5′-Deoxy Congeners of 9-(3-Amido-3-deoxy-β-D-xylofuranosyl)-N^6-cyclopentyladenine: New Adenosine A_1 Receptor Antagonists and Inverse Agonists

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The synthesis and structure−activity relationship of N^6-cyclopentyl-3′-substituted-xylofuranosyladenosine analogues with respect to various adenosine receptors were explored in order to identify selective and potent antagonists and inverse agonists for the adenosine A_1 receptor. In particular, the effects of removal of the 5′-OH group and introduction of selected substituents at the 3′-NH_2 position of 9-(3-amino-3-deoxy-β-D-xylofuranosyl)-N^6-cyclopentyladenine were probed. A solid phase-assisted synthetic approach was used to optimize the 3′-amide functionality. In view of the general concern of the presence of a 5′-OH moiety with regard to cellular toxicity, the present study describes 5′-deoxy compounds with reasonable affinity for the human adenosine A_1 receptor. Interestingly, this study shows that optimization of the 3′-"up" amide sustituent can substantially compensate for the drop in affinity for the adenosine A_1 receptor, which is generally observed upon removal of the 5′-OH group. The fact that for several 3′-amido-substituted (5′-deoxy)-N^6-cyclopentyladenosine derivatives, guanosine 5′-triphosphate-induced shifts in K_i values were significantly lower than 1 implies that these analogues behave as inverse agonists. This is further supported by their 1,3-dipropyl-8-cyclopentylxanthine-like capacity to increase forskolin-induced adenosine cyclic 3′,5′-phosphate production.

Introduction

Recent reports have demonstrated that several potent and selective adenosine A_1 receptor (A_1AR) antagonists have diuretic and saliuretic properties; hence, they might be useful in the treatment of diseases such as salt-induced hypertension and for their renal protective effect. FK 838, for instance, is undergoing phase-2 clinical trials as a diuretic antihypertensive agent.[1] FK 838 was developed to improve the poor aqueous solubility, which is inherent to many adenosine antagonists of fused heteroaromatic nature. Other potential therapeutic indications of A_1AR antagonists are cognitive defects.[2] Furthermore, the A_1AR is an underrecognized but fundamental mediator of asthma, and clinical trials have begun with a phosphorothioate RASON (respirable antisense oligonucleotide) that targets the A_1AR.[3]

The biological relevance of the A_1ARs in humans and the molecular interactions between A_1ARs and their ligands need to be understood more profoundly with the aim of developing new therapeutic agents. Despite considerable research efforts toward providing insights into ligand−A_1AR interactions,[4] progress in this area still relies heavily on information on structure−activity relationships (SAR) that is collected from identification of new ligands that were discovered by trial and error. The effects of numerous modifications of the adenosine scaffold on affinity and intrinsic activity toward A_1AR are well-documented. Most modifications at the 2′- and 3′-positions of the ribose moiety or configurational inversion of these chiral centers are found to abolish A_1AR binding.[5] Furthermore, the secondary hydroxyl groups of the ribose moiety are believed to be determinants for the intrinsic activity of A_1AR agonists. Removal of the 2′- or 3′-hydroxyl groups of different prototypical A_1AR agonists, i.e., N^6-cyclopentyladenosine (CPA), N^6-cyclohexyladenosine (CHA), or N^6-(*R*)-(1-phenyl-2-propyl)adenosine (*R*-PIA), has been shown to result in partial agonists,[6] or, in the case of the 2′,3′-dideoxy analogue of CHA, antagonist properties.[7] Such changes also affect affinity, taking into account that a decrease in A_1 affinity caused by deletion of the 2′-hydroxyl moiety is significantly more pronounced than the decrease caused by removal of the 3′- or 5′-OH groups.[6]

Recently, we showed that substitution of the ribofuranosyl residue of CPA for a 3-amido-3-deoxyxylofuranos-1-yl moiety gives rise to potent and selective A_1AR antagonists (e.g., **8a**; see Table 1).[8] Here, we describe our continuing investigations in the SAR of such 3′-amido-3′-deoxyxylofuranosyl-N^6-cyclopentyladenine analogues. Therefore, we developed a solid phase synthetic approach, which greatly facilitates purification of targeted compounds.

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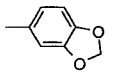
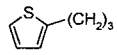
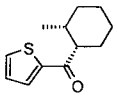
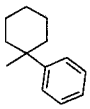
Table 1. Affinities [K_i (Values ± SEM) in the Presence and Absence of GTP] of Selected 9-(3-Amido-3(5)-(di)deoxy-β-D-xylofuranosyl)-N^6-cyclopentyladenine Analogues at Rat and Human A_1 Receptors, GTP Shifts of Selected Analogues at Rat A_1AR, and Forskolin-Induced cAMP Production of Selected Analogues at Human A_1AR

Compound Code	$R_{5'}$	$R_{3'}$	A_1 (rat) K_i -GTP (nM)	A_1 (rat) K_i +GTP (nM)	A_1 (rat) GTP shift	A_1 (human) K_i (nM)	A_1 (human) cAMP production (% of forskolin)
8a[8]	OH	} 3,4-diMe-Ph	24±3	17±4	0.73±0.11	137±17	126±4
8b	H		236±9				
9b	H	4-Et-Ph	240±33				
10a	OH	} 4-*i*Pr-Ph	171±15				
10b	H		270±14				
13a	OH	} 3-F-4-Me-Ph	112±8			773±171	135±11
13b	H		47%[a]				
15a	OH	} 3-Cl-4-F-Ph	78±4	54±2	0.70±0.02	579±90	125±10
15b	H		44%[a]				
18a	OH		102±1			443±151	126±6
23a	OH		67±1	46±3	0.69±0.04	630±97	152±19
23b	H		55±1	38±1	0.70±0.01	419±48	148±7
24b	H	Ph-O-$(CH_2)_3$	473±17				
26b	H		98±1	70±2	0.72±0.02	971±105	182±13
27b	H		138±13	114±4	0.84±0.08		
28b	H		286±3	210±4	0.74±0.02		
3'-deoxy-N^6-cyclopentyladenosine			110±30	470±40	4.3±1.2		
5'-deoxy-N^6-cyclopentyladenosine			70±20	450±20	6.4±1.9		
DPCPX			1.46±0.12	1.20±0.11	0.77±0.03	2.13±0.03	157±4
N0840			279±16	259±18	0.94±0.09	1185±200	139±5

[a] Percentage radioligand displacement in the presence of 10^{-6} M ligand.

