Synthesis and Structure–Activity Relationships of Analogs of 2′-Deoxy-2′-(3-methoxybenzamido)adenosine, a Selective Inhibitor of Trypanosomal Glycosomal Glyceraldehyde-3-phosphate Dehydrogenase

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In continuation of a project aimed at the structure-based design of drugs against sleeping sickness, analogs of 2′-deoxy-2′-(3-methoxybenzamido)adenosine (**1**) were synthesized and tested to establish structure–activity relationships for inhibiting glycosomal glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Compound **1** was recently designed using the NAD:GAPDH complexes of the human enzyme and that of *Trypanosoma brucei*, the causative agent of sleeping sickness. In an effort to exploit an extra hydrophobic domain due to Val 207 of the parasite enzyme, several new 2′-amido-2′-deoxyadenosines were synthesized. Some of them displayed an interesting improvement in inhibitory activity compared to **1**. Carbocyclic or acyclic analogs showed marked loss of activity, illustrating the importance of the typical (C-2′-*endo*) puckering of the ribose moiety. We also describe the synthesis of a pair of compounds that combine the beneficial effects of a 2- and 8-substituted adenine moiety on potency with the beneficial effect of a 2′-amido moiety on selectivity. Unfortunately, in both cases, IC_{50} values demonstrate the incompatibility of these combined modifications. Finally, introduction of a hydrophobic 5′-amido group on 5′-deoxyadenosine enhances the inhibition of the protozoan enzyme significantly, although the gain in selectivity is mediocre.

Introduction

Sleeping sickness is still a serious threat to the health of inhabitants of subsaharan Africa. It is caused by *Trypanosoma brucei*, a protozoan belonging to the Trypanosomatidae. The bloodstream form of trypanosomes is completely dependent on glycolysis, its sole source of energy.[1] The glycolytic enzymes are sequestered in specialized organelles, called glycosomes.[2] This unique localization allows glucose uptake and utilization by the bloodstream form of *T. brucei* to be extremely high: *ca.* 50 times faster than that of human erythrocytes.[3] It is obvious that most of the enzymes involved in this indispensable glycolytic system are attractive targets for antitrypanosomal therapy. Within the framework of a project aimed at developing new drugs for the treatment of sleeping sickness, the current work focuses on glycosomal glyceraldehyde-3-phosphate dehydrogenase (gGAPDH) as a target for structure-based inhibitor design. As this approach involves inhibition of a parasite enzyme that has an isofunctional counterpart in the host, it is obvious that the inhibitors have to be selective.

Recently, several 2′-substituted 2′-deoxyadenosine derivatives were designed as selective inhibitors of gGAPDH of *T. brucei*. As predicted the compounds inhibited gGAPDH and had virtually no effect on the equivalent mammalian enzyme.[4,5] This selectivity was achieved by exploitation of a "selectivity cleft" created by a unique backbone conformation of the trypanosomal enzyme near the 2′-hydroxyl of the adenosine ribose of the NAD cofactor. In the human isozyme, the corresponding domain is largely occupied by the side chain of Ile 37. Moreover these inhibitors were also effective when evaluated against gGAPDH of *Leishmania mexicana*, another parasite of medical importance. This may be explained by the fact that the local sequences responsible for binding the adenosine part of the NAD cofactor are almost completely identical in both enzymes. The highest inhibition was observed with 2′-deoxy-2′-(3-methoxybenzamido)adenosine (**1**). This compound inhibits the human enzyme only marginally but enhances inhibition of *T. brucei* gGAPDH 45-fold when compared to adenosine, which was chosen as a molecular scaffold. For *Leishmania mexicana* gGAPDH, it has an IC_{50} (concentration at which enzyme remains 50% active) of 0.3 mM compared to 50 mM for adenosine, whereas for the rabbit muscle GAPDH, the IC_{50} is 3-fold higher than that of adenosine, resulting in a 500-fold gain in selectivity compared to this reference compound. As part of our efforts to improve the inhibitory activity against the protozoan enzyme and to investigate the structure–activity relationships, we prepared a series of new derivatives of **1** and evaluated their biological activity.

