Nucleosides and Nucleotides. 200. Reinvestigation of 5′-*N*-Ethylcarboxamidoadenosine Derivatives: Structure−Activity Relationships for P_3 Purinoceptor-like Proteins[1]

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The non-P_1 and non-P_2 muscle relaxant effect of ATP in rabbit thoracic aorta has recently been attributed to a putative P_3 purinoceptor, which is activated by either adenosine or ATP. Since the physiological roles of this putative P_3 purinoceptor and of a new [^{3}H]-5′-*N*-ethylcarboxamidoadenosine (NECA)-binding protein from rat brain membranes called P_3 purinoceptor-like protein (P_3LP), due to its ligand specificity, have not been fully elucidated, we needed a specific ligand to obtain further information about the receptor. We examined the structure−activity relationship (SAR) of various 5′-*N*-substituted-carboxamidoadenosine derivatives toward P_3LP and discovered a hydrophobic binding region near the 5′-*N*-substituted-carboxamide group. From the linear alkyl *N*-substituted derivatives, the *N*-*n*-pentyl derivative **10** was found to be the most potent ligand with a K_i value of 12 nM. In the series of the *N*-cycloalkyl derivatives, the *N*-cyclohexyl derivative **27** was the strongest ligand with a K_i value of 18 nM. On the other hand, the *N*-substituents having branched alkyl side chains and bulky cycloalkyl groups did not show any potent affinities for P_3LP. Therefore, the hydrophobic pocket accommodates approximately a 10-carbon-atom-long linear alkyl side chain, while a considerably stronger hydrophobic binding region of about a 5-carbon-atom-long depth exists near the nitrogen atom of the amide group. This pocket also allows substitution with bulky hydrophobic groups since the 5′-*N*-cycloalkyl derivatives have high affinities. We also examined the receptor selectivity for the selected nucleosides **10** and **27** with **1** [9-(6,7-dideoxy-β-D-*allo*-hept-5-ynofuranosyl)adenine, HAK2701] and NECA versus P_1 purinoceptor subtypes, such as adenosine A_1, A_{2A}, A_{2B}, and A_3 receptors, and found that **27** is the most selective ligand for P_3LP.

Introduction

Adenine nucleosides and nucleotides exert a large variety of physiological responses in various tissues and cells via specific receptors, i.e., purinoceptors, on the cell surface membranes.[2−4] Purinoceptors have been classified as P_1 and P_2 based on their pharmacological properties. P_1 purinoceptors, which are usually called adenosine receptors, are selective for adenosine and its analogues, while P_2 purinoceptors are specific for adenine nucleotides such as ATP and their analogues. P_1 purinoceptors are subclassified as A_1, A_{2A}, A_{2B}, and A_3 adenosine receptors. P_2 purinoceptors are also further divided into several subtypes. Although the presence of such purinoceptor subtypes explains many of the functions of adenine nucleosides and nucleotides, it may be necessary and helpful to identify additional subtypes to fully explain the functional roles of these substances in various tissues or cells.

Evidence for the presence of non-P_1 and non-P_2 purinoceptors in several tissues has been accumulated using various classical ligands.[5−17] Electrically evoked release of noradrenaline in rat caudal arteries was reported to be activated by 2-chloroadenosine as well as ATP.[5] The muscle relaxant effect of ATP in rabbit thoracic aortas was attributed to a putative P_3 purinoceptor, which is activated by either adenosine or ATP.[9,12] Facilitation of norepinephrine release in the adrenergic nerves of rabbit ear arteries by either 2-chloroadenosine or ATP was also reported to be caused by a putative P_3 purinoceptor.[13] Induction of K^+ currents in the follicle cell layer of *Xenopus* oocytes was also attributed to non-P_1 and non-P_2 purinoceptors.[16] Saitoh and Nakata purified a new [^{3}H]-5′-*N*-ethylcarboxamidoadenosine (NECA)-binding protein from rat brain membranes[17] and demonstrated that its ligand specificity followed the order NECA > adenosine ≥ AMP > ADP > inosine > ATP > N^6-cyclopentyladenosine ≫ 2-chloroadenosine, and most xanthines were inactive. This result is very similar to the ranking of potency toward the muscle receptor reported by Chinellato et al. (NECA > adenosine > ATP)[9,12] but is slightly different from the relative order of potency in adrenergic nerves of rat caudal arteries (2-chloroadenosine > ATP > adenosine)[5] and in the follicle cell layer of *Xenopus* oocytes (ATP > adenosine > β,γ-methylene-ATP).[16]

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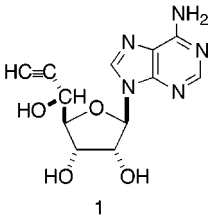
Table 1. P_3LP Binding Activity of Various NECA Analogues[a]

compd	R[b]	K_i (nM)	compd	R[b]	K_i (nM)	compd	R[b]	K_i (nM)
5	H	64 ± 9	**18**	*s*-Bu*	198 ± 27	**31**	*trans*-4-Me-cHex	12.9 ± 3
6	Me	51 ± 8	**19**	*t*-Bu	6850 ± 1610	**32**	2-Me-cHex*	69.5 ± 14
7	Et	37 ± 3	**20**	$H_2N(CH_2)_2$	167 ± 42	**33**	2-norbornyl*	640 ± 60
8	*n*-Pr	31 ± 4	**21**	$H_2N(CH_2)_8$	29 ± 10	**34**	1-adamantyl	1040 ± 200
9	*n*-Bu	17 ± 3	**22**	$AcHN(CH_2)_2$	46 ± 10	**35**	2-adamantyl	2000 ± 600
10	*n*-Pent	12 ± 2	**23**	$AcHN(CH_2)_8$	10 ± 4	**36**	3-noradamantyl	833 ± 112
11	*n*-Hex	19 ± 5	**24**	cPr	96 ± 11	**37**	HO	41 ± 10
12	*n*-Hept	20 ± 3	**25**	cBu	88 ± 12	**38**	MeO	58 ± 13
13	*n*-Oct	21 ± 3	**26**	cPent	49 ± 8	**39**	EtO	67 ± 10
14	*n*-Non	31 ± 4	**27**	cHex	18 ± 2	**40**	*i*-BuO	20 ± 9
15	*n*-Dec	27 ± 7	**28**	cHept	22 ± 5	**41**	Bn	42 ± 4
16	*n*-Undec	123 ± 34	**29**	cOct	23 ± 5	**42**	3,4-$(OMe)_2$Bn	140 ± 35
17	*n*-Dodec	163 ± 29	**30**	*cis*-4-Me-cHex	55.6 ± 12			

[a] P_3LP binding activity to [^{3}H]NECA (40 nM) was determined as described previously. P_3LP was partially purified by hydroxylapatite chromatography from a CHAPS-solubilized preparation of rat brain membranes. A_1, A_{2A}, A_{2B} and A_3 adenosine receptors and adenotin were not present in this preparation. K_i values are expressed as mean ± SEM (n = 3). [b] See Scheme 1 for R.

Therefore, this [^{3}H]NECA-binding protein from rat brain membranes was thought to be a subtype of putative P_3 purinoceptors or P_3 purinoceptor-like proteins (P_3LP).