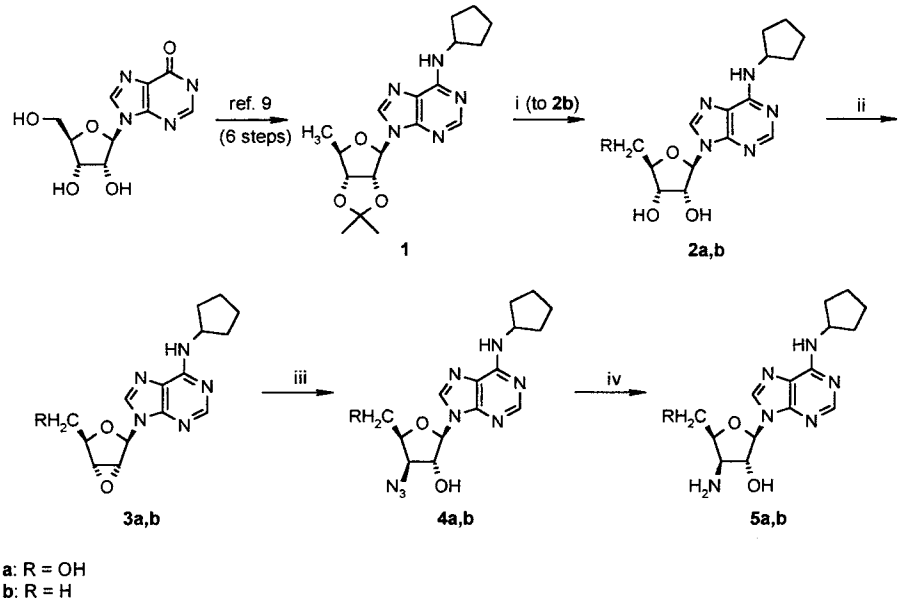
Despite the high affinities of several of our original lead compounds, e.g., **8a**, for the A_1 receptor, the presence of a 5′-OH functionality presents a conceivable difficulty. Indeed, there is a general concern that this hydroxyl group might be susceptible to intracellular phosphorylation and incorporation into DNA, therefore possibly impeding therapeutical applications. In this regard, the present study deals with the synthesis of 5′-deoxy derivatives of the above-mentioned aminonucleosides. Such modification might be accompanied by a decrease in affinity for the A_1AR;[6] hence, we further modified the 3′-functionality to cope with this feature and to restore the affinity.

Results and Discussion

Chemistry. Previously, we have described the synthesis of **5a** from CPA (**2a**).[8] Attempts to execute 5′-deoxygenation in the intermediate **4a** were unsuccessful due to formation of the N^3,5′-cyclonucleoside salt as a major reaction product on treatment of the corresponding 5′-tosylate with sodium iodide. The electron-donating property of the N^6-cyclopentylamine moiety, which renders N^3 more nucleophilic, explains this reaction.[9] The reduced propensity for such intramolecular displacement in the inosine series[10] led us to carry out 5′-deoxygenation at an earlier stage in the synthetic scheme. The pathway for the synthesis of 9-(3-amino-3,5-dideoxy-β-D-xylofuranosyl)-N^6-cyclopentyladenine (**5b**) is depicted in Scheme 1. According to a procedure developed by Davidson and Fiore,[9] inosine was converted to N^6-cyclopentyl-5′-deoxy-2′,3′-*O*-isopropylideneadenosine (**1**) in six steps. Deprotection of the hydroxyl groups was accomplished using a HCl−dioxane mixture at room temperature, which gave a higher yield as compared to treatment with 50% formic acid.[9] N^6-Cyclopentyl-5′-deoxyadenosine (**2b**) was converted to its 3′-azidoxylosyl analogue **4b**, following a modification of the method of Moffatt and co-workers[11] by Hansske and Robins.[12] Subsequent reduction of azide **4b** to amine **5b** by catalytic hydrogenation proceeded smoothly.

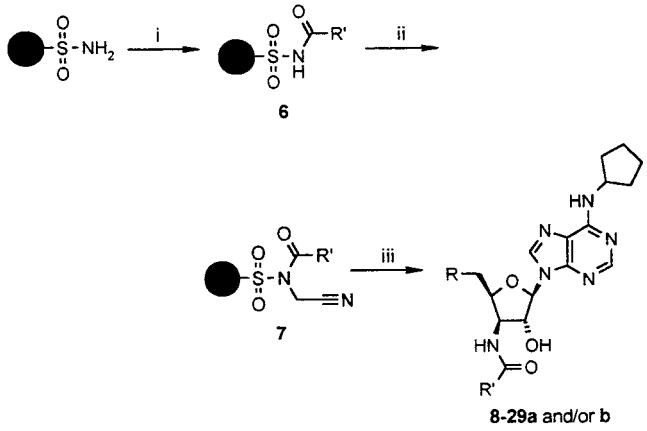
The synthesis of compounds **8**−**20** and **22**−**24** (**a** and/or **b**, Figure 1) was achieved by coupling selected acids to the Kenner safety-catch linker, as improved by Ellman et al. (Scheme 2).[13] Thus, various resin aliquots **6** were prepared from commercially available acids, while the reaction course could be monitored by Fourier transform infrared spectroscopy. Activation for nucleophilic cleavage was accomplished by substituting the acylsulfonamide moiety with an electron-withdrawing cyanomethyl group, as described by Ellman et al.[14] The resulting highly activated polymer-bound acids **7** could be transformed to compounds **8**−**20** and **22**−**24** upon stirring with amines **5a**,**b** in dimethylformamide (DMF) at 60 °C. Workup consisted of removal of the polymer beads by filtration and subsequent removal of the solvent. The crude compounds were typically >90% pure, as determined by high-performance liquid chromatography (HPLC), and they were characterized by

Scheme 1[a]



[a] Reagents: (i) HCl 1 N/1,4-dioxane (1:1); (ii) $Me_2C(OAc)COBr$, CH_3CN, H_2O (trace), then Na, MeOH; (iii) NaN_3, DMF; (iv) H_2/Pd, MeOH.

Scheme 2[a]



[a] Reagents: (i) R′COOH, 1,3-diisopropylcarbodiimide, *N*,*N*-diisopropylethylamine, DMAP, CH_2Cl_2; (ii) $BrCH_2CN$, DIEA, 1-methyl-2-pyrrolidinone; (iii) **5a** or **5b**, DMF, 60 °C.

high-resolution mass spectrometry (HRMS). Only compounds with desired potencies (i.e., more than 50% radioligand displacement at 10^{-6} M concentration) were purified by short-column chromatography over Dowex 1×2 (OH^-), fully characterized, and assayed to obtain exact K_i values. The *N*-benzylurea derivative **21b** was prepared by reacting **5b** with (isocyanatomethyl)benzene. Attempts to synthesize **25b** or **26b** by the above-described solid phase-assisted approach resulted in significant levels of cis−trans epimerization. Also, steric hindrance impeded efficient coupling of acids **27** and **28**. In these cases, the desired analogues were obtained by conventional amidation of amines **5a** or **5b** with the appropriate carboxylic acid in DMF, using *N*,*N*′-diisopropylcarbodiimide and 1-hydroxybenzotriazole as coupling agents. The 2-amino-4-phenylbutanamide diastereomers of **29b** were prepared using a similar coupling reaction between the FMOC-protected D,L-homophenylalanine and amine **5b**. FMOC removal with piperidine in tetrahydrofuran (THF) afforded the desired diastereomers, which could be separated by flash chromatography on silica.