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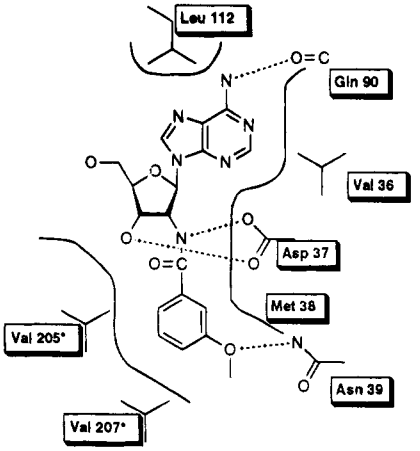


Figure 1. Schematic diagram of the predicted binding mode of 1 to gGAPDH of *T. brucei*. The so-called "selectivity cleft" is occupied by the 3-methoxybenzamido substituent. The adenosine moiety of 1 is assumed to bind to gGAPDH as observed in the crystal structure of the *T. brucei* gGAPDH: NAD^+ complex.[21] Hydrogen bonds are in dashed lines. Amino acids originating from a different subunit of the gGAPDH tetramer are highlighted by an asterisk.

Rationale

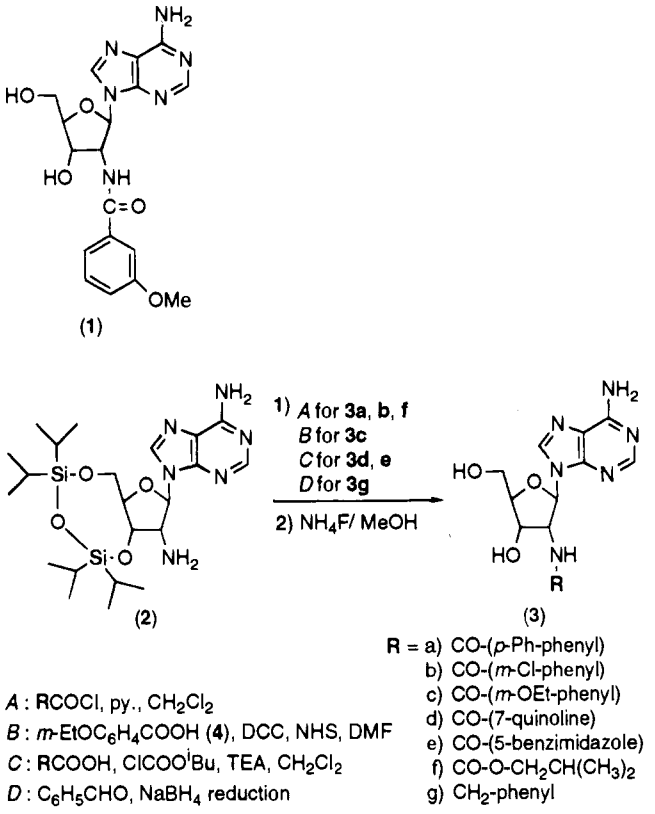
Figure 1 depicts the modeled binding mode of **1** to gGAPDH. Compounds **3a–c** were synthesized to investigate if the unique cleft of the enzyme near the ribosyl C-2' of the adenosine part of the NAD cofactor can accommodate different hydrophobic substitutions on the phenyl ring of the 2'-benzamide group. The phenylbenzamido moiety may produce tighter binding to gGAPDH because of the presence of an extra hydrophobic patch due to Val 207, which is on a different subunit of the gGAPDH tetramer. Replacement of the *m*-methoxy group of **1** by a *m*-ethoxy in **3c** could reinforce this interaction. Moreover a hydrogen bond between the *m*-ethoxy group and Asn 39 of *T. brucei* GAPDH would be conserved. This Asn 39 has a Ser as counterpart in *L. mexicana* gGAPDH.

Modeling studies suggested that compounds **3d,e** could likewise mimic **1**, by hydrogen-bonding interactions between Asn 39 and a nitrogen atom of the quinoline or benzimidazole moiety and by hydrophobic interactions between Val 207 and the C-2 of the benzimidazole or the C-2 and C-3 of the quinoline moiety.

As it is the final goal of this project to synthesize cost-effective inhibitors, we began by simplifying the nucleoside structure of **1**. The 1,2-substituted cyclopentane derivatives **10a–d** were synthesized to examine the possibility of replacing the ribose ring by a 1,2-substituted carbocyclic moiety. A further simplification, namely, the opening of the ring, was explored through the acyclic analogs (**13a–c**).