On the basis of these results, we became interested in understanding the functions of the putative P_3 purinoceptors or P_3LP. However, further characterization is hampered by the lack of specific ligands for the putative P_3 purinoceptors. We previously reported that 9-(6,7-dideoxy-β-D-*allo*-hept-5-ynofuranosyl)adenine (HAK 2701, **1**) was a potent and relatively selective ligand for



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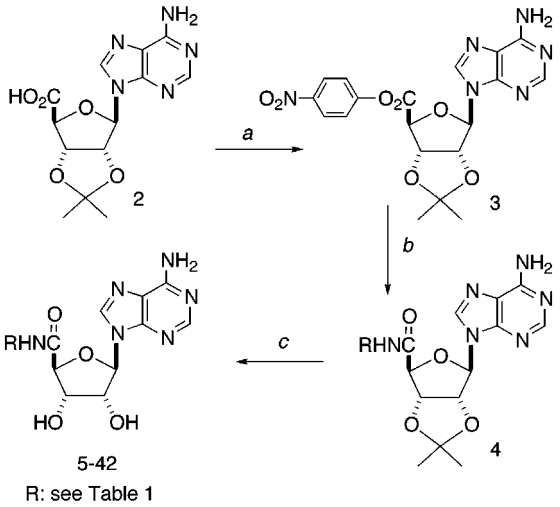
P_3LP.[18] During the course of the structure−activity relationship (SAR) study, we also found that the 5′-*N*-alkyl substituents of the carboxamide moiety of 5′-carboxamidoadenosine derivatives affected P_3LP binding affinity.[18] The ligand specificity was shown to follow the order NECA > 5′-*N*-methylcarboxamidoadenosine > 5′-carboxamidoadenosine ≫ 5′-*N*,*N*-dimethylcarboxamidoadenosine. The larger the alkyl group at the 5′-*N*-position, the better the affinity. This finding strongly suggested the presence of a hydrophobic pocket around the 5′-position of NECA. Herein we describe the structural requirements of various 5′-*N*-substituted-carboxamidoadenosine analogues with regard to P_3LP binding to find new selective ligands for P_3LP and show a descriptive rendering of the shape of the hydrophobic pocket.

Chemistry

Various 5′-*N*-substituted analogues of 5′-carboxamidoadenosine have been prepared from 2′,3′-*O*-isopropylideneadenosine-5′-carboxylic acid (**2**), which was readily obtained from adenosine in two steps.[19−23] Compound **2** was converted into its *p*-nitrophenyl ester **3**, which, without isolation, was treated with an appropriate monosubstituted amine or a hydroxylamine derivative to give the 5′-*N*-substituted-carboxamido-2′,3′-*O*-isopropylideneadenosine derivative **4**. Compound **4** was then treated with 80% aqueous trifluoroacetic acid to give a

Scheme 1[a]



[a] (a) *p*-Nitrophenol, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide·HCl, DMF; (b) RNH_2 or R′ONH_2; (c) 80% aq TFA.

variety of 5′-*N*-monosubstituted-carboxamidoadenosines (**5**−**42**, Scheme 1 and Table 1).

Biological Evaluation and Discussion

P_3LP binding assays were carried out using P_3LP that was partially purified from rat brain membranes by [^{3}H]-NECA (40 nM) in the presence of various concentrations of NECA analogues.[17] This preparation does not contain adenosine receptors (A_1, A_{2A}, A_{2B}, and A_3) and adenotin 1 and 2. K_i values were calculated using Graph Pad software (ISI Software), and the results are summarized in Table 1.

Previously, we found that 5′-carboxamidoadenosine (**5**), 5′-*N*-methylcarboxamidoadenosine (**6**), and NECA (**7**) were good ligands with K_i values of 64, 51, and 37 nM, respectively.[18] When the length of the linear 5′-*N*-alkyl chain was increased, the affinity was proportionally enhanced up to the 5′-*N*-*n*-pentyl derivative **10**, which was 3-fold more potent than NECA (**7**) (Figure 1) with a K_i value of 12 nM. Increasing the side chain length to *n*-decyl did not decrease the affinity dramatically; the K_i value of the 5′-*N*-*n*-decyl derivative **15** (27 nM) was similar to that of NECA (**7**). However, the *n*-undecyl **16** and the *n*-dodecyl **17** derivatives showed 10- and 14-fold less affinity than **10**. Interestingly, the 5′-*N*-aminoethyl derivative **20** had a K_i value of 167 nM

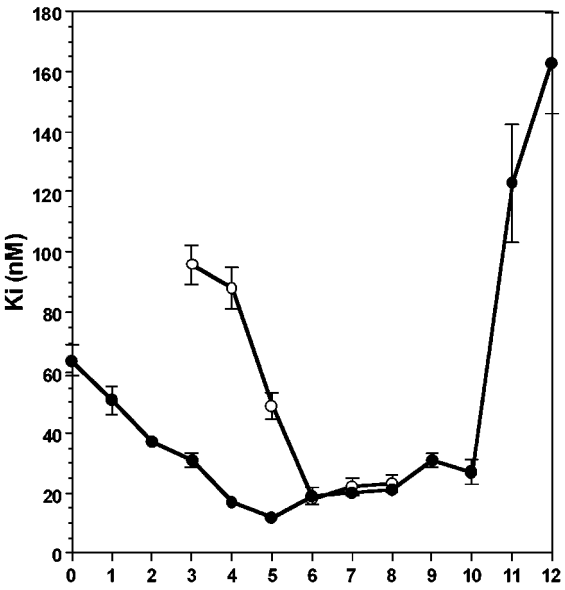


Figure 1. Effects of the carbon number of the linear alkyl side chain in compounds **5**−**17** (●) and the ring size of the cycloalkane side chain in compounds **24**−**29** (○) toward P_3LP binding.

versus P_3LP, although the length of the side chain is similar to an *n*-propyl group, while the 5′-*N*-aminooctyl derivative **21** acted as a potent ligand with a K_i value of 29 nM. After acetylation of the terminal amino groups of **20** and **21**, the affinities of the products **22** and **23** were increased to about 4- and 3-fold, respectively. On the other hand, compounds bearing 5′-*N*-branched alkyl chains, such as the secondary butyl derivative **18** (K_i = 198 nM) and the tertiary butyl derivative **19** (K_i = 6850 nM) had much less affinity for P_3LP, although the length of the alkyl chains is similar to that of ethyl and propyl groups. From these results, the hydrophobic pocket accommodates up to 10 carbon atoms in the linear alkyl side chain of the 5′-*N*-substituents in the NECA derivatives, while a relatively strong hydrophobic binding region of about a 5-carbon-atom-long depth exists near the nitrogen atom of the amide group. Near the 5′-NH region, there would be a narrow hydrophobic interaction region. The presence of the NH group is essential for affinity for P_3LP, because *N*,*N*-dimethylcarboxamidoadenosine did not bind well with a K_i value of 21 000 nM.