Binding Studies. All analogues were tested in radioligand binding assays with A_1, A_{2A}, and A_3 receptors. The results at adenosine A_1 receptors of the most potent compounds are given in Table 1. K_i values of 3′- and 5′-deoxy-N^6-cyclopentyladenosine are included for comparison. Removal of the 5′-OH group in the lead **8a** led to an increase in K_i toward rat A_1AR with 1 order of magnitude. A similar tendency could be observed for couples **13a**,**b**, **15a**,**b**, and (less pronounced) **10a**,**b**. Remarkably, upon 3′-substitution with a 4-(2-thienyl)-butanamide or a 4-phenoxybutanamide moiety, 5′-deoxygenation appeared to slightly promote both rat and human A_1 receptor binding (**23a**,**b**, **24a**,**b**; **24a** causes only 46% radioligand displacement at 10^{-6} M, data not shown). Compounds **25b**, **26b**, **27b**, and **28b** were selected to probe the possibility to connect the amide moiety to the (hetero-)aromatic part via an aliphatic ring. For **26b**, a stereoselective binding mode was apparent, since this compound exhibited appreciable A_1AR affinity in contrast to the trans isomer **25b**. The homophenylalanine derivatives **29b**, having an amine moiety in the α-position of the amide group, were synthesized to improve the water solubility of this series. Unfortunately, both diastereoisomers were endowed with markedly reduced affinity for the A_1AR (both diastereoisomers of **29b** cause less than 35% radioligand displacement at 10^{-6} M, data not shown).

The affinity at human A_1 receptors, stably expressed at high density in CHO cells, was measured only for the more active compounds **8a**, **13a**, **15a**, **18a**, **23a**, **23b**, and **26b**. To further classify these compounds, adenosine cyclic 3′,5′-phosphate (cAMP) production was determined in the same cell line (Table 1). DPCPX (1,3-dipropyl-8-cyclopentylxanthine) and N0840 (N^6-cyclopentyl-9-methyladenine) are included for comparison. In general, affinities were lower at human A_1 receptors, as compared to rat; i.e., K_i values were increased 3−10-fold at human receptors. Especially compounds **23a**,

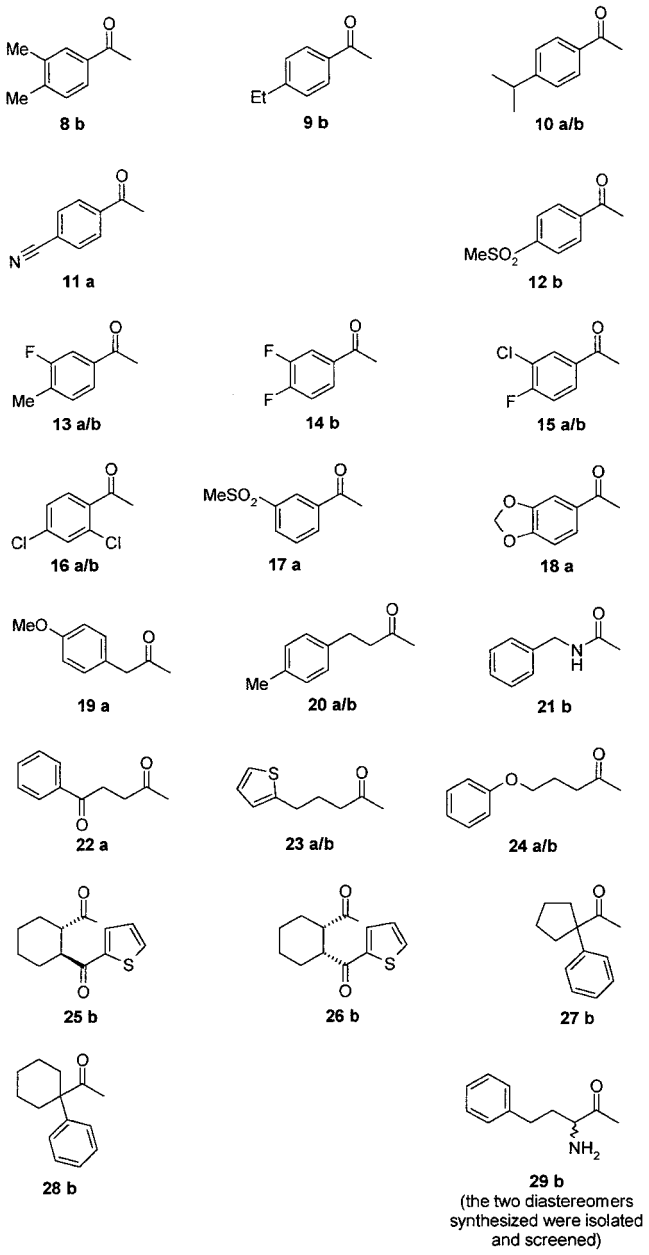


Figure 1. Overview of all analogues synthesized.

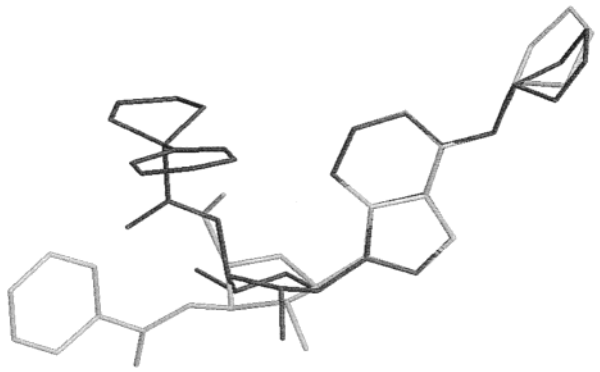


Figure 2. Comparison of the X-ray structures of 9-[(3-deoxy-3-benzoylamino)-β-D-xylofuranosyl]-N^6-cyclopentyladenine[8](pale gray) and a 5′-deoxygenated analogue **27b** (dark gray). For reasons of clarity, H atoms have been omitted. All nonhydrogen atoms of the adenine base moieties were superposed. This superposition clearly reveals a distinct orientation of the 3′-β-substituents, originating from a different sugar pucker.

23b, and **26b** showed decreased affinity for the human A_1 receptor. It may be that the thiophene substituent is less-tolerated by the human than the rat A_1 receptor. On the other hand, **23a**, **23b**, and **26b** showed the largest increase in forskolin-induced cAMP production. Their increase was comparable to or even larger than seen with DPCPX, which has been classified as an inverse agonist at human A_1 receptors for the same reason by Shryock et al.[15] The other compounds tested (**8a**, **13a**, **15a**, and **18a**) increased forskolin-induced cAMP production to a similar or lower level as N0840, a neutral antagonist according to the same authors.[15] Thus, in our hands, these analogues acted as (partial) inverse agonists, but some may behave as neutral antagonists in a different system. Furthermore, for **8a**, **15a**, **23a**, **23b**, **26b, 27b**, and **28b**, guanosine 5′-triphosphate (GTP)-induced shifts in K_i values at rat A_1 receptors were significantly smaller than 1. This may be indicative that the compounds behave as (partial) inverse agonists, since the partial agonist, 3′-deoxy-N^6-cyclopentyladenosine, and the full agonist, 5′-deoxy-N^6-cyclopentyladenosine, showed GTP-induced shifts in affinity significantly greater than unity, 4.3 and 6.1, respectively.

Another explanation for the observed effects on cAMP production might be the presence of endogenous adenosine in the assay, which would then be displaced by antagonists, e.g., the compounds described. However, during the cAMP generation, adenosine deaminase was present in a high concentration. Therefore, all of the adenosine possibly present would have been converted into inactive inosine. Furthermore, the different compounds showed varying responses in their capacity to increase cAMP production, suggesting that the observed effects are related to the compounds themselves.