In our original studies,[4] significant improvement in potency was obtained by introduction of a 2-thienyl group on C-8 or a methyl group on C-2 of adenosine. Therefore, we combined the selectivity-enhancing properties of the benzamido or 3-methoxybenzamido group in compounds **17** and **1** with the potency-enhancing properties of the 8-(2-thienyl) and 2-methyl moieties, giving **19a** and **23**, respectively. Modeling studies[4] unfortunately suggested that in the enzyme-bound conformation, the amide oxygen atom in **19a** would interact unfavorably with C-2 and C-3 atoms of the thienyl ring. In contrast, the modeling studies revealed

Scheme 1



that the combination of a 2-methyl and a 2'-(3-methoxybenzamido) substituent would not be sterically prohibited. To overcome the conformational problems of compound **19a**, we considered the possibility of deleting the amide C=O function. Therefore, we first prepared the 2'-benzylamine analog (**3g**) of **1**. This strategy should retain the hydrogen bond formed with Asp 37 and make ionic interactions with this amino acid possible. Modeling predicts that the extra hydrogen of the protonated benzylamine has no hydrogen-bonding partner, since it points toward Met 38. In another pair of compounds (**15** and **16**), the 2-thienyl moiety on C-8 was combined with an acyclic chain. The thienyl group might stabilize the interaction with the target enzyme, and the protonated secondary amino group of **16** (and the primary amino group of **15**) may be able to interact ionically with the carboxyl group of Asp 37.

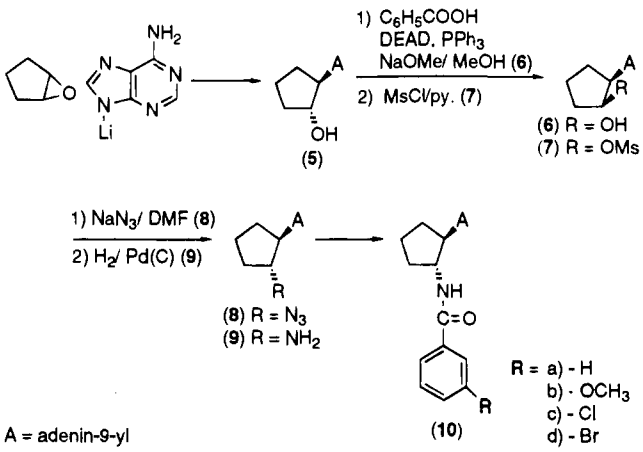
In an effort to exploit the presence of a hydrophobic domain created by the Leu 112 side chain, which explains the affinity-enhancing properties of a 2-thienyl substituent on C-8 of adenosine, we synthesized adenosine derivatives bearing a hydrophobic thioether substituent on C-8 (**25a,b**).

Finally, the possibility was investigated to increase the activity by introduction of the large hydrophobic amido groups at C-5' of the molecule (**27a,b**), which would be tolerated in this part of the molecule and might increase binding to the enzyme.

Chemistry

The strategy for the synthesis of **3a–f** (Scheme 1) was essentially the same as previously used.[5] Compounds **3a,b** were prepared by amidation of the 3',5'-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl) (TIPS)-protected amino nucleoside **2** with a suitable acyl chloride and subsequent desilylation with NH_4F in MeOH.

Scheme 2



Compound **3c** was prepared by amidation of amine **2** with *m*-ethoxybenzoic acid (**4**) using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide (NHS) as coupling agents followed by removal of the TIPS group. For the preparation of compounds **3d**,**e**, the previously employed method for amido formation (*i.e.*, by use of DCC and NHS) failed for quinoline-7-carboxylic acid (prepared by CrO_3 oxidation of 7-methylquinoline[6]) and N^1-trityl-protected benzimidazole-5-carboxylic acid. Therefore we used the mixed anhydride method to condense these acids with **2**. Subsequent removal of the protecting groups yielded the desired compounds. In both cases a considerable amount of a side product was isolated and identified as **3f**. This may be explained by incomplete anhydride formation or nucleophilic attack on the "wrong" carbonyl of the mixed anhydride. Compound **3f**, which was also prepared from **2** and isobutyl chloroformate, is the first example of a substituted 2′-carbamoyl-2′-deoxyadenosine. The 2′-benzylamino derivative **3g** was prepared by reaction of amine **2** with benzaldehyde followed by reduction of the resulting Shiff base with $NaBH_4$ and desilylation.