We next compared the affinities of various 5′-*N*-cycloalkyl-substituted analogues of NECA. As shown in Table 1, the *N*-cyclohexyl derivative **27** had the most potent affinity in the series with a K_i value of 18 nM. The analogues having smaller and larger rings than cyclohexane showed less potent affinities than **27** (Figure 1). Furthermore, the 5′-*N*-*trans*-4-methylcyclohexyl derivative **31** was more potent (K_i = 12.9 nM) than the 5′-*N*-*cis*-4-methylcyclohexyl derivative **30** with a K_i value of 55.6 nM. Compound **31** is slightly more potent than the cyclohexyl derivative **27**, and its potency is similar to that of the *n*-pentyl derivative **10**. On the basis of these observations, the 4-methylcyclohexane moiety in compounds **30** and **31** would exist in a chair form rather than in a boat form, where the methyl group should be in the axial orientation in the *cis*-analogue **30** but in the equatorial orientation in the *trans*-analogue **31**. The steric bulkiness of the axial methyl group in **30** should be larger than that of the equatorial methyl group in **31**. The distance between the amide nitrogen and the terminal methyl group is similar to that of the 5′-*N*-*n*-pentyl group in **10**. Therefore, the differences between **30** and **31** would be related to the affinity for P_3LP. Moreover, the analogues having bulky 5′-*N*-substituents such as **33**−**36** showed much less affinity for P_3LP. These data are consistent with the above-mentioned data for compounds **18** and **19**.

We have shown that the acidic proton of the 5′-amide group is essential for binding to P_3LP. A hydroxylamino or alkoxyamino group instead of an alkylamino group in the amide function would increase the acidity of the NH group. However, the derivatives **37**−**42** did not show clear SARs as did the *N*-alkyl derivatives.

On the basis of these SARs, we propose the following guidelines for recognition of the 5′-*N*-substituted-carboxamidoadenosine derivatives by P_3LP: (1) For 5′-*N*-substituents, there is a hydrophobic binding region to accommodate the linear 5′-*N*-alkyl side chain and the cycloalkyl groups with a certain depth and width. The depth of the region is about 10-carbon-atoms-long; within about a five-carbon-atom-long depth from the nitrogen of the amide group, there is a relatively strong hydrophobic region. However, near the nitrogen atom of the amide group, the receptor only accommodates linear alkyl substituents but not branched alkyl substituents. Therefore, the region for the side chain must be narrow but can accept cycloalkyl groups. (2) Acidic protons such as the 5′-OH group in **1** and the NH group in the 5′-*N*-substituted-carboxamidoadenosines are needed to bind the receptor.

We next compared the receptor selectivity for selected nucleosides **10** and **27** with **1** and NECA versus P_1 purinoceptor subtypes, such as adenosine A_1, A_{2A}, A_{2B}, and A_3 receptors. As described in Table 2, NECA showed ligand selectivity for A_{2B} receptors but almost none versus A_1, A_{2A}, and A_3 receptors. On the other hand, **1** showed much better selectivity versus all of the adenosine receptor subtypes than NECA. However, the newly synthesized compound **27** is a more selective ligand for A_1, A_{2A}, and A_{2B} than **1**, since they have almost the same affinities for P_3LP. Versus the adenosine A_3 receptor, compound **27** has about 20-fold less selectivity than **1**, but both affinities would be entirely negligible compared to the affinity for P_3LP. Compound **10** is also selective, but still has NECA-like affinity for A_1 and A_{2A} receptors. Therefore, compound **27** is the most selective ligand for P_3LP.

Because 2-[[4-(2-carboxyethyl)phenethyl]amino]-5′-*N*-ethylcarboxamidoadenosine (CGS21680) did not show any binding affinity to the partially purified P_3LP preparation, P_3LP seems not to be related to the atypical adenosine binding site, which is responsive to [^{3}H]-CGS21680 proposed by Cunha et al.[26]

In summary, we have studied the SAR of 5′-*N*-substituted-carboxamidoadenosine derivatives versus P_3LP. We found a hydrophobic binding pocket around the *N*-substituted-carboxamide group. Further studies will be needed to elucidate the SARs of adenosine analogues versus P_3LP in greater detail, particularly with regard to the pharmacological activity of **27**.

Table 2. Affinities of Selected Ligands to Adenosine A_1, A_{2A}, A_{2B}, and A_3 Receptors and to P_3LP[a]

compd	K_i (nM) P_3LP[b]	K_i (nM) A_1[c]	A_1/P_3LP	K_i (nM) A_{2A}[c]	A_{2A}/P_3LP	agonist activity A_{2B}[d]	K_i (nM) A_3[e]	A_3/P_3LP
10	12.2 ± 1.6	979 ± 18	80.2	605 ± 95	49.6	3.4% at 100 μM	5560 ± 30	456
27	18.2 ± 2.1	5020 ± 240	275	2500 ± 90	137	1.9% at 100 μM	15100 ± 300	830
1	20 ± 1.4	897 ± 14	44.9	2110 ± 160	105	10% at 100 μM	310000 ± 43000	15500
NECA	27 ± 3.8	7.7 ± 1.9	0.29	4.13 ± 0.88	0.152	100% at 100 μM	412 ± 1	15.3

[a] K_i values are expressed as mean ± SEM ($n = 3$). [b] See Table 1 for the binding assay. [c] The activities of A_1 and A_{2A} adenosine receptors were measured by binding [^{3}H]8-cyclopentyl-1,3-dipropylxanthine (DPCPX, 2 nM) and [^{3}H]2-[[4-(2-carboxyethyl)phenethyl]amino]-5′-*N*-ethylcarboxamidoadenosine (CGS21680, 6 nM) to rat brain membranes, respectively.[24,25] [d] Because specific radiolabeled ligands for A_{2B} adenosine receptor binding were not commercially available at this time, A_{2B} adenosine receptor agonist activity was determined by measuring cAMP production in CHO cells transfected with rat A_{2B} adenosine receptor cDNA. The activity of each compound at 100 μM is expressed as the percentage of NECA-induced activity. It was also confirmed that no antagonist activity of each test compound for A_{2B} adenosine receptor was detected because NECA (10 μM)-induced cAMP production was not inhibited at all by addition of each test compound (100 μM) (data not shown). [e] The activity of A_3 adenosine receptor was measured by binding [^{125}I]N^6-(3-iodophenyl)-5′-(*N*-methylcarboxamido)adenosine (IB-MECA, 0.3 nM) to cell membranes prepared from CHO cells transfected with rat A_3 adenosine receptor in the presence of 100 nM DPCPX and 100 μM 5′-adenylimidodiphosphate (AppNHp) (A) and in the presence of 100 μM DPCPX, 100 μM AppNHp and 10 nM IB-MECA (B). Specific A_3 adenosine receptor activity was calculated from the difference between the binding activity in (A) and (B).

Experimental Section

Melting points were measured on a Yanagimoto MP-3 micromelting point apparatus (Yanagimoto, Japan) and are uncorrected. Fast atom bombardment mass spectrometry (FAB-MS) was performed on a JEOL JMS-HX110 instrument at an ionizing voltage of 70 eV. The ^{1}H NMR spectra were recorded on a JEOL JNM-GX 270 (270 MHz) or Bruker ARX 500 (500 MHz) spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), m (multiplet), or br (broad). All exchangeable protons were detected by disappearance on the addition of D_2O. UV absorption spectra were recorded with a Shimadzu UV-240 spectrophotometer. IR spectra were recorded with a JEOL A-102 spectrometer. TLC was done on Merck Kieselgel F254 precoated plates (Merck, Germany). The silica gel used for column chromatography was YMC gel 60A (70−230 mesh) (YMC Co., Ltd., Japan).

