 (br s, H-2), 8.40 (s, H-8), 9.19 (d, NHCO); ^{13}C NMR (DMSO-d_6) δ 23.67, 32.22, 51.82 (cyclopentyl), 55.63 (OCH_3), 57.37 (C-3′), 60.54 (C-5′), 78.01 (C-2′), 80.57 (C-4′), 90.15 (C-1′), 114.00 (2 C_m), 120.82 (C-5), 126.66 (C_{ipso}), 129.18 (2 C_o), 140.65 (C-8), 147.8 (C-4), 152.40 (C-2), 154.73 (C-6), 162.04 (C_p), 166.44 (CO); MS (LSIMS, thioglycerol) *m/z* 491 $(M + Na)^+$, 469 $(M + H)^+$, 266 $(M - B)$, 246 (s_1), 232 (s_2), 204 $(B + 2H)^+$, 136 $(B - \text{cyclopentyl} + 2H)^+$, 135 ($COC_6H_5$-*p*-OMe)$^+$. Anal. ($C_{23}H_{28}N_6O_5$) C, H, N.

9-[3-Deoxy-3-(4-methylbenzamido)-β-D-xylofuranosyl]-N^6-cyclopentyladenine (7d): mp 239.5−241 °C; ^{1}H NMR (DMSO-d_6) δ 1.5−1.75 (m, 6H), 1.93 (br s, 2H) (cyclopentyl), 2.40 (s, CH_3), 3.51 (m, H-5B′), 3.66 (m, H-5A′), 4.30 (app q, H-4′), 4.51 (br s, cyclopentyl C*H*-NH), 4.60 (app q, H-3′), 4.75 (app q, H-2′), 5.25 (br s, 5′-OH), 5.85 (d, $J = 4.5$ Hz, H-1′), 6.00 (d, $J = 4.9$ Hz, 2′-OH), 7.38 (d, arom H-3,5), 7.79 (d, arom H-2,6), 7.93 (br s, N*H*-cyclopentyl), 8.17 (br s, H-2), 8.40 (s, H-8), 9.35 (br s, NH−CO); ^{13}C NMR (DMSO-d_6) δ 21.19 (CH_3), 23.67, 32.18, 51.72 (cyclopentyl), 57.37 (C-3′), 60.54 (C-5′), 78.07 (C-2′), 80.59 (C-4′), 90.19 (C-1′), 127.36 (2 C_o), 129.29 (2 C_m), 131.81 (C_{ipso}), 140.63 (C-8), 141.70 (C_p), 152.34 (C-2), 154.71 (C-6), 166.86 (CO); MS (LSIMS, thioglycerol) *m/z* 475 $(M + Na)^+$, 453 $(M + H)^+$, 246 (s_1), 232 (s_2), 204 $(B + 2H)^+$, 136 $(B - \text{cyclopentyl} + 2H)^+$, 119 ($COC_6H_4$-*p*-Me)$^+$. Anal. ($C_{23}H_{28}N_6O_4$) C, H, N.

9-[3-Deoxy-3-(4-nitrobenzamido)-β-D-xylofuranosyl]-N^6-cyclopentyladenine (7e): mp 235 °C slow dec; ^{1}H NMR (DMSO-d_6) δ 1.5−1.8 (m, 6H), 1.93 (br s, 2H) (cyclopentyl), 3.45 (m, H-5B′), 3.68 (m, H-5A′), 4.32 (app q, H-4′), 4.50 (cyclopentyl C*H*-NH), 4.62 (app q, H-3′), 4.80 (app q, H-2′), 5.30 (br s, 5′-OH), 5.88 (d, $J = 4.7$ Hz, H-1′), 6.02 (d, $J = 5.0$ Hz, 2′-OH), 7.93 (d, N*H*-cyclopentyl), 8.10 (m, 3H, H-2, arom H-2,6), 8.40 (d, arom H-3,5), 8.42 (s, H-2); ^{13}C NMR (DMSO-d_6) δ 23.67, 32.20, 51.70 (cyclopentyl), 57.46 (C-3′), 60.54 (C-5′), 77.63 (C-2′), 80.36 (C-4′), 90.00 (C-1′), 120.1 (C-5), 124.06 (2 C_m), 128.92 (2 C_o), 140.30 (C_{ipso}), 140.63 (C-8), 147.5 (C-4), 149.41 (C_p), 152.43 (C-2), 154.69 (C-6), 165.46 (CO); MS (LSIMS, thioglycerol) *m/z* 506 $(M + Na)^+$, 484 $(M + H)^+$, 246 (s_1), 232 (s_2), 204 $(B + 2H)^+$, 136 $(B - \text{cyclopentyl} + 2H)^+$. Anal. ($C_{22}H_{25}N_7O_6$) C, H, N.