The synthesis of **10a**–**d** is depicted in Scheme 2. Ring-opening reaction of cyclopentane epoxide with the lithium salt of adenine gave an enantiomeric mixture of the *N*-9-alkylated *trans*-substituted cyclopentanol **5**. Inversion of the 2-hydroxyl group was achieved under Mitsunobu conditions. The benzoyl ester was subsequently removed by base-catalyzed hydrolysis giving the *cis*-isomer (**6**) of the above-mentioned cyclopentanol derivative.

Mesylation of **6** and nucleophilic displacement of the mesylate by an azido group gave **8**, which after catalytic hydrogenation yielded *trans*-1-(adenin-9-yl)-2-aminocyclopentane (**9**). The amino group was then acylated to yield the desired carbocyclic analog **10a**–**d**. Protection of the adenine moiety during the acylation reactions is not necessary.

Scheme 3 outlines the synthesis of the acyclic analogs of **1**. The compounds **13a**–**c** were synthesized from (*N*-*t*-BOC-amino)ethanol. Alkylation of adenine with (*N*-*t*-BOC-amino)ethanol under Mitsunobu conditions gives the *N*-*t*-BOC-protected 2-(adenin-9-yl)ethylamine **11**. Deprotection with trifluoroacetic acid in methylene chloride and subsequent chromatography on DOWEX 1 × 2 (OH^-) resin provided the free amine **12**. This amine was acylated using acyl chlorides in pyridine to yield **13a**–**c**.

Compound **11** was brominated at C-8 by reaction with bromine at pH 4.3 (1 M sodium acetate, acetic acid buffer–MeOH, 1:1) to yield **14**. Palladium-catalyzed cross-coupling reaction with 2-(tributylstannyl)thiophene (generated by quenching the α-lithio anion of thiophene with tributylstannyl chloride[7]) followed by deprotection of the amino function with trifluoroacetic acid provided the salt form of **15** in acceptable yields. Introduction of the benzyl moiety of **16** on the primary amino function of **15** was performed as described for **3g**.

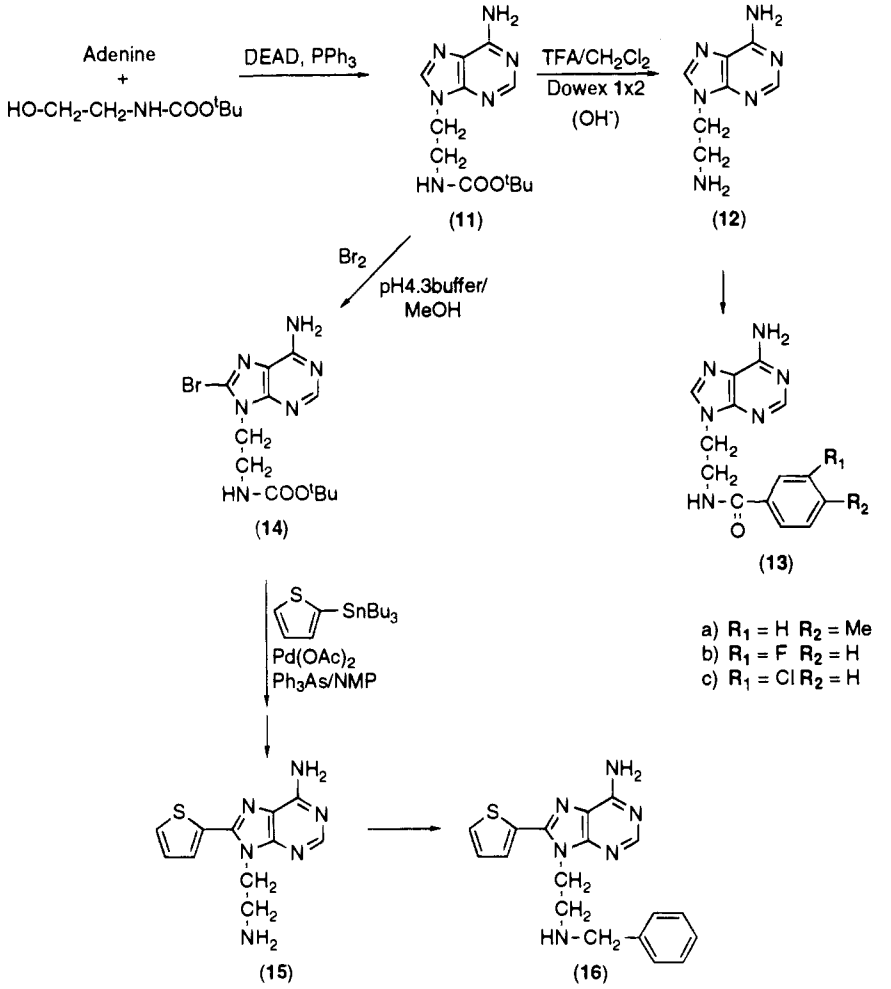
By using the same synthetic methodology, the thiophene moiety was also introduced on C-8 of 2′-benzamido-2′-deoxyadenosine (**17**)[5] to yield **19a** (Scheme 4). Compound **17** was also converted into the 8-MeO derivative **19b** by passage of its 8-bromo derivative **18** through a Dowex 1 × 2 (OH^-) resin with MeOH as the eluent.