At ligand concentrations of 10^{-5} M, all analogues displayed [^{125}I]-ABMECA displacement by less than 50%; therefore, they have only low affinity for human A_3 receptors. A similar observation held true for rat A_{2A} receptors (see Table 1 of Supporting Information). Only compound **10a** had appreciable affinity for the rat A_{2A} receptor with a K_i value of 437 ± 32 nM.

The observed different A_1AR binding behavior of the 5′-deoxygenated analogues can possibly be ascribed to the different sugar puckering upon deletion of the 5′-OH. An X-ray analysis of compound **27b** reveals a T(wisted) C4′-exo, O4′-endo sugar puckering with P = 63.2(3)° and ν_{max} = 45.2(2)°. This conformation clearly differs from that observed by X-ray analysis of a 5′-OH analogue.[8] The ^{2}E sugar pucker of the latter analogue was stabilized by an intramolecular H bond C(5′)-OH···N(3), which is excluded in the 5′-deoxy analogue. As a consequence of the change in sugar pucker, the orientation of the 3′-β-directed amide substituent drastically differs (Figure 2). This may explain why the optimal substituents for binding the A_1AR vary for both series.

Conclusion

Our observations confirm that the 3′-β-directed groups contribute to A_1AR binding. This result may provide a rationale for designing probes that can identify specific residues in this region of the receptor. Furthermore, it was demonstrated that the 5′-OH group is not a

prerequisite for A_1AR inhibition. In fact, we showed that a proper choice of the nature of the 3′-substituent eliminates the need for a 5′-hydroxyl group. All "xylo-CPA" analogues show a conspicuously selective character for A_1AR vs A_2AR and A_3AR. They exhibit GTP shift values at rat A_1AR that are strongly indicative for their antagonistic or inverse agonistic character. This was confirmed in effect studies, since from cAMP determinations at human A_1AR the xylo-CPA analogues may indeed be classified as (partial) inverse agonists.

Experimental Section

(i) Radioligand Binding Studies. Adenosine A_1 receptor affinities were determined using rat cortical membranes with [^{3}H]DPCPX as radioligand according to a protocol published previously.[16] K_i values and GTP shifts were determined for all compounds that displaced the radioligand to an extent greater than 50% at 10^{-6} M. The GTP concentration used in the experiments was 1 mM.

For some compounds, K_i values were also determined at human adenosine A_1 receptors with membranes from CHO cells expressing these receptors at high density (~3 pmol/mg of protein). These CHO cells were kindly provided by Prof. S. Hill (Nottingham Trent University, U.K.). Membranes (6 μg) were incubated for 1 h at 25 °C in 50 mM Tris HCl (pH 7.4) in the presence of ~1.6 nM [^{3}H]DPCPX and increasing concentrations of the compound of interest. Incubations were stopped by rapid dilution with 2 mL of ice-cold 50 mM Tris HCl buffer (pH 7.4), and bound radioactivity was recovered by filtration through Whatman GF/B filters using a Brandel harvester.

Adenosine A_{2A} receptor affinities were determined using rat striatal membranes with [^{3}H]ZM241385 as radioligand according to Jarvis et al.[17] Adenosine A_3 receptor affinities were determined using membranes prepared from HEK 293 cells stably transfected with the human A_3 receptor cDNA, with [^{125}I]ABMECA as radioligand.[18] All data reflect at least three independent experiments, performed in duplicate. For data analysis (K_i values), the software program PRISM (GraphPad, San Diego, CA) was used.

(ii) cAMP Determinations. CHO cells were seeded in 24 well plates at a density of 2×10^5 cells/well. The next day, normal growth medium was replaced by Hepes-buffered medium (pH 7.4), supplemented with adenosine deaminase (5 U/mL), cilostamide (50 μM), and rolipram (50 μM). After 30 min of incubation at 37 °C, the compound of interest ($10 \times K_i$) was added for another 10 min. Subsequently, forskolin (10 μM) was added. After 15 min, the incubations were stopped by aspirating the assay medium and by adding 200 μL of ice-cold 0.1 N HCl to the cells. The amount of cAMP was determined by competition with [^{3}H]cAMP for protein kinase A (PKA). Briefly, sample or cAMP standard (0−16 pmol), ~ 1.8 nM [^{3}H]-cAMP, and 100 μL of PKA solution were incubated on ice for 2.5 h. The incubations were stopped by rapid dilution with 2 mL of ice-cold 50 mM Tris HCl buffer (pH 7.4), and bound radioactivity was immediately recovered by filtration through Whatman GF/C filters using a Brandel harvester. All data reflect at least three independent experiments, performed in duplicate. For data analysis, the software program PRISM (GraphPad, San Diego, CA) was used.

(iii) Structure Determination of 27b by X-ray Crystallography. $C_{27}H_{34}N_6O_3$, $M_r = 490.61$, orthorhombic, $P2_12_12_1$; $a = 8.1071(6)$ Å, $b = 12.4691(4)$ Å, $c = 25.9880(10)$ Å, $V = 2627.1(2)$ Å^3, $Z = 4$, $D_c = 1.235$ mg m^{-3}; graphite monochromated Cu Kα radiation; $\lambda = 1.541\,84$ Å; 2759 observed reflections [$I > 2\sigma(I)$], 3224 independent reflections [R(int) = 0.0202]; $\mu = 0.670$ mm^{-1}, $F(000) = 1040$, $T = 293(2)$ K, final $R = 0.0632$ [$I > 2\sigma(I)$], $\Delta\rho_{max}$ 0.515 e Å^{-3}, $\Delta\rho_{min}$ −0.217 e Å^{-3}; structure solution using Direct Methods,[19] structure refinement using SHELX97.[20]

(iv) Synthesis. General. ^{1}H NMR spectra were obtained with a Bruker WH 500 spectrometer. The residual solvent signal of DMSO-d_6 (2.48 ppm) was used as secondary reference. All signals assigned to amino and hydroxyl groups were exchangeable with D_2O. Mass spectra were recorded using liquid secondary ion mass spectrometry (LSIMS) on a magnetic sector instrument (Kratos Concept IH, Kratos, Manchester, U.K.). Exact mass measurements were performed on a quadrupole/orthogonal-acceleration time-of-flight (Q/oaTOF) tandem mass spectrometer (qTof 2, Micromass, Manchester, U.K.) equipped with a standard electrospray ionization (ESI) interface. Samples were infused in a 2-propanol:water (1:1) mixture at 3 μL/min. Elemental analyses were performed at the University of Konstanz, Germany, and are within ±0.4% of theoretical values unless otherwise specified. Compositions of polymer-bound acids were determined at the University of Hamburg, Germany.

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).

N,*N*-Dimethylformamide (puriss) and 1-methyl-2-pyrrolidone (purum) were purchased from Fluka and stored over 4 Å molecular sieves. *N*,*N*-Diisopropylethylamine, redistilled, was purchased from Aldrich and kept under nitrogen atmosphere.