9-[3-Deoxy-3-(3,4-dimethylbenzamido)-β-D-xylofuranosyl]-N^6-cyclopentyladenine (7f): ^{1}H NMR (DMSO-d_6) δ 1.5−1.8 (m, 6H), 1.95 (br s, 2H) (cyclopentyl), 2.30 (s, $2CH_3$), 3.52 (m, H-5B′), 3.65 (m, H-5A′), 4.31 (app q, H-4′), 4.53 (br s, cyclopentyl C*H*-NH), 4.61 (ddd, H-3′), 4.77 (app q, H-2′), 5.25 (dd, 5′-OH), 5.85 (d, $J = 4.4$ Hz, H-1′), 5.99 (d, $J = 5$ Hz, 2′-OH), 7.31 (d), 7.60 (d) (arom H-5,6), 7.64 (s, arom H-2), 7.90 (d, N*H*-cyclopentyl), 8.15 (br s, H-2), 8.40 (s, H-8), 9.27 (d, $J = 8.1$ Hz, NHCO); ^{13}C NMR (DMSO-d_6) δ 19.39 (2Me), 23.51, 32.07, 51.62 (cyclopentyl), 57.25 (C-3′), 60.38 (C-5′), 77.90 (C-2′), 80.45 (C-4′), 90.04 (C-1′), 120.04 (C-5), 124.64, 128.20, 129.57, 132.06, 136.45, 140.21 (aromatic C's), 140.44 (C-8), 147.60 (C-4), 152.11 (C-2), 154.58 (C-6), 166.89 (CO); MS (LSIMS, thioglycerol) *m/z* 467 $(M + H)^+$, 246 (s_1), 232 (s_2), 204 $(B + 2H)^+$, 136 $(B - \text{cyclopentyl} + 2H)^+$, 133 ($COC_6H_4$-3,4-diMe)$^+$. Anal. ($C_{24}H_{30}N_6O_4 \cdot 1/2H_2O$) C, H, N.

9-[3-Deoxy-3-(3,4-dichlorobenzamido)-β-D-xylofuranosyl]-N^6-cyclopentyladenine (7g). ^{1}H NMR (DMSO-d_6) δ 1.5−1.8 (m, 6H), 1.97 (br s, 2H) (cyclopentyl), 3.52 (m, H-5B′), 3.66 (m, $J_{5A',5B'} = -12.3$ Hz, H-5A′), 4.33 (m, H-4′), 4.53 (br s, cyclopentyl C*H*-NH), 4.62 (app q, H-3′), 4.83 (app q, H-2′), 5.33 (dd, 5′-OH), 5.86 (d, $J = 5.0$ Hz, H-1′), 5.97 (d, $J = 5.1$ Hz, 2′-OH), 7.85 (s, 2H), 8.10 (s) (aromatic H's), 7.93 (d, N*H*-cyclopentyl), 8.17 (br s, H-2), 8.38 (s, H-8), 9.45 (d, $J = 7.9$ Hz, NHCO); ^{13}C NMR (DMSO-d_6) δ 23.51, 32.10, 51.60 (cyclopentyl), 57.25 (C-3′), 60.41 (C-5′), 77.06 (C-2′), 80.03 (C-4′), 89.55 (C-1′), 120.01 (C-5), 127.57, 129.24, 130.98, 131.44, 134.32,

134.78 (aromatic C's), 140.31 (C-8), 147.74 (C-4), 152.16 (C-2), 154.56 (C-6), 164.65 (CO); MS (LSIMS, thioglycerol) *m/z* 507 $(M + H)^+$, 246 (s_1), 232 (s_2), 204 $(B + 2H)^+$, 173 $(COC_6H_4$-3,4-diCl$)^+$, 136 $(B -$ cyclopentyl $+ 2H)^+$. Anal. ($C_{22}H_{24}N_6O_4$-$Cl_2 \cdot 1/_2H_2O$) C, H, N.