General Procedure for Preparation of 1-(Adenin-9-yl)-1-deoxy-*N*-ethyl-β-D-ribofuranuronamide (NECA) Derivatives. *p*-Nitrophenol (167 mg, 1.2 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (211 mg, 1.1 mmol) were added to a suspension of 2′,3′-*O*-isopropylideneadenosine-5′-carboxylic acid (**2**;[19] 321 mg, 1.0 mmol) in dry DMF (5 mL). The reaction mixture was stirred for 3 h at room temperature. Each amine or hydroxylamine was added to the reaction mixture, which was further stirred for 1 h at room temperature. The reaction was monitored by TLC (EtOH−$CHCl_3$, 1:15). The mixture was concentrated in vacuo, and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with H_2O, followed by brine. The organic layer was dried (Na_2SO_4) and concentrated to dryness. The residue was dissolved in 80% aqueous TFA (8 mL), and the solution was stirred for 1−3 h at room temperature. The volitile was removed in vacuo, and the residue was coevapolated several times with EtOH and purified by silica gel column chromatography.

1-(Adenin-9-yl)-1-deoxy-*N*-*n*-pentyl-β-D-ribofuranuronamide (10): yield 289 mg (82%); mp 117−118 °C (crystallized from 2-propanol); EI-MS *m*/*z* 350 (M^+); ^{1}H NMR (DMSO-d_6 + D_2O) 0.82 (t, 3 H, CH_3CH_2, J = 6.6 Hz), 1.20−1.50 (m, 6 H, CH_2 × 3), 3.17 (dd, 2 H, CH_2NH, J = 6.6, J = 13.2 Hz), 4.10 (dd, 1 H, H-3′, $J_{3',2'}$ = 4.6, $J_{3',4'}$ = 1.3 Hz), 4.30 (d, 1 H, H-4′, $J_{4',3'}$ = 1.3 Hz), 4.59 (dd, 1 H, H-2′, $J_{2',1'}$ = 7.3, $J_{2',3'}$ = 4.6 Hz), 5.93 (d, 1 H, H-1′, $J_{1',2'}$ = 7.3 Hz), 8.16 (s, 1 H, H-2 or H-8), 8.35 (s, 1 H, H-2 or H-8). Anal. ($C_{15}H_{22}N_6O_4\cdot{}^1/_5H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-*n*-hexyl-β-D-ribofuranuronamide (11): yield 245 mg (66%); mp 144−146 °C (crystallized from EtOH−hexane) (lit.[20] 104−106 °C); FAB-MS *m*/*z* 365 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 0.81 (t, 3 H, CH_3CH_2, J = 6.6 Hz), 1.22−1.47 (m, 8 H, CH_2 × 4), 3.17 (dd, 2 H, CH_2NH, J = 6.6 J = 13.2 Hz), 4.09 (dd, 1 H, H-3′, $J_{3',2'}$ = 4.6, $J_{3',4'}$ =1.3 Hz), 4.29 (d, 1 H, H-4′, $J_{4',3'}$ = 1.3 Hz), 4.59 (dd, 1 H, H-2′, $J_{2',1'}$ = 7.9, $J_{2',3'}$ = 4.6 Hz), 5.92 (d, 1 H, H-1′, $J_{1',2'}$ = 7.9 Hz), 8.15 (s, 1 H, H-2 or H-8), 8.35 (s, 1 H, H-2 or H-8). Anal. ($C_{16}H_{24}N_6O_4\cdot{}^1/_2H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-*n*-heptyl-β-D-ribofuranuronamide (12): yield 231 mg (60%); mp 105−106 °C (crystallized from EtOH−hexane); FAB-MS *m*/*z* 379 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 0.81 (t, 3 H, CH_3CH_2, J = 6.6 Hz), 1.20−1.46 (m, 10 H, CH_2 × 5), 3.18 (t, 2 H, CH_2N*H*, J = 6.6 Hz), 4.09 (d, 1 H, H-3′, $J_{3',2'}$ = 4.6 Hz), 4.29 (s, 1 H, H-4′), 4.57 (dd, 1 H, H-2′, $J_{2',1'}$ = 7.9, $J_{2',3'}$ = 4.6 Hz), 5.94 (d, 1 H, H-1′, $J_{1',2'}$ = 7.9 Hz), 8.15 (s, 1 H, H-2 or H-8), 8.35 (s, 1 H, H-2 or H-8). Anal. ($C_{17}H_{26}N_6O_4\cdot{}^1/_2H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-*n*-octyl-β-D-ribofuranuronamide (13): yield 357 mg (87%); mp 108−109 °C (crystallized from EtOH); EI-MS *m*/*z* 392 (M^+); ^{1}H NMR (DMSO-d_6 + D_2O) 0.84 (dd, 3 H, CH_3CH_2, J = 7.3, 5.9 Hz), 1.22−1.47 (m, 12 H, CH_2 × 6), 3.20 (dd, 2 H, CH_2N*H*, J = 6.6, 13.2 Hz), 4.12 (dd, 1 H, H-3′, $J_{3',2'}$ = 4.6, $J_{3',4'}$ =1.3 Hz), 4.32 (d, 1 H, H-4′, $J_{4',3'}$ = 1.3 Hz), 4.60 (dd, 1 H, H-2′, $J_{2',1'}$ = 7.9, $J_{2',3'}$ = 4.6 Hz), 5.95 (d, 1 H, H-1′, $J_{1',2'}$ = 7.9 Hz), 8.19 (s, 1 H, H-2 or H-8), 8.39 (s, 1H, H-2 or H-8). Anal. ($C_{18}H_{28}N_6O_4\cdot H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-*n*-nonyl-β-D-ribofuranuronamide (14): yield 399 mg (97%); mp 106−107 °C (crystallized from MeOH); FAB-MS *m*/*z* 407 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 0.80 (t, 3 H, CH_3CH_2, J = 6.6 Hz), 1.18−1.44 (m, 14 H, CH_2 × 7), 3.14 (t, 2 H, CH_2N*H*, J = 6.6 Hz), 4.12 (dd, 1 H, H-3′, $J_{3',2'}$ = 4.6, $J_{3',4'}$ = 1.3 Hz), 4.32 (d, 1 H, H-4′, $J_{4',3'}$ = 1.3 Hz), 4.56 (dd, 1 H, H-2′, $J_{2',1'}$ = 7.3, $J_{2',3'}$ = 4.6 Hz), 5.97 (d, 1 H, H-1′, $J_{1',2'}$ = 7.3 Hz), 8.29 (s, 1 H, H-2 or H-8), 8.54 (s, 1 H, H-2 or H-8). Anal. ($C_{19}H_{30}N_6O_4\cdot{}^1/_3H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-*n*-decyl-β-D-ribofuranuronamide (15): yield 399 mg (94%); mp 124−125 °C (crystallized from MeOH); FAB-MS *m*/*z* 421 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 0.81 (t, 3 H, CH_3CH_2, J = 6.6 Hz), 1.19−1.45 (m, 16 H, CH_2 × 8), 3.14 (t, 2 H, CH_2N*H*, J = 6.6 Hz), 4.10 (dd, 1 H, H-3′, $J_{3',2'}$ = 4.6, $J_{3',4'}$ = 1.3 Hz), 4.30 (d, 1 H, H-4′, $J_{4',3'}$ = 1.3 Hz), 4.57 (dd, 1 H, H-2′, $J_{2',1'}$ = 7.3, $J_{2',3'}$ = 4.6 Hz), 5.95 (d, 1 H, H-1′, $J_{1',2'}$ = 7.3 Hz), 8.20 (s, 1 H, H-2 or H-8), 8.43 (s, 1 H, H-2 or H-8). Anal. ($C_{20}H_{32}N_6O_4\cdot{}^1/_5H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-*n*-undecyl-β-D-ribofuranuronamide (16): yield 416 mg (95%); mp 103−104 °C (crystallized from aqueous MeOH); FAB-MS *m*/*z* 435 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 0.82 (t, 3 H, CH_3CH_2, J = 6.6 Hz), 1.19−1.46 (m, 18 H, CH_2 × 9), 3.17 (t, 2 H, CH_2N*H*, J = 6.6 Hz), 4.10 (d, 1 H, H-3′, $J_{3',2'}$ = 4.6 Hz), 4.30 (s, 1 H, H-4′), 4.57 (dd, 1 H, H-2′, $J_{2',1'}$ = 7.3, $J_{2',3'}$ = 4.6 Hz), 5.94 (d, 1 H, H-1′, $J_{1',2'}$ = 7.3 Hz), 8.18 (s, 1 H, H-2 or H-8), 8.39 (s, 1 H, H-2 or H-8). Anal. ($C_{21}H_{34}N_6O_4\cdot{}^1/_{10}H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-*n*-dodecyl-β-D-ribofuranuronamide (17): yield 352 mg (72%); mp 144−146 °C (crystallized from aqueous MeOH); FAB-MS *m*/*z* 449 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 0.82 (t, 3 H, CH_3CH_2, J = 6.6 Hz), 1.17−1.44 (m, 20 H, CH_2 × 10), 3.16 (t, 2 H, CH_2N*H*, J = 6.6 Hz), 4.10 (d, 1 H, H-3′, $J_{3',2'}$ = 4.6 Hz), 4.30 (s, 1 H, H-4′), 4.57 (dd, 1 H, H-2′, $J_{2',1'}$ = 7.3, $J_{2',3'}$ = 4.6 Hz), 5.94 (d, 1 H, H-1′,