***N*^{6}-Cyclopentyl-5′-deoxyadenosine (2b).** A solution of 6.0 g (16.7 mmol) of *N*^{6}-cyclopentyl-5′-deoxy-2′,3′-*O*-(1-methylethylidene)adenosine[9] in 100 mL of a 1:1 1,4-dioxane 1 N aqueous HCl solution was kept at room temperature for 14 h. Monitoring by TLC showed almost quantitative deprotection. The reaction mixture was diluted with 100 mL of saturated $NaHCO_3$ solution and extracted three times with ethyl acetate. The combined organic layers were dried ($MgSO_4$), the solvent was evaporated, and the residue was purified by column chromatography (CH_2Cl_2−MeOH, 94:4). All fractions containing the desired compound were pooled, and solvent removal yielded 4.25 g (80%) of the title compound as a white solid. The ^{1}H NMR (DMSO-d_6) spectrum was identical as described before.[9]

9-(2,3-Anhydro-5-deoxy-β-D-ribofuranosyl)-*N*^{6}-cyclopentyladenine (3b). A solution of 490 mg (1.54 mmol) of *N*^{6}-cyclopentyl-5′-deoxyadenosine in 20 mL of acetonitrile and 2.0 mL of acetonitrile−water (100:1) was treated with 1.0 mL (6.8 mmol) of 1-bromocarbonyl-1-methylethyl acetate. After the mixture was stirred for 2 h at room temperature, the reaction mixture was diluted with 50 mL of a saturated $NaHCO_3$ solution and extracted twice with 50 mL of ethyl acetate. The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated.

The residue was dissolved in 50 mL of MeOH and 0.5 g of Na was added. After 2 h, the mixture was neutralized by addition of a 10% aqueous acetic acid solution (±12 mL), and the solvent was evaporated. Column chromatography of the residue (CH_2Cl_2−MeOH, 97.5:2.5) yielded 320 mg (69%) of the title compound as a white semisolid. ^{1}H NMR (DMSO-d_6): δ 1.17 (d, $J = 6.8$ Hz, 3H, CH_3), 1.45−1.75 (m, 6H), 1.92 (br s, 2H) (cyclopentyl), 4.12 (d, $J = 2.6$ Hz, H-3′), 4.31 (q, $J = 6.8$ and 13.7 Hz, H-4′), 4.49 (d, $J = 2.6$ Hz, H-2′), 4.5 (br s, cyclopentyl C*H*-NH), 6.18 (s, H-1′), 7.74 (d, $J = 7.5$ Hz, NH), 8.22 (br s, H-2), 8.30 (s, H-8). LSIMS *m*/*z* 301.1 [M + H]$^+$, 233.1 [M − cyclopentyl + 2H]$^+$, 99.1 [sugar]$^+$.

9-(3-Azido-3,5-dideoxy-β-D-xylofuranosyl)-*N*^{6}-cyclopentyladenine (4b). A mixture of 276 mg of 2′,3′-anhydronucleoside **3b** (0.92 mmol) and 300 mg of NaN_3 (4.62 mmol) in 10 mL of dry DMF was stirred at 80 °C. After 24 h, a second crop of NaN_3 (120 mg) was added and the mixture was further stirred. TLC revealed completeness of the reaction after another 12 h. The reaction mixture was concentrated and partitioned between H_2O (50 mL) and ethyl acetate (50 mL). The water layer was washed with 50 mL of ethyl acetate, and the combined organic layers were dried ($MgSO_4$) and evaporated. Column chromatography (CH_2Cl_2−MeOH, 97.5:2.5) of the residue yielded 192 mg (61%) of the title compound as a white semisolid. ^{1}H NMR (DMSO-d_6): δ 1.33 (d, $J = 6.4$ Hz, 3H, CH_3), 1.50−1.80 (m, 6H), 1.95 (br s, 2H) (cyclopentyl), 4.26 (app t, $J = 4.5$ Hz, H-3′), 4.46 (quintet, H-4′), 4.55 (br s,

cyclopentyl C*H*-NH), 4.79 (m, H-2′), 5.83 (d, J = 4.0 Hz, H-1′), 6.24 (d, J = 4.6 Hz, 2′-OH), 7.69 (d, J = 7.6 Hz, NH), 8.23 (br s, 2H, H-2,8). LSIMS m/z 344.2 $[M + H]^+$, 203.4 $[B + H]^+$, 135.6 $[B -$ cyclopentyl $+ 2H]^+$.

9-(3-Amino-3,5-dideoxy-β-D-xylofuranosyl)-N^6-cyclopentyladenine (5b). A solution of 1.033 g (3.0 mmol) of **4b** in 30 mL of MeOH was hydrogenated at room temperature at 1100 psi of pressure in the presence of 10% Pd/C (0.5 g). The reaction mixture was filtered over a Celite pad, the solvent was evaporated, and the residue was purified by column chromatography (CH_2Cl_2−MeOH, 92.5:7.5) to yield 831 mg (87%) of **5b** as a white solid. HRMS (ESI-MS) for $C_{15}H_{22}N_6O_2$ $[M + H]^+$: found, 319.1896; calcd, 319.1882.

General Procedure for the Parallel Derivatization of Amines 5a and 5b. To a flask containing 1.0 g of dry 4-sulfamylbenzoylaminomethyl polystyrene with an initial loading level of 1.0 mmol/g as determined by elemental analysis (prepared from very high-loaded aminomethylated polystyrene, purchased from Novabiochem, Läufelfingen, Switzerland) was added 10 mL of dichloromethane. The resin was allowed to swell at room temperature for 2 h. In another flask, 4 mmol of the appropriate acid was dissolved in 20 mL of dichloromethane or dichloromethane/DMF (when necessary in order to obtain a solution) and preactivated by adding 700 μL (4.5 mmol) of *N*,*N*-diisopropylcarbodiimide (DIC). The mixture was kept at room temperature for 10 h, and the precipitated *N*,*N*-diisopropylurea was removed. After addition of 540 μL of Hünig's base (3.2 mmol) and 11 mg (0.09 mmol) of 4-(dimethylamino)pyridine as catalyst, the mixture was added to the swollen resin. The resulting slurry was agitated at room temperature for 24 h. Resin beads were filtered and washed exhaustively with DMF, CH_2Cl_2, and MeOH. After the beads were dried, the increase in weight and the elemental composition were determined. An amount of resin, corresponding to 0.30 mmol acid, was alkylated, as described by Ellman et al.[14] using 450 μL (6.8 mmol) of bromoacetonitrile in 4 mL of *N*-methylpyrrolidone containing 225 μL (1.29 mmol) of Hünig's base. Subsequently, the slurry was agitated at 50−60 °C in a solution containing 0.11 mmol of amines **5a** or **5b** in DMF. The reaction was monitored by HPLC. After complete consumption of **5a**,**b** (2−12 h), the resin was filtered off and washed with DMF. The DMF solutions were combined, and the solvent was evaporated. A white semisolid was obtained after coevaporation with water. If desirable, the residue was dissolved in MeOH−H_2O (1:1) and eluted over Dowex 1 × 2 (OH^-) using the same eluent. The relevant fractions were collected, and evaporation of the solvent furnished pure amides, as described below. Typically, this acylation procedure gave 91−98% conversion to the desired products.