9-(3-Deoxy-3-phenylacetamido-β-D-xylofuranosyl)-N^6-cyclopentyladenine (7h): Mp 110.5−112.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.5−1.8 (m, 6H), 1.95 (br s, 2H) (cyclopentyl), 3.40 (m, H-5B′), 3.52 (d, A of AB, $J = -13$ Hz), 3.56 (m, H-5A′), 3.58 (d, B of AB, PhCH_2), 4.21 (m, H-4′), 4.43 (app q, H-3′), 4.55 (br s, cyclopentyl C*H*-NH), 4.69 (app q, H-4′), 5.47 (dd, 5′-OH), 5.79 (d, $J = 5.5$ Hz, H-1′), 5.89 (d, $J = 5.4$ Hz, 2′-OH), 7.19−7.33 (m, 5H, Ph), 7.90 (d, N*H*-cyclopentyl), 8.25 (br s, H-2), 8.33 (s, H-8), 8.78 (d, $J = 7.9$ Hz, N*H*CO); ^{13}C NMR (DMSO-d_6) δ 23.71, 32.24, 51.76 (cyclopentyl), 42.60 (COCH_2), 56.13 (C-3′), 60.68 (C-5′), 76.70 (C-2′), 79.90 (C-4′), 89.30 (C-1′), 120.18 (C-5), 126.65 (C_p), 128.47, 129.22 (2 C_o, 2 C_m), 136.45 (C_{ipso}), 140.45 (C-8), 147.91 (C-4), 152.39 (C-2), 154.73 (C-6), 170.78 (CO); MS (LSIMS, thioglycerol) *m/z* 475 $(M + Na)^+$, 453 $(M + H)^+$, 246 (s_1), 232 (s_2), 204 $(B + 2H)^+$, 136 $(B -$ cyclopentyl $+ 2H)^+$, 119 $(PhCH_2CO)^+$. Anal. ($C_{23}H_{28}N_6O_4$) H, N; C: calcd, 61.03; found, 60.22.

9-[3-Deoxy-3-(3-phenylpropionamido)-β-D-xylofuranosyl]-N^6-cyclopentyladenine (7i): mp 103.5−105 °C; ^{1}H NMR (DMSO-d_6) δ 1.48−1.82 (m, 6H), 1.96 (br s, 2H) (cyclopentyl), 2.54 (dd, 2H), 2.86 (app t, 2H, CO(CH_2)$_2$), 3.35 (m, H-5B′), 3.51 (m, H-5A′), 4.20 (m, H-4′), 4.44 (app q, H-3′), 4.53 (br s, cyclopentyl C*H*-NH), 4.62 (app q, H-4′), 5.41 (dd, 5′-OH), 5.79 (d, $J = 5.4$ Hz, H-1′), 5.87 (d, $J = 5.4$ Hz, 2′-OH), 7.12−7.30 (m, 5H, Ph), 7.88 (d, N*H*-cyclopentyl), 8.22 (br s, H-2), 8.32 (s, H-8), 8.60 (d, $J = 7.9$ Hz, N*H*CO); ^{13}C NMR (DMSO-d_6) δ 23.72, 32.29, 51.78 (cyclopentyl), 31.35 (PhCH_2), 37.19 (COCH_2), 56.05 (C-3′), 60.63 (C-5′), 76.81 (C-2′), 79.94 (C-4′), 89.34 (C-1′), 120.18 (C-5), 126.12 (C_p), 128.47 (2 C_o, 2 C_m), 140.41 (C-8), 141.34 (C_{ipso}), 147.91 (C-4), 152.32 (C-2), 154.74 (C-6), 172.03 (CO); MS (LSIMS, thioglycerol) *m/z* 467 $(M + H)^+$, 264 $(M -$ B$)^+$, 246 (s_1), 232 (s_2), 204 $(B + 2H)^+$, 136 $(B -$ cyclopentyl $+ 2H)^+$. Anal. ($C_{24}H_{30}N_6O_4$) H, N; C: calcd, 61.77; found, 62.70.