$J_{1',2'}$ = 7.3 Hz), 8.19 (s, 1 H, H-2 or H-8), 8.40 (s, 1 H, H-2 or H-8). Anal. ($C_{22}H_{36}N_6O_4$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-*sec*-butyl-β-D-ribofuranuronamide (18): yield 311 mg (93%, mixture of two diastereomers, ratio 1:1); mp 156−157 °C (crystallized from 2-propanol−hexane); FAB-MS *m*/*z* 337 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 0.76 (t, 1.5 H, CH_3, J = 7.3 Hz), 0.84 (t, 1.5 H, CH_3, J = 7.3 Hz), 1.05 (d, 1.5 H, CH_3, J = 6.6 Hz), 1.11 (d, 1.5 H, CH_3, J = 6.6 Hz), 1.29−1.57 (m, 2 H, CH_2), 3.70−3.86 (m, 1 H, C*H*NH), 4.09 (m, 1 H, H-3′), 4.29 (m, 1 H, H-4′), 4.56−4.62 (m, 1 H, H-2′), 5.76 (m, 1 H, H-1′), 8.13 (s, 0.5 H, H-2 or H-8), 8.14 (s, 0.5 H, H-2 or H-8), 8.35 (s, 0.5 H, H-2 or H-8), 8.38 (s, 0.5 H, H-2 or H-8). Anal. ($C_{14}H_{20}N_6O_4$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-*tert*-butyl-β-D-ribofuranuronamide (19): yield 320 mg (95%); mp 135−136 °C (crystallized from aqueous MeOH) (lit.[23] 140 °C); FAB-MS *m*/*z* 337 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 1.28 (s, 9 H, CH_3 × 3), 4.11 (dd, 1 H, H-3′, $J_{3',2'}$ = 4.5, $J_{3',4'}$ = 1.4 Hz), 4.23 (d, 1 H, H-4′, $J_{4',3'}$ = 1.4 Hz), 4.66 (dd, 1 H, H-2′, $J_{2',1'}$ = 7.3, $J_{2',3'}$ = 4.5 Hz), 5.92 (d, 1 H, H-1′, $J_{1',2'}$ = 7.3 Hz), 8.13 (s, 1 H, H-2 or H-8), 8.40 (s, 1 H, H-2 or H-8). Anal. ($C_{14}H_{20}N_6O_4 \cdot {}^1/_{10}H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-aminoethyl-β-D-ribofuranuronamide (20): yield 363 mg (92%, white solid); FAB-MS *m*/*z* 324 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 2.87 (dd, 2 H, CH_2-CH_2, J = 5.9, J = 10.6 Hz), 3.37 (dd, 2 H, CH_2CH_2, J = 5.9, J = 10.6 Hz), 4.26 (d, 1 H, H-3′, $J_{3',2'}$ = 4.6 Hz), 4.39 (s, 1 H, H-4′), 4.63 (dd, 1 H, H-2′, $J_{2',1'}$ = 6.6, $J_{2',3'}$ = 4.6 Hz), 6.03 (d, 1 H, H-1′, $J_{1',2'}$ = 6.6 Hz), 8.50 (s, 1 H, H-2 or H-8), 8.76 (s, 1 H, H-2 or H-8). Anal. ($C_{12}H_{17}N_7O_4 \cdot 2HCl$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-aminooctyl-β-D-ribofuranuronamide dihydrochloride (21): yield 401 mg (82%, white solid); FAB-MS *m*/*z* 408 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 1.41 (m, 12 H, CH_2 × 6), 2.29 (t, 2 H, CH_2NH, J = 6.6 Hz), 2.70 (t, 2 H, CH_2NH, J = 7.2 Hz), 4.15 (d, 1 H, H-3′, $J_{3',2'}$ = 4.6 Hz), 4.36 (s, 1 H, H-4′), 4.56 (dd, 1 H, H-2′, $J_{2',1'}$ = 6.6, $J_{2',3'}$ = 4.6 Hz), 6.02 (d, 1 H, H-1′, $J_{1',2'}$ = 6.6 Hz), 8.45 (s, 1 H, H-2 or H-8), 8.77 (s, 1 H, H-2 or H-8). Anal. ($C_{18}H_{29}N_7O_4 \cdot 2HCl \cdot {}^1/_2H_2O$) C, H, N. Ref 22 describes the synthesis of a free amine of **21**.