9-{3,5-Dideoxy-3-[(3,4-dimethylbenzoyl)amino]-β-D-xylofuranosyl}-N^6-cyclopentyladenine (8b). ^{1}H NMR (DMSO-d_6): δ 1.14 (d, J = 6.0 Hz, 4′-CH_3), 1.47−1.55 (m, 4H), 1.70 (br s, 2H), 1.93 (br s, 2H) (cyclopentyl), 2.30 (s, 2CH_3), 4.36 (app t, $J \approx$ 5.3 Hz, H-4′), 4.41−4.57 (overlap, 2H, H-3′ and cyclopentyl C*H*-NH), 4.67 (s, H-2′), 5.77 (d, J = 2.8 Hz, H-1′), 6.06 (s, 2′-OH), 7.34 (d, J = 7.2 Hz), 7.63 (d, J = 8.2 Hz) (arom H-5,6), 7.65 (s, arom H-2), 7.93 (br s, N*H*-cyclopentyl), 8.11 (br s, H-2), 8.36 (s, H-8), 9.70 (d, J = 8.5 Hz, NHCO). HRMS (ESI-MS) for $C_{24}H_{30}N_6O_3$ $[M + H]^+$: found, 451.2469; calcd, 451.2457. Anal. ($C_{24}H_{30}N_6O_3 \cdot 1/2H_2O$) H, N; C: calcd, 62.73; found, 63.17.

9-{3,5-Dideoxy-3-[(4-ethylbenzoyl)amino]-β-D-xylofuranosyl}-N^6-cyclopentyladenine (9b). ^{1}H NMR (DMSO-d_6): δ 1.14 (d, 3H, J = 6.2 Hz, 4′-CH_3), 1.21 (t, 3H, J = 7.6 Hz, CH_3−CH_2), 1.45−1.75 (m, 6H), 1.92 (br s, 2H, cyclopentyl), 2.69 (q, 2H, J = 7.4 and 14.9 Hz, Ph-CH_2CH_3), 4.36 (dq, H-4′), 4.46 (m, dd after D_2O exchange, H-3′), 4.50 (br s, cyclopentyl C*H*-NH), 4.67 (br s, H-2′), 5.77 (d, J = 3.2 Hz, H-1′), 6.17 (br s, 2′-OH), 7.41 (d, 2H, J = 7.4 Hz), 7.83 (d, 2H, J = 8.0 Hz) (arom H), 7.95 (br s, N*H*-cyclopentyl), 8.15 (s, H-2), 8.36 (s, H-8), 9.74 (d, J = 7.9 Hz, 3′-NH). HRMS (ESI-MS) for $C_{24}H_{30}N_6O_3$ $[M + H]^+$: found, 451.2431; calcd, 451.2457. Anal. ($C_{24}H_{30}N_6O_3 \cdot 2H_2O$) C, H; N: calcd, 17.27; found, 16.69.

9-{3-Deoxy-3-[(4-isopropylbenzoyl)amino]-β-D-xylofuranosyl}-N^6-cyclopentyladenine (10a). ^{1}H NMR (DMSO-d_6): δ 1.24 (d, 6H, J = 6.9 Hz, $CH(CH_3)_2$), 1.5−2.0 (8H) (cyclopentyl), 2.98 (dq, $CH(CH_3)_2$), 3.51 (m, H-5B′), 3.65 (m, H-5A′), 4.30 (app q, H-4′), 4.53 (br s, cyclopentyl C*H*-NH), 4.61 (H-3′), 4.76 (app d, H-2′), 5.23 (br s, 5′-OH), 5.85 (d, J = 4.3 Hz, H-1′), 6.01 (br s, 2′-OH), 7.43 (d, 2H, J = 7.6 Hz), 7.81 (d, 2H, J = 7.7 Hz) (arom H), 7.96 (br s, N*H*-cyclopentyl), 8.19 (s, H-2), 8.40 (s, H-8), 9.30 (br s, 3′-NH). HRMS (ESI-MS) for $C_{25}H_{32}N_6O_4$ $[M + H]^+$: found, 481.2559; calcd, 481.2563. Anal. ($C_{25}H_{32}N_6O_4 \cdot H_2O$) C, H, N.

9-{3,5-Dideoxy-3-[(4-isopropylbenzoyl)amino]-β-D-xylofuranosyl}-N^6-cyclopentyladenine (10b). ^{1}H NMR (DMSO-d_6): δ 1.14 (d, 3H, J = 6.2 Hz, 4′-CH_3), 1.24 (d, 6H, J = 6.9 Hz, $CH(CH_3)_2$), 1.45−1.75 (m, 6H), 1.92 (br s, 2H) (cyclopentyl), 2.98 (dq, $CH(CH_3)_2$), 4.35 (dq, H-4′), 4.46 (m, H-3′), 4.51 (br s, cyclopentyl C*H*-NH), 4.66 (s, H-2′), 5.76 (d, J = 3.2 Hz, H-1′), 6.08 (br s, 2′-OH), 7.45 (d, 2H, J = 7.5 Hz), 7.83 (d, 2H, J = 8.1 Hz) (arom H), 7.96 (br s, N*H*-cyclopentyl), 8.18 (s, H-2), 8.36 (s, H-8), 9.71 (d, J = 8.7 Hz, 3′-NH). HRMS (ESI-MS) for $C_{25}H_{32}N_6O_3$ $[M + H]^+$: found, 465.2657; calcd, 465.2613. Anal. ($C_{25}H_{32}N_6O_3 \cdot 1/2H_2O$) C, H, N.

9-{3-Deoxy-3-[(3-fluoro-4-methylbenzoyl)amino]-β-D-xylofuranosyl}-N^6-cyclopentyladenine (13a). ^{1}H NMR (DMSO-d_6): δ 1.49−1.75 (m, 6H), 1.95 (br s, 2H) (cyclopentyl), 2.30 (s, 3H, CH_3), 3.50 (dd, J = 3.9 and 12.1 Hz, H-5B′), 3.63 (dd, J = 2.6 and −12.4 Hz, H-5A′), 4.31 (app q, J = 5.3 and 8.7 Hz, H-4′), 4.52 (br s, cyclopentyl C*H*-NH), 4.59 (app q, J = 6.2 and 12.2 Hz, H-3′), 4.80 (br s, H-2′), 5.35 (br s, 5′-OH), 5.85 (d, J = 4.8 Hz, H-1′), 6.12 (br s, 2′-OH), 7.48 (t, J = 7.6 Hz, arom H-5), 7.63 (d, J = 10.8 Hz, arom H-2), 7.65 (d, J = 8.2 Hz, arom H-6), 7.96 (d, N*H*-cyclopentyl), 8.18 (s, H-2), 8.41 (s, H-8). HRMS (ESI-MS) for $C_{23}H_{27}FN_6O_4$ $[M + H]^+$: found, 471.2149; calcd, 471.2155. Anal. ($C_{23}H_{27}FN_6O_4 \cdot 1/2H_2O$) C, H, N.