As a route to compound **23**, we decided to use a direct transglycosylation reaction between the suitably modified pyrimidine nucleoside **21** as the glycosyl donor and silylated N^6-decanoyl-protected 2-methyladenine (Scheme 5). Thus, 2′-azido-2′-deoxyuridine was obtained from uridine in a "one-pot" reaction using the method of Verheyden *et al.*[8] as modified by Hobbs and Eckstein.[9] Subsequent reduction to 2′-amino-2′-deoxyuridine (**20**) was performed by catalytic hydrogenation.[8] One should be careful in this reduction not to exceed the specified atmospheric pressure or the hydrogenation time in order to avoid reduction of the 5,6-double bond. Compound **21** was obtained by acylation of amino alcohol **20** with excess *m*-anisoyl chloride and treatment of the crude reaction mixture (containing at least three different reaction products) with NaOMe to remove the *O*-*m*-anisoyl groups. Introduction of the *N*-*m*-anisoyl group into **20** was also accomplished in 60% yield by selective *N*-acylation with *m*-anisoic acid using *N*,*N*′-dicyclohexylcarbodiimide and *N*-hydroxysuccinimide in DMF at 0 °C.

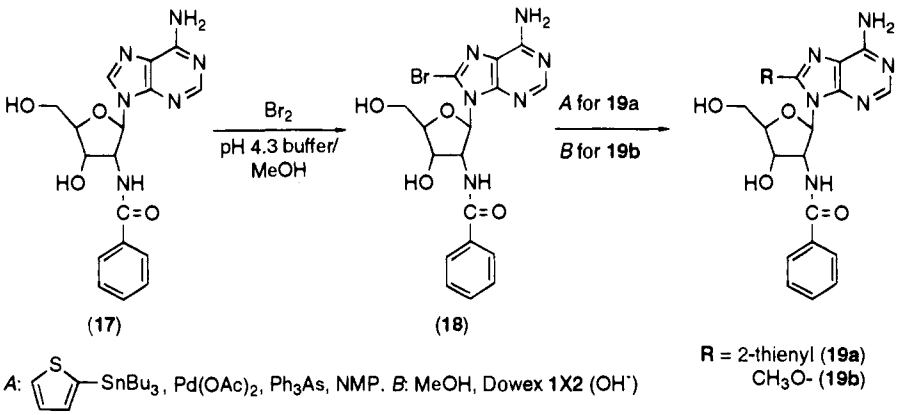
As was previously noted[8] for the 2′-acetamido derivative, the presence of the amido moiety in compound **21** significantly increases the $J_{1',2'}$ value (7.5 Hz) in comparison with most simple uridine derivatives (showing $J_{1',2'}$ values ranging from 0 to 6 Hz), illustrating the striking effect of this amido function upon the furanose sugar ring conformation.

To obtain **23**, a one-pot silylation–transglycosylation reaction was carried out between N^6-decanoyl-2-methyladenine (**22**; prepared by treatment of the commercially available 2-methyladenine with *n*-decanoic anhydride as described by Furukawa *et al.* for the synthesis of N^6-octanoyladenine[10]) and **21** in acetonitrile, using a slight excess of bis(trimethylsilyl)acetamide (BSA) and trimethylsilyl trifluoromethanesulfonate (TMSTF) according to Imazawa and Eckstein.[11] Partition of the reaction mixture between dichloromethane and water prior to NaOMe deprotection allowed removal of the liberated uracil at this stage and facilitated purification. The desired compound **23** was obtained as the main product, and no 9α-isomer could be detected. Apparently the participation of the *N*-(*m*-methoxybenzoyl) group at C-1′ leads to stereoselective reaction. Steric factors may also contribute to stereoselectivity. Such participation was observed to a smaller extent with a *N*-(trifluoroacetyl) group on C-2′, where an anomeric mixture was observed.[12] To our knowledge, this is a first application