1-(Adenin-9-yl)-1-deoxy-*N*-acetamidoethyl-β-D-ribofuranuronamide (22): yield 323 mg (88%, white solid); FAB-MS *m*/*z* 366 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 1.71 (s, 3 H, CH_3), 3.10 (m, 4 H, CH_2 × 2), 4.13 (d, 1 H, H-3′, $J_{3',2'}$ = 4.6 Hz), 4.28 (s, 1 H, H-4′), 4.57 (dd, 1 H, H-2′, $J_{2',1'}$ = 7.9, $J_{2',3'}$ = 4.6 Hz), 5.92 (d, 1 H, H-1′, $J_{1',2'}$ = 7.9 Hz), 8.22 (s, 1 H, H-2 or H-8), 8.32 (s, 1 H, H-2 or H-8). Anal. ($C_{14}H_{19}N_7O_5 \cdot {}^1/_5H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-acetamidooctyl-β-D-ribofuranuronamide (23): yield 132 mg (29%, white foam); FAB-MS *m*/*z* 450 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 1.19 (m, 12 H, CH_2 × 6), 1.73 (s, 3 H, Ac), 2.94 (t, 2 H, CH_2NH, J = 6.6 Hz), 3.16 (t, 2 H, CH_2NH, J = 7.2 Hz), 4.08 (d, 1 H, H-3′, $J_{3',2'}$ = 4.6 Hz), 4.29 (s, 1 H, H-4′), 4.57 (dd, 1 H, H-2′, $J_{2',1'}$ = 7.9, $J_{2',3'}$ = 4.6 Hz), 5.92 (d, 1 H, H-1′, $J_{1',2'}$ = 7.9 Hz), 8.15 (s, 1 H, H-2 or H-8), 8.34 (s, 1 H, H-2 or H-8). Anal. ($C_{20}H_{31}N_7O_5 \cdot {}^1/_5H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-cyclopropyl-β-D-ribofuranuronamide (24): yield 253 mg (79%); mp 249−251 °C (crystallized from 2-propanol−hexane) (lit.[20] mp 249−250 °C); EI-MS *m*/*z* 320 (M^+); ^{1}H NMR (DMSO-d_6 + D_2O) 0.39−0.53 (m, 2 H, CH_2), 0.62−0.76 (m, 2 H, CH_2), 2.70 (m, 1 H, C*H*NH), 4.11 (dd, 1 H, H-3′, $J_{3',2'}$ = 4.6, $J_{3',4'}$ =1.3 Hz), 4.26 (d, 1 H, H-4′, $J_{4',3'}$ = 1.3 Hz), 4.55 (dd, 1 H, H-2′, $J_{2',1'}$ = 7.3, $J_{2',3'}$ = 4.6 Hz), 5.92 (d, 1 H, H-1′, $J_{1',2'}$ = 7.3 Hz), 8.13 (s, 1 H, H-2 or H-8), 8.37 (s, 1 H, H-2 or H-8). Anal. ($C_{13}H_{16}N_6O_4$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-cyclobutyl-β-D-ribofuranuronamide (25): yield 303 mg (91%); mp 235 °C (crystallized from aqueous EtOH) (lit.[20] mp 234−235 °C); FAB-MS *m*/*z* 335 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 1.59−1.75 (m, 2 H, CH_2), 1.83−2.07 (m, 2 H, CH_2), 2.13−2.29 (m, 2 H, CH_2), 4.09 (dd, 1 H, H-3′, $J_{3',2'}$ = 4.6, $J_{3',4'}$ =1.3 Hz), 4.21−4.36 (m, 2 H, H-4′, C*H*NH), 4.59 (dd, 1H, H-2′, $J_{2',1'}$ = 7.3, $J_{2',3'}$ = 4.6 Hz), 5.93 (d, 1H, H-1′, $J_{1',2'}$ = 7.3 Hz), 8.18 (s, 1H, H-2 or H-8), 8.37 (s, 1H, H-2 or H-8). Anal. ($C_{14}H_{18}N_6O_4$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-cyclopentyl-β-D-ribofuranuronamide (26): yield 163 mg (47%); mp 199−200 °C (crystallized from MeOH) (lit.[20] mp 165−170 °C); FAB-MS *m*/*z* 349 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 1.28−1.86 (m, 8 H, CH_2 × 4), 4.00 (m, 1 H, C*H*NH), 4.14 (dd, 1 H, H-3′, $J_{3',2'}$ = 4.6, $J_{3',4'}$ = 1.9 Hz), 4.34 (d, 1 H, H-4′, $J_{4',3'}$ = 1.9 Hz), 4.57 (dd, 1 H, H-2′, $J_{2',1'}$ = 6.6, $J_{2',3'}$ = 4.6 Hz), 5.98 (d, 1H, H-1′, $J_{1',2'}$ = 6.6 Hz), 8.32 (s, 1H, H-2 or H-8), 8.68 (s, 1H, H-2 or H-8). Anal. ($C_{15}H_{20}N_6O_4$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-cyclohexyl-β-D-ribofuranuronamide (27): yield 197 mg (54%, white foam); FAB-MS *m*/*z* 363 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 1.15−1.81 (m, 10 H, CH_2 × 5), 3.62 (m, 1 H, C*H*NH), 4.09 (dd, 1 H, H-3′, $J_{3',2'}$ = 4.6, $J_{3',4'}$ = 1.3 Hz), 4.29 (d, 1 H, H-4′, $J_{4',3'}$ = 1.3 Hz), 4.60 (dd, 1 H, H-2′, $J_{2',1'}$ = 7.3, $J_{2',3'}$ = 4.6 Hz), 5.93 (d, 1 H, H-1′, $J_{1',2'}$ = 7.3 Hz), 8.37 (s, 1 H, H-2 or H-8), 8.47 (s, 1 H, H-2 or H-8). Anal. ($C_{16}H_{22}N_6O_4 \cdot {}^1/_4H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-cycloheptyl-β-D-ribofuranuronamide (28): yield 333 mg (89%, colorless foam); FAB-MS *m*/*z* 377 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 1.38−1.81 (m, 12 H, CH_2 × 6), 3.79 (m, 1 H, C*H*NH), 4.09 (d, 1 H, H-3′, $J_{3',2'}$ = 4.3 Hz), 4.28 (s, 1 H, H-4′), 4.59 (dd, 1 H, H-2′, $J_{2',1'}$ = 7.6, $J_{2',3'}$ = 4.3 Hz), 5.92 (d, 1 H, H-1′, $J_{1',2'}$ = 7.6 Hz), 8.15 (s, 1 H, H-2 or H-8), 8.37 (s, 1 H, H-2 or H-8). Anal. ($C_{17}H_{24}N_6O_4$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-cyclooctyl-β-D-ribofuranuronamide (29): yield 328 mg (84%, white foam); FAB-MS *m*/*z* 391 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 1.45−1.72 (m, 14 H, CH_2 × 7), 3.84 (m, 1 H, C*H*NH), 4.09 (d, 1 H, H-3′, $J_{3',2'}$ = 4.6 Hz), 4.28 (s, 1 H, H-4′), 4.58 (dd, 1 H, H-2′, $J_{2',1'}$ = 7.5, $J_{2',3'}$ = 4.6 Hz), 5.92 (d, 1 H, H-1′, $J_{1',2'}$ = 7.5 Hz), 8.38 (s, 1 H, H-2 or H-8), 8.45 (s, 1 H, H-2 or H-8). Anal. ($C_{18}H_{26}N_6O_4$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-(4-methylcyclohexyl)-β-D-ribofuranuronamides (30, 31): yield 371 mg (98%, white solid). This material contained both *cis*- and *trans*-isomers (ratio 37:63, respectively), which were separated by C-18 HPLC (YMC-D-ODS-5) with 50% aqueous MeOH at a flow rate of 10 mL/min to give **30** (retention time 37 min, white solid) and **31** (retention time 54 min, white solid).