9-{3,5-Dideoxy-3-[(3-fluoro-4-methylbenzoyl)amino]-β-D-xylofuranosyl}-N^6-cyclopentyladenine (13b). ^{1}H NMR (DMSO-d_6): δ 1.15 (d, 3H, J = 6.4 Hz, 4′-CH_3), 1.5−1.8 (m, 6H), 1.93 (br s, 2H) (cyclopentyl), 2.35 (s, 3H, CH_3), 4.38 (dq, H-4′), 4.46 [m, dd after D_2O exchange, J (after D_2O exchange) = 2.0 and 4.0 Hz, H-3′], 4.52 (br s, cyclopentyl C*H*-NH), 4.71 (br s, H-2′), 5.79 (d, J = 3.5 Hz, H-1′), 6.22 (s, 2′-OH), 7.53 (t, J = 7.5 Hz, arom H-5), 7.62 (dd, J = 1.3 and 10.4 Hz, arom H-2), 7.68 (dd, J = 1.3 and 7.8 Hz, arom H-6), 7.99 (br s, N*H*-cyclopentyl), 8.16 (s, H-2), 8.39 (s, H-8). HRMS (ESI-MS) for $C_{23}H_{27}FN_6O_3$ $[M + H]^+$: found, 455.2220; calcd, 455.2206. Anal. ($C_{23}H_{27}FN_6O_3$) C, H, N.

9-{3-[(3-Chloro-4-fluorobenzoyl)amino]-3-deoxy-β-D-xylofuranosyl}-N^6-cyclopentyladenine (15a). ^{1}H NMR (DMSO-d_6): δ 1.45−1.75 (m, 6H), 1.93 (br s, 2H) (cyclopentyl), 3.47 [br d, dd after D_2O exchange, J (after D_2O exchange) = 5.0 and 12.5 Hz, H-5B′], 3.62 (br d, H-5A′), 4.32 (app q, H-4′), 4.47 (br s, cyclopentyl C*H*-NH) 4.58 [t after D_2O exchange, J (after D_2O exchange) = 5.9 Hz, H-3′], 4.79 [br s, t after D_2O exchange, J (after D_2O exchange) = 5.3 Hz, H-2′], 5.37 (br s, 5′-OH), 5.85 (d, J = 5.0 Hz, H-1′), 6.13 (br s, 2′-OH), 7.57 (t, J = 8.8 Hz, arom H-5), 7.86 (m, 2H, arom H-2,6), 8.09 [dd after D_2O exchange, J (after D_2O exchange) = 2.3 and 7.4 Hz, N*H*-cyclopentyl], 8.12 (s, H-2), 8.35 (s, H-8), 9.48 (br s, 3′-NH). HRMS (ESI-MS) for $C_{22}H_{24}ClFN_6O_4$ $[M + H]^+$: found, 491.1605; calcd, 491.1609. Anal. ($C_{22}H_{24}ClFN_6O_4$) C, H, N.

9-{3-[(3-Chloro-4-fluorobenzoyl)amino]-3,5-dideoxy-β-D-xylofuranosyl}-N^6-cyclopentyladenine (15b). ^{1}H NMR (DMSO-d_6): δ 1.17 (d, J = 6.1 Hz, 4′-CH_3), 1.5−1.76 (m, 6H), 1.93 (br s, 2H) (cyclopentyl), 4.39 (app t, H-4′), 4.46−4.60 (2H, cyclopentyl C*H*-NH and H-3′), 4.84 (br s, H-2′), 5.79 (d, J = 3.1 Hz, H-1′), 6.09 (d, J = 4.2 Hz, 2′-OH), 7.68 (t, arom H-5), 7.87−8.02 (2H, arom H-2,6), 8.07 (d, J = 5.6 Hz, NH-cyclopentyl), 8.16 (s, H-2), 8.37 (s, H-8), 9.84 (br s, 3′-NH). HRMS (ESI-MS) for $C_{22}H_{34}ClFN_6O_3$ $[M + H]^+$: found, 475.1640; calcd, 475.1660. Anal. ($C_{22}H_{24}ClFN_6O_3 \cdot 1/2H_2O$) C, N; H: calcd, 5.21; found, 5.77.

9-{3-[(1,3-Benzodioxol-5-ylcarbonyl)amino]-3-deoxy-β-D-xylofuranosyl}-N^6-cyclopentyladenine (18a). ^{1}H NMR

(DMSO-d_6): δ 1.45−1.76 (m, 6H, cyclopentyl), 1.94 (br s, 2H) (cyclopentyl), 3.50 (m, H-5B′), 3.63 (dt, H-5A′), 4.29 (app q, H-4′), 4.53 (app q, cyclopentyl C*H*-NH), 4.57 (app q, H-3′), 4.76 (app q, H-2′), 5.25 (br s, 5′-OH), 5.84 (d, J = 4.6 Hz, H-1′), 5.98 (d, J = 4.6 Hz, 2′-OH), 6.13 (d, 2H, J = 1.9 Hz, O−CH_2−O), 7.09 (d, J = 8.0 Hz, arom H-7), 7.39 (s, arom H-4), 7.46 (dd, J = 1.7 and 8.1 Hz, arom H-6), 7.95 (br s, N*H*-cyclopentyl), 8.18 (s, H-2), 8.39 (s, H-8), 9.18 (br d, J = 7.6 Hz, 3′-NH). HRMS (ESI-MS) for $C_{23}H_{26}N_6O_6$ [M + H]$^+$: found, 483.2029; calcd, 483.1991. Anal. ($C_{23}H_{26}N_6O_6$) H, N; C: calcd, 57.26; found, 56.76.

9-{3-Deoxy-3-[(4-thien-2-ylbutanoyl)amino]-β-D-xylofuranosyl}-N^6-cyclopentyladenine (23a). ^{1}H NMR (DMSO-d_6): δ 1.45−1.77 (m, 6H, cyclopentyl), 1.8−2.0 (m, 4H, thienyl-CH_2 and 2 cyclopentyl H), 2.27 (m, 2H, thienyl-CH$_2$−CH_2), 2.81 (t, 2H, J = 7.6 Hz, CO−CH_2), 3.47 (overlap with H_2O signal, H-5B′), 3.57 (dd, J = 3.0 and −12.2 Hz, H-5A′), 4.21 (dt, H-4′), 4.41 [q, t after D_2O exchange, J (after D_2O exchange) = 6.3 Hz, H-3′], 4.53 (br s, cyclopentyl C*H*-NH), 4.63 (app t, J = 5.6 Hz, H-2′), 5.40 (s, 5′-OH), 5.78 (d, J = 5.3 Hz, H-1′), 5.89 (s, 2′-OH), 6.85 (dd, large J = 3.1 Hz), 7.31 (dd, J = 1.1 and 5.1 Hz) (thienyl H-2 and H-4), 6.93 (dd, J = 3.4 and 5.1 Hz, thienyl H-3), 7.92 (br s, N*H*-cyclopentyl), 8.20 (s, H-2), 8.36 (s, H-8), 8.70 (d, J = 7.6 Hz, 3′-NH). HRMS (ESI-MS) for $C_{23}H_{30}N_6O_4S$ [M + H]$^+$: found, 487.2134; calcd, 487.2127. Anal. ($C_{23}H_{30}N_6O_4S\cdot 1/3H_2O$) C, H, N.