Scheme 3



Scheme 4



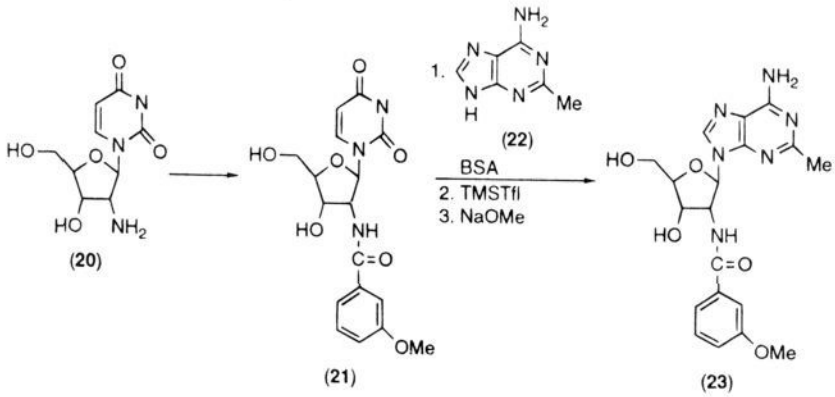
of the transglycosylation method to produce a purine nucleoside substituted on both the sugar and base moieties.

Nucleophilic substitution of 8-bromoadenosine (**24**)[13] with the sodium salts of cyclohexylmercaptan and 2-mercaptopyrimidine yielded compounds **25a,b** (Scheme 6). The synthesis of the 5'-amido-5'-deoxyadenosines **27a,b** (Scheme 7) was performed by amidation of the 5'-amino function of 5'-amino-5'-deoxyadenosine (**26**)[14,15] using DCC and NHS.

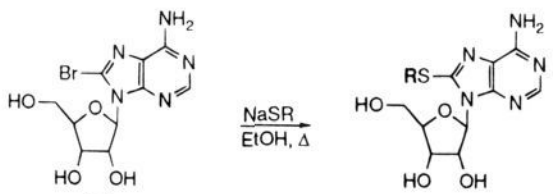
X-ray Structure of Compound 1. The asymmetric unit contains two molecules, A and B. In molecule A the *N*-glycosidic torsion angle χ has a value of $-142.1(5)°$ in the *anti* range. The sugar pucker is $^{0}T_{1}$ with $P = 96.6°$ and $\Psi_m = 43.3°$. The C-4'−C-5' conformation is *−ap* with $\gamma = -166.0(5)°$. In molecule B the *N*-glycosidic torsion angle has a value of $-155.8(5)°$ in the *anti* range. The sugar pucker is $_{3}T^{2}$ with $P = 188.3°$ and $\Psi_m = 36.1°$. The C-4'−C-5' conformation is *+sc* with $\gamma = 42.4(8)°$. Most of the nitrogen and oxygen atoms are involved in a network of hydrogen bonds. A PLUTON[16] view of molecules A and B with the atomic numbering scheme is shown in Figure 2.

2D-NOESY Experiment of Compound 19a. Because of the importance of the base orientation relative to the sugar moiety in compound **19a**, a 2D-NOESY

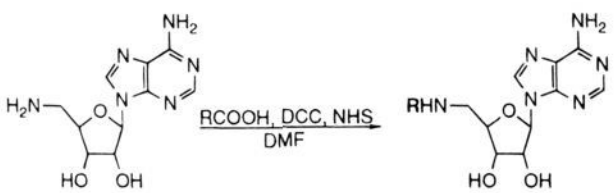
Scheme 5



Scheme 6



Scheme 7



experiment was performed after initial assignment of resonances via a COSY experiment. The 2D-NOESY spectrum was obtained with a mixing time of 100 ms.

A clear NOE contact is observed between H-1′ and H-2″/H-6″ of the benzamido group, indicating that one of the phenyl hydrogens is close to H-1′. In addition, H-2″/H-6″ as well as H-3″/H-5″ show NOE contacts with both C-5′ hydrogens (H-4″ only with one hydrogen on C-5′). This is only possible when the orientation of the benzamide is *trans* to the adenine vs the imaginary plane of the sugar ring and the plane of the phenyl ring lies below the ribose ring.