1-(Adenin-9-yl)-1-deoxy-*N*-(*cis*-4-methylcyclohexyl)-β-D-ribofuranuronamide (30): FAB-MS *m*/*z* 377 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 0.85 (d, 3 H, CH_3, J = 6.6 Hz), 1.17−1.56 (m, 9 H, CH_2 × 4, CH), 3.75 (m, 1 H, C*H*NH), 4.13 (dd, 1 H, H-3′, $J_{3',2'}$ = 4.6, $J_{3',4'}$ = 1.9 Hz), 4.35 (d, 1 H, H-4′, $J_{4',3'}$ = 1.9 Hz), 4.62 (dd, 1 H, H-2′, $J_{2',1'}$ = 7.3, $J_{2',3'}$ = 4.6 Hz), 5.94 (d, 1 H, H-1′, $J_{1',2'}$ = 7.3 Hz), 8.12 (s, 1 H, H-2 or H-8), 8.43 (s, 1 H, H-2 or H-8). Anal. ($C_{17}H_{24}N_6O_4 \cdot {}^1/_5H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-(*trans*-4-methylcyclohexyl)-β-D-ribofuranuronamide (31): FAB-MS *m*/*z* 377 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 0.85 (d, 3 H, CH_3, J = 6.6 Hz), 0.93−1.83 (m, 9 H, CH_2 × 4, CH), 3.50 (m, 1H, C*H*NH), 4.08 (dd, 1 H, H-3′, $J_{3',2'}$ = 4.6, $J_{3',4'}$ = 1.3 Hz), 4.27 (d, 1 H, H-4′, $J_{4',3'}$ = 1.3 Hz), 4.58 (dd, 1 H, H-2′, $J_{2',1'}$ = 7.9, $J_{2',3'}$ = 4.6 Hz), 5.92 (d, 1 H, H-1′, $J_{1',2'}$ = 7.9 Hz), 8.15 (s, 1 H, H-2 or H-8), 8.36 (s, 1 H, H-2 or H-8). Anal. ($C_{17}H_{24}N_6O_4 \cdot {}^1/_2H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-(2-methylcyclohexyl)-β-D-ribofuranuronamide (32): yield 365 mg (95%, white foam, mixture of four diastereomers, ratio = 2:2:3:3); FAB-MS *m*/*z* 377 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 0.70−0.85 (m, 3 H, CH_3), 0.99−1.75 (m, 9 H, CH_2 × 4, CH), 3.27−3.40 (m, 0.7 H, CHNH), 3.86−3.91 (m, 0.3 H, CHNH), 4.11 (m, 1 H, H-3′), 4.31 (d, 0.3 H, H-4′, $J_{4',3'}$ = 1.4 Hz), 4.32 (d, 0.3 H, H-4′, $J_{4',3'}$ = 1.4 Hz), 4.41 (d, 0.2 H, H-4′, $J_{4',3'}$ = 2.4 Hz), 4.45 (d, 0.2 H, H-4′, $J_{4',3'}$ = 2.2 Hz), 4.54−4.63 (m, 1 H, H-2′), 5.92−5.98 (m, 1 H, H-1′), 8.17 (s, 0.3 H, H of 2 or 8), 8.19 (br s, 0.7 H, H of 2 or 8), 8.39 (s, 0.3 H, H of 2 or 8), 8.45 (s, 0.3 H, H of 2 or 8), 8.50 (s, 0.2 H, H of 2 or 8), 8.55 (s, 0.2 H, H of 2 or 8). Anal. ($C_{17}H_{24}N_6O_4 \cdot {}^1/_3H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-(*exo*-norbornan-2-yl)-β-D-ribofuranuronamide (33): yield 365 mg (95%, mixture of two diastereomers, ratio = 1:1); mp 159−161 °C (crystallized from aqueous MeOH); FAB-MS *m*/*z* 375 (MH^+); ^{1}H NMR (270 MHz, DMSO-d_6 + D_2O) 1.07−1.65 (m, 8 H, CH_2 × 4), 2.03 (s, 0.5 H, CH), 2.14 (s, 0.5 H, CH), 2.25 (br s, 1 H, CH), 3.54 (br s, 0.5 H, C*H*NH), 3.62 (br s, 0.5 H, C*H*NH), 4.08 (m, 1 H, H-3′), 4.28 (s,