9-[3-Deoxy-3-(4-phenylbutyramido)-β-D-xylofuranosyl]-N^6-cyclopentyladenine (7j): mp 91.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.48−1.78 (m, 6H), 1.95 (br s, 2H) (cyclopentyl), 1.84 (m, 2H), 2.23 (m, 2H), 2.60 (t, 2H) (3 CH_2 of butyramide), 3.49 (m, H-5B′), 3.60 (m, H-5A′), 4.24 (m, H-4′), 4.44 (app q, H-3′), 4.52 (br s, cyclopentyl C*H*-NH), 4.65 (app q, H-4′), 5.39 (dd, 5′-OH), 5.80 (d, $J = 5.2$ Hz, H-1′), 5.89 (d, $J = 5.3$ Hz, 2′-OH), 7.14−7.22 (m, 3H), 7.28 (t, 2H, Ph), 7.89 (d, $J = 7.2$ Hz, N*H*-cyclopentyl), 8.18 (br s, H-2), 8.35 (s, H-8), 8.69 (d, $J = 7.9$ Hz, N*H*CO); ^{13}C NMR (DMSO-d_6) δ 23.71, 32.26, 51.80 (cyclopentyl), 27.52, 34.87, 35.16 (3 CH_2 of butyramide), 56.18 (C-3′), 60.70 (C-5′), 77.11 (C-2′), 80.07 (C-4′), 89.48 (C-1′), 120.18 (C-5), 125.99 (C_p), 128.53 (2 C_o, 2 C_m), 140.47 (C-8), 141.92 (C_{ipso}), 147.93 (C-4), 152.31 (C-2), 154.74 (C-6), 172.51 (CO); MS (LSIMS, thioglycerol) *m/z* 481 $(M + H)^+$, 278 $(M - B)^+$, 246 (s_1), 232 (s_2), 204 $(B + 2H)^+$, 136 $(B -$ cyclopentyl $+ 2H)^+$. Anal. ($C_{25}H_{32}N_6O_4$) H, N; C: calcd, 62.47; found, 61.93.

9-[3-Deoxy-3-(4-cyclohexylbutyramido)-β-D-xylofuranosyl]-N^6-cyclopentyladenine (7l): mp 110 °C dec; ^{1}H NMR (DMSO-d_6) δ 0.80 (dd, 2H), 1.1−1.2 (m, 6H), 1.5−1.8 (m, 13H), 1.92 (br s, 2H), 2.18 (m, 2H) ((CH_2)$_3C_6H_{11}$), cyclopentyl), 3.47 (m, H-5B′), 3.57 (m, $J_{5A',5B'} = -12.3$ Hz, H-5A′), 4.21 (m, H-4′), 4.40 (app q, H-3′), 4.53 (br s, cyclopentyl C*H*-NH), 4.61 (app q, H-2′), 5.35 (dd, 5′-OH), 5.78 (d, $J = 5.1$ Hz, H-1′), 5.86 (d, $J = 6.3$ Hz, 2′-OH), 7.90 (d, N*H*-cyclopentyl), 8.15 (s, H-2), 8.35 (s, H-8), 8.61 (d, $J = 8.0$ Hz, 3′-NH); ^{13}C NMR (DMSO-d_6) δ 22.75, 23.52, 25.81, 26.20, 32.11, 32.77, 32.82, 35.79, 36.42, 36.77, 51.62 ((CH_2)$_3C_6H_{11}$, cyclopentyl), 56.04 (C-3′), 60.44 (C-5′), 77.11 (C-2′), 79.93 (C-4′), 89.37 (C-1′), 140.18 (C-8), 152.08 (C-2), 154.57 (C-6), 172.55 (CO); MS (LSIMS, thioglycerol) *m/z* 487 $(M + H)^+$, 246 (s_1), 232 (s_2), 204 $(B + 2H)^+$, 136 $(B -$ cyclopentyl $+ 2H)^+$. Anal. ($C_{25}H_{38}N_6O_4$) C, H, N.

Acknowledgment. This research was supported by a grant from the U. G. Onderzoeksfonds.

Supporting Information Available: All further information concerning the X-ray analysis (atomic coordinates, equivalent isotropic displacement parameters, anisotropic displacement parameters, bond lengths, and bond angles) (7 pages). Ordering information is given on any current masthead page.