9-{3,5-Dideoxy-3-[(4-thien-2-ylbutanoyl)amino]-β-D-xylofuranosyl}-N^6-cyclopentyladenine (23b). ^{1}H NMR (DMSO-d_6): δ 1.12 (d, J = 6.2 Hz, 4′-CH_3), 1.5−1.75 (6H, cyclopentyl), 1.85−2.0 (m, 4H, thienyl-CH_2 and 2 cyclopentyl H), 2.31 (m, 2H, thienyl-CH$_2$−CH_2), 2.84 (t, 2H, J = 7.6 Hz, CO−CH_2), 4.24 (m, H-3′), 4.29 (dq, H-4′), 4.55 (2H, cyclopentyl C*H*-NH and H-2′), 5.72 (d, J = 3.7 Hz, H-1′), 5.89 (s, 2′-OH), 6.85 (d, J = 2.7 Hz), 7.31 (d, J = 4.6 Hz) (thienyl H-2 and H-4), 6.93 (dd, J = 3.5 and 4.9 Hz, thienyl H-3), 7.90 (d, J = 7.2 Hz, N*H*-cyclopentyl), 8.20 (br s, H-2), 8.35 (s, H-8), 9.19 (d, J = 8.2 Hz, 3′-NH). HRMS (ESI-MS) for $C_{23}H_{30}N_6O_3S$ [M + H]$^+$: found, 471.2137; calcd, 471.2178. Anal. ($C_{23}H_{30}N_6O_3S\cdot 1/2H_2O$) H, N; C: calcd, 57.60; found, 58.09.

9-{3,5-Dideoxy-3-[(4-phenoxybutanoyl)amino]-β-D-xylofuranosyl}-N^6-cyclopentyladenine (24b). δ 1.10 (d, J = 6 Hz, 4′-CH_3), 1.45−1.75 (m, 6H, cyclopentyl), 1.85−2.05 (m, 4H, O−CH$_2$−CH_2 and 2 cyclopentyl H), 2.42 (m, 2H, CO−CH_2), 3.99 (t, 2H, J = 6.5 Hz, OCH_2), 4.25 (m, 2H, H-3′,4′), 4.52 (2H, cyclopentyl C*H*-NH and H-2′), 5.71 (d, J = 3.9 Hz, H-1′), 5.96 (d, J = 4.8 Hz, 2′-OH), 6.86−6.93 (m, 3H, arom H-2,4,6), 7.25 (dd, J = 7.2 and 9.3 Hz, arom H-3,5), 7.89 (d, J = 7 Hz, N*H*-cyclopentyl), 8.30 (br s, H-2), 8.31 (s, H-8), 9.24 (d, J = 8.4 Hz, 3′-NH). HRMS (ESI-MS) for $C_{25}H_{32}N_6O_4$ [M + H]$^+$: found, 481.2546; calcd, 481.2563. Anal. ($C_{25}H_{32}N_6O_4\cdot 1/2H_2O$) C, H, N.

General Procedure for the Synthesis of the Remaining Derivatives 25b, 26b, 27b, and 28b. An amount of 100 mg (0.31 mmol) of **5b**, 45 mg (0.33 mmol) of 1-hydroxybenzotriazole (HOBT), and 0.33 mmol of the respective carboxylic acid were dissolved in 10 mL of CH_2Cl_2 and 50 μL (0.32 mmol) of DIC was added. After the mixture was stirred for 2 h at room temperature, it was evaporated, and the residue was purified on silica gel eluted with CH_2Cl_2−MeOH (97:3). The desired compounds were obtained as white foams.

9-[3,5-Dideoxy-3-({*cis*-[2-(thien-2-ylcarbonyl)cyclohexyl]carbonyl}amino)-β-D-xylofuranosyl]-N^6-cyclopentyladenine (26b). Yield: 86%. ^{1}H NMR (DMSO-d_6): δ 1.03 (d, 3H, J = 6.2 Hz, 4′-CH_3), 1.25−2.05 (16H, 8 cyclopentyl and 8 cyclohexyl H), 2.77 (dq), 3.79 (d, cyclohexyl CH−CO), 4.14 (m, H-3′), 4.19 (dq, H-4′), 4.5 (br s, 2H, H-2′ and cyclopentyl C*H*-NH), 5.67 (d, J = 3.3 Hz, H-1′), 5.98 (br s, 2′-OH), 7.14 (dd, J = 3.9 and 4.8 Hz), 7.8−7.95 (3H, 2 thienyl H and N*H*-cyclopentyl), 8.20 (s, H-2), 8.30 (s, H-8), 8.96 (d, J = 7.3 Hz, 3′-NH). HRMS (ESI-MS) for $C_{27}H_{34}N_6O_2S$ [M + H]$^+$: found, 539.2433; calcd, 539.2440. Anal. ($C_{27}H_{34}N_6O_4S\cdot 1/2H_2O$) C, H, N.

9-(3,5-Dideoxy-3-{[(1-phenylcyclopentyl)carbonyl]amino}-β-D-xylofuranosyl)-N^6-cyclopentyladenine (27b). Yield: 79% ^{1}H NMR (DMSO-d_6): δ 0.82 (d, J = 6 Hz, 4′-CH_3), 1.42−1.78 (m, 10H), 1.80−2.02 (m, 4H), 2.52−2.72 (m, 2H, cyclopentyl H), 4.12−4.27 (m, 2H, H-4′,H-3′), 4.47 (2H, cyclopentyl C*H*-NH and H-2′), 5.62 (d, J = 3 Hz, H-1′), 5.94 (d, J = 4.5 Hz, 2′-OH), 7.17 (tt, H, J = 1.5 and 7.5 Hz, arom H-4), 7.28 (t, 2H, J = 7.5 Hz, arom H-3,5), 7.42 (dd, arom H-2,6), 7.94 (br d, N*H*-cyclopentyl), 8.25 (br s, H-2), 8.28 (s, H-8), 8.57 (d, J = 8.1 Hz, 3′-NH). HRMS (ESI-MS) for $C_{27}H_{34}N_6O_3$ [M + H]$^+$: found, 491.2791; calcd, 491.2770. Anal. ($C_{27}H_{34}N_6O_3\cdot 1/2H_2O$) C, H, N.

9-(3,5-Dideoxy-3-{[(1-phenylcyclohexyl)carbonyl]amino}-β-D-xylofuranosyl)-N^6-cyclopentyladenine (28b). Yield: 76%. ^{1}H NMR (DMSO-d_6): δ 0.83 (d, J = 6 Hz, 4′-CH_3), 1.47−2.00 (m, 18H, cyclopentyl H and cyclohexyl H), 4.18 (m,H-3′), 4.29 (dd, J = 4.5 and 8.4 Hz, H-3′), 4.50 (2H, cyclopentyl C*H*-NH and H-2′), 5.62 (d, J = 3 Hz, H-1′), 5.96 (d, J = 4 Hz, 2′-OH), 7.16 (t, H, J = 7.4 Hz, arom H-4), 7.29 (t, 2H, arom H-3,5), 7.45 (d, arom H-2,6), 7.93 (br d, N*H*-cyclopentyl), 8.23 (br s, H-2), 8.29 (s, H-8), 8.50 (d, J = 8.7 Hz, 3′-NH). HRMS (ESI-MS) for $C_{28}H_{36}N_6O_3$ [M + H]$^+$: found, 505.2939; calcd, 505.2926. Anal. ($C_{28}H_{36}N_6O_3\cdot 1/2H_2O$) C, H, N.

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Supporting Information Available: Affinity data of selected ligands for A_{2A} receptors, all further information concerning the X-ray analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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