1 H, H-4′), 4.58 (m, 1 H, H-2′), 5.92 (m, 1 H, H-1′), 8.08 (s, 1 H, H-2 or H-8), 8.37 (s, 0.5 H, H-2 or H-8), 8.38 (s, 0.5 H, H-2 or H-8). Anal. ($C_{17}H_{22}N_6O_4 \cdot {}^1/_5H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-(adamantan-1-yl)-*β*-D-ribofuranuronamide (34): yield 386 mg (92%); mp 201−202 °C (crystallized from MeOH); FAB-MS *m*/*z* 415 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 1.61 (br s, 6 H, $CH_2 \times 3$), 1.94 (br s, 6 H, $CH_2 \times 3$), 2.01 (br s, 3 H, $CH \times 3$), 4.09 (dd, 1 H, H-3′, $J_{3',2'} = 4.8$, $J_{3',4'} = 1.3$ Hz), 4.21 (d, 1 H, H-4′, $J_{4',3'} = 1.3$ Hz), 4.66 (dd, 1 H, H-2′, $J_{2',1'} = 7.4$, $J_{2',3'} = 4.8$ Hz), 5.91 (d, 1 H, H-1′, $J_{1',2'} = 7.4$ Hz), 8.13 (s, 1 H, H-2 or H-8), 8.39 (s, 1 H, H-2 or H-8). Anal. ($C_{20}H_{26}N_6O_4 \cdot {}^1/_3H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-(adamantan-2-yl)-*β*-D-ribofuranuronamide (35): yield 249 mg (60%); mp 158−159 °C (crystallized from MeOH); FAB-MS *m*/*z* 415 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 1.43−1.48 (m, 2 H, CH_2), 1.65−1.88 (m, 12 H, $CH_2 \times 4$, $CH \times 4$), 3.86 (m, 1 H, C*H*NH), 4.15 (dd, 1 H, H-3′, $J_{3',2'} = 4.6$, $J_{3',4'} = 2.1$ Hz), 4.43 (d, 1 H, H-4′, $J_{4',3'} = 2.1$ Hz), 4.68 (dd, 1 H, H-2′, $J_{2',1'} = 6.9$, $J_{2',3'} = 4.6$ Hz), 5.95 (d, 1 H, H-1′, $J_{1',2'} = 6.9$ Hz), 8.07 (s, 1 H, H-2 or H-8), 8.45 (s, 1 H, H-2 or H-8). Anal. ($C_{20}H_{26}N_6O_4 \cdot {}^1/_{10}H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-(noradamantan-3-yl)-*β*-D-ribofuranuronamide (36): yield 64 mg (16%, white solid); FAB-MS *m*/*z* 401 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 1.47−1.56 (m, 4 H, $CH_2 \times 2$), 1.83−2.04 (m, 6 H, $CH_2 \times 3$), 2.20 (br s, 2 H, $CH \times 2$), 2.36 (t, 1 H, CH, $J = 6.5$ Hz), 4.11 (d, 1 H, H-3′, $J_{3',2'} = 4.7$ Hz), 4.27 (s, 1 H, H-4′), 4.64 (dd, 1 H, H-2′, $J_{2',1'} = 7.3$, $J_{2',3'} = 4.7$ Hz), 5.92 (d, 1 H, H-1′, $J_{1',2'} = 7.3$ Hz), 8.12 (s, 1 H, H-2 or H-8), 8.37 (s, 1 H, H-2 or H-8). Anal. ($C_{19}H_{24}N_6O_4 \cdot {}^1/_5H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-hydroxy-*β*-D-ribofuranuronamide (37): yield 178 mg (58%, white solid); FAB-MS *m*/*z* 297 (MH^+); ^{1}H NMR (270 MHz, DMSO-d_6 + D_2O) 4.15 (dd, 1 H, H-3′, $J_{3',2'} = 4.6$, $J_{3',4'} = 2.6$ Hz), 4.27 (d, 1 H, H-4′, $J_{4',3'} = 2.6$ Hz), 4.51 (dd, 1 H, H-2′, $J_{2',1'} = 6.6$, $J_{2',3'} = 4.6$ Hz), 5.94 (d, 1 H, H-1′, $J_{1',2'} = 6.6$ Hz), 8.15 (s, 1 H, H-2 or H-8), 8.44 (s, 1 H, H-2 or H-8). Anal. ($C_{10}H_{12}N_6O_5 \cdot {}^1/_2H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-methoxy-*β*-D-ribofuranuronamide (38): yield 195 mg (63%, white solid) (lit.[20] mp 113 °C, dec, lit.[23] mp 125 °C); FAB-MS *m*/*z* 311 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 3.64 (s, 3 H, CH_3), 4.21 (dd, 1 H, H-3′, $J_{3',2'} = 4.6$, $J_{3',4'} = 2.0$ Hz), 4.28 (d, 1 H, H-4′, $J_{4',3'} = 2.0$ Hz), 4.54 (dd, 1 H, H-2′, $J_{2',1'} = 7.2$, $J_{2',3'} = 4.6$ Hz), 5.95 (d, 1 H, H-1′, $J_{1',2'} = 7.2$ Hz), 8.16 (s, 1 H, H-2 or H-8), 8.38 (s, 1 H, H-2 or H-8). Anal. ($C_{11}H_{14}N_6O_5 \cdot {}^4/_5H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-ethoxy-*β*-D-ribofuranuronamide (39): yield 204 mg (63%); mp 159−161 °C (crystallized from EtOH−hexane); FAB-MS *m*/*z* 325 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 1.96 (t, 3 H, CH_3, $J = 7.3$ Hz), 3.85 (q, 2 H, CH_2CH_3, $J = 7.3$ Hz), 4.19 (dd, 1 H, H-3′, $J_{3',2'} = 4.6$, $J_{3',4'} = 2.0$ Hz), 4.29 (d, 1 H, H-4′, $J_{4',3'} = 2.0$ Hz), 4.53 (dd, 1 H, H-2′, $J_{2',1'} = 7.2$, $J_{2',3'} = 4.6$ Hz), 5.95 (d, 1 H, H-1′, $J_{1',2'} = 7.2$ Hz), 8.15 (s, 1 H, H-2 or H-8), 8.37 (s, 1 H, H-2 or H-8). Anal. ($C_{12}H_{16}N_6O_5$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-isobutyloxy-*β*-D-ribofuranuronamide (40): yield 357 mg (99%); mp 147−150 °C (crystallized from aqueous MeOH); FAB-MS *m*/*z* 353 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 0.88 (d, 6 H, $CH_3 \times 2$, $J = 6.6$ Hz), 1.86 (m, 1 H, CH), 3.59 (d, 2 H, CH_2, $J = 6.6$ Hz), 4.19 (dd, 1 H, H-3′, $J_{3',2'} = 4.6$, $J_{3',4'} = 2.0$ Hz), 4.28 (d, 1 H, H-4′, $J_{4',3'} = 2.0$ Hz), 4.53 (dd, 1 H, H-2′, $J_{2',1'} = 7.2$, $J_{2',3'} = 4.6$ Hz), 5.95 (d, 1 H, H-1′, $J_{1',2'} = 7.2$ Hz), 8.14 (s, 1 H, H-2 or H-8), 8.39 (s, 1 H, H-2 or H-8). Anal. ($C_{14}H_{20}N_6O_5 \cdot {}^1/_2H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-benzyloxy-*β*-D-ribofuranuronamide (41): yield 309 mg (78%); mp 131−134 °C (crystallized from aqueous MeOH); EI-MS *m*/*z* 386 (M^+); ^{1}H NMR (DMSO-d_6 + D_2O) 4.18 (dd, 1 H, H-3′, $J_{3',2'} = 4.6$, $J_{3',4'} = 2.0$ Hz), 4.30 (d, 1 H, H-4′, $J_{4',3'} = 2.0$ Hz), 4.48 (dd, 1 H, H-2′, $J_{2',1'} = 6.6$, $J_{2',3'} = 4.6$ Hz), 4.85 (s, 2 H, CH_2), 5.94 (d, 1 H, H-1′, $J_{1',2'} = 6.6$ Hz), 7.31−7.43 (m, 5 H, *o*,*m*,*p*-Ph), 8.04 (s, 1 H, H-2 or H-8), 8.42 (s, 1 H, H-2 or H-8). Anal. ($C_{17}H_{18}N_6O_5 \cdot {}^1/_2H_2O$) C, H, N.

1-(Adenin-9-yl)-1-deoxy-*N*-(3,4,-dimethoxybenzyloxy)-*β*-D-ribofuranuronamide (42): yield 77 mg (17%, white solid); FAB-MS *m*/*z* 447 (MH^+); ^{1}H NMR (DMSO-d_6 + D_2O) 3.69 (s, 6 H, $CH_3O \times 2$), 4.16 (dd, 1 H, H-3′, $J_{3',2'} = 4.6$, $J_{3',4'} = 1.3$ Hz), 4.29 (d, 1 H, H-4′, $J_{4',3'} = 1.3$ Hz), 4.45 (dd, 1 H, H-2′, $J_{2',1'} = 7.3$, $J_{2',3'} = 4.6$ Hz), 4.76 (d, 2 H, CH_2, $J = 4.0$ Hz), 5.92 (d, 1 H, H-1′, $J_{1',2'} = 7.3$ Hz), 6.85−6.99 (m, 3 H, *o*,*m*, −Ph), 7.96 (s, 1 H, H-2 or H-8), 8.35 (s, 1 H, H-2 or H-8). Anal. ($C_{19}H_{22}N_6O_7 \cdot {}^1/_5H_2O$) C, H, N.

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Supporting Information Available: Elemental analyses for compounds **10**−**42**. This material is available free of charge via the Internet at http://pubs.acs.org.

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