References

(1) Nyce, J. W.; Metzger, W. J. DNA antisense therapy for asthma in an animal model. *Nature* **1997**, *385*, 721−725.
(2) Jacobson, K. A. Adenosine (P_1) and ATP (P_2) Receptors. In *Comprehensive Medicinal Chemistry; The Rational Design, Mechanistic Study & Therapeutic Application of Chemical Compounds*; Hansch, C., Sammes, P. G., Taylor, J. B., Eds.; Emmett, J. C., Ed.; Pergamon Press: Oxford, 1990; Vol. 3: Membranes and Receptors, pp 601−642.
(3) Stiles, G. L. Adenosine Receptors. *J. Biol. Chem.* **1992**, *267*, 6451−6454.
(4) Jacobson, M. Cloning and Expression of Human Adenosine Receptor Subtypes. In *Adenosine and Adenine Nucleotides: From Molecular Biology to Integrative Physiology*; Bellardinelli, L., Pelleg, A., Eds.; Kluwer: Norwell, MA, 1995; pp 5−13.
(5) Moos, W. H.; Szotek, D. S.; Bruns, R. F. N^6-Cycloalkyladenosines. Potent, A_1−Selective Adenosine Agonists. *J. Med. Chem.* **1985**, *28*, 1383−1384.
(6) Hutchison, A. J.; Williams, M.; de Jesus, R.; Yokoyama, R.; Oei, H. H.; Ghai, G. R.; Webb, R. L.; Zoganas, H. C.; Stone, G. A.; Jarvis, M. F. 2-(Arylalkylamino)adeosin-5′-uronamides: A New Class of Highly Selective Adenosine A_2 Receptor Ligands. *J. Med. Chem.* **1990**, *33*, 1919−1924.
(7) Bruns, R. F.; Fergus, J. H.; Badger, E. W.; Bristol, J. A.; Santay, L. A.; Hartman, J. D.; Hays, S. J.; Huang, C. C. Binding of the A_1-Selective Adenosine Antagonist 8-Cyclopentyl-1,3-dipropylxanthine to Rat Brain Membranes. *Naunyn-Schmiedberg's Arch. Pharmacol.* **1987**, *335*, 59−63.
(8) Francis, J. E.; Cash, W. D.; Psychoyos, S.; Ghai, G.; Wenk, P.; Friedmann, R. C.; Atkins, C.; Warren, V.; Furness, P.; Hyun, J. L.; Stone, G. A.; Desai, M.; Williams, M. Structure−Activity Profile of a Series of Novel Triazoloquinazoline Adenosine Antagonists. *J. Med. Chem.* **1988**, *31*, 1014−1020.
(9) Kim, H. O.; Ji, X.-d.; Siddiqi, S. M.; Olah, M. E.; Stiles, G. L.; Jacobson, K. A. 2-Substitution of N^6-Benzyladenosine-5′-uronamides Enhances Selectivity for A_3 Adenosine Receptors. *J. Med. Chem.* **1994**, *37*, 3614−3621.
(10) Taylor, M. D.; Moos, W. H.; Hamilton, H. W.; Szotek, D. S., Patt, W. C.; Badger, E. W.; Bristol, J. A.; Bruns, R. F.; Heffner, T. G.; Mertz, T. E. Ribose-Modified Adenosine Analogues as Adenosine Receptor Agonists. *J. Med. Chem.* **1986**, *29*, 346−353.
(11) van der Wenden, E. M.; von Frijtag Drabbe Künzel, J. K.; Mathôt, R. A. A.; Danhof, M.; IJzerman, A. P.; Soudijn, W. Ribose-Modified Adenosine Analogues as Potential Partial Agonists for the Adenosine Receptor. *J. Med. Chem.* **1995**, *38*, 4000−4006.
(12) Lohse, M. J.; Klotz, K.-N.; Diekmann, E.; Friedrich, K.; Schwabe, U. 2′,3′-Dideoxy-N^6-cyclohexyladenosine: an Adenosine Derivative with Antagonist Properties at Adenosine Receptors. *Eur. J. Pharmacol.* **1988**, *156*, 157−160.
(13) Van Calenbergh, S.; Van Den Eeckhout, E.; Herdewijn, P.; De Bruyn, A.; Verlinde, C.; Hol, W.; Callens, M.; Van Aerschot, A.; Rozenski, J. Synthesis and Conformational Analysis of 2′-Deoxy-2′-(3-methoxybenzamido)adenosine, a Rational Designed Inhibitor of Trypanosomal Glyceraldehyde Phosphate Dehydrogenase. *Helv. Chim. Acta* **1994**, *77*, 631−644.
(14) Van Calenbergh, S.; Verlinde, C. L. M. J.; Soenens, J.; De Bruyn, A.; Callens, M.; Blaton, N. M.; Peeters, O. M.; Rozenski, J.; Hol, W. G. J.; Herdewijn, P. Synthesis and Structure−Activity Relationships of Analogues of 2′-Deoxy-2′-(3-methoxybenzamido)adenosine, a Selective Inhibitor of Trypanosomal Glycosomal Glyceraldehyde-3-phosphate Dehydrogenase. *J. Med. Chem.* **1995**, *38*, 3838−3849.
(15) Soenens, J.; François, G; Van den Eeckhout, E.; Herdewijn, P. Synthesis of 3′-Amino-3′-Deoxyadenosine Derivatives as Potential Drugs for the Treatment of Malaria. *Nucleosides Nucleotides* **1995**, *14*, 409−411.
(16) Robins, M. J.; Fouron, Y.; Mengel, R. Adenosine 2′,3′-*ribo*-Epoxide. Synthesis, Intramolecular Degradation, and Transformation into 3′-Substituted Xylofuranosyl Nucleosides and the *lyxo*-Epoxide. *J. Org. Chem.* **1974**, *39*, 1564−1570.
(17) Russel, A. F.; Greenberg, S.; Moffatt, J. G. Reactions of 2-Acyloxyisobutyryl Halides with Nucleosides. II. Reactions of Adenosine. *J. Am. Chem. Soc.* **1973**, *95*, 4025−4030.
(18) Hansske, F.; Robins M. J. Regiospecific and Stereoselective Conversion of Ribonucleotides to 3′-Deoxynucleotides. A High Yield Three-Stage Synthesis of Cordyceptin from Adenosine. *Tetrahedron. Lett.* **1985**, *26*, 4295−4298.
(19) Ehlert, F. J. The relationship between muscarinic receptor occupancy and adenylate cyclase inhibition in the rabbit myocardium. *Mol. Pharmacol.* **1985**, *28*, 410−421.

(20) Van der Wenden, E. M.; Hartog-Witte, H. R.; Roelen, H. C. P. F.; von Frijtag Drabbe Künzel, J. K.; Pirovano, I. M.; Mathôt, R. A. A.; Danhof, M.; Van Aerschot, A.; Lidaks, M. J.; IJzerman, A. P.; Soudijn, W. 8-Substituted adenosine and theophylline-7-riboside analogues as potential partial agonists for the adenosine A_1 receptor. *Eur. J. Pharmacol.—Mol. Pharm. Sect.* **1995**, *290*, 189−199.

(21) Thompson, R. D.; Secunda, S.; Daly, J. W.; Olsson, R. A. N^6, 9-Disubstituted Adenines: Potent, Selective Antagonists at the A_1 Adenosine Receptor. *J. Med. Chem.* **1991**, *34*, 2877−2882.

(22) Jacobson, K. A.; Siddiqi, S. M.; Olah, M. E.; Ji, X.,-d.; Melman, N.; Bellamkonda, K.; Meshulam, Y.; Stiles, G. L.; Kim, H. O. Structure−Activity Relationships of 9-Alkyladenine and Ribode-Modified Adenosine Derivatives at Rat A_3 Adenosine Receptor. *J. Med. Chem.* **1995**, *38*, 1729−1735.

(23) Pirovano, I. M.; IJzerman, A. P.; Van Galen, P. J. M.; Soudijn, W. The influence of molecular structure of N^6-(ω-aminoalkyl)-adenosines on adenosine receptor affinity and intrinsic activity. *Eur. J. Pharmacol.* **1989**, *172*, 185−193.

(24) Jarvis, M. F.; Schultz, R.; Hutchison, A. J.; Hoi Do, U.; Sills, M.; Williams, M. [^{3}H]CGS 21680, a selective A_2 adenosine receptor agonist directly labels A_2 receptors in rat brain. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 888−893.

(25) Altomore, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Polidori, G. SIR92 *J. Appl. Crystallogr.* **1994**, *27*, 435.

(26) Sheldrick, G. M. *SHELXL93: Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, 1993.

(27) Lichtenthaler, F. W.; Kitahara, K.; Strobel, K. A Simple Access to 3′-Amino-xylo- and 3′,4′-Unsaturated Purine Nucleosides. *Synthesis* **1974**, 860−862.

(28) s_1 and s_2 refer to fragments containing the heterocyclic base and a part of the sugar, see: Crow, F. W.; Tomer, K. B.; Gross, M. L.; McCloskey, J. A.; Bergstrom, D. E. Fast Atom Bombardment combined with Tandem Mass Spectrometry for the Determination of Nucleosides. *Anal. Biochem.* **1984**, *23*, 243−262.

JM970176K