Important for the determination of the base conformation (*syn* or *anti*) are clear NOE contacts with the thienyl protons. The thienyl H-3‴ shows a NOE contact with one C-5′ hydrogen and the H-5‴ with both of the C-5′ hydrogens, proving that the thiophene moiety is situated over the sugar ring and a clear *anti* conformation around the glycosidic bond. These NOE contacts are only possible if the 5′-OH is turned away from the ring (excluding the +*sc* rotamer of the C-4′−C-5′ bond).

Structure−Activity Relationships

Considering the main conformational features (*i.e.*, the glycosidic torsional angle χ, the sugar puckering, and

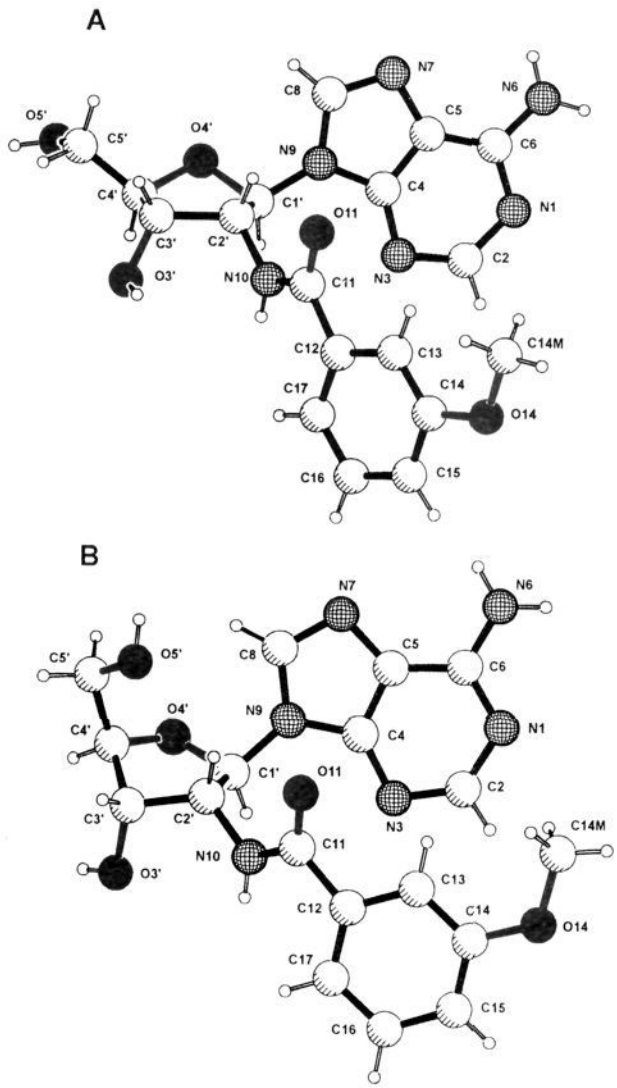


Figure 2. Structure of compound **1** as determined by X-ray crystallography.

the conformation about the C-4′−C-5′ bond), we investigated the relationship between the X-ray structure, the solution state, and the modeled conformation of the lead compound **1**.

According to the X-ray study, the values of the glycosidic torsional angles χ for both molecules A and B fall in the *anti* range, while the data of the NOESY experiment[5] suggested a *syn/anti* equilibrium about the

glycosidic bond. In the modeled conformation, the torsional angle χ is −75° and falls in the high *anti* range.

The ring puckering of molecule A is $^0T_1$ which lies in the O-4'-*endo* range. Molecule B has a phase angle of pseudorotation $P = 188°$. In the pseudorotational cycle, this value corresponds with an asymmetrical twist with a C-3'-*exo*/C-2'-*endo* conformation, which agrees with the puckering determined in solution.[5] The ribose moiety as it is puckered in the modeled conformation is characterized by the following torsional angles: v_0 = C-4'−O-4'−C-1'−C-2' = −31.7°, v_1 = O4'−C-1'−C-2'−C-3' = 39.6°, v_2 = C-1'−C-2'−C-3'−C-4' = −31.6°, v_3 = C-2'−C-3'−C-4'−O-4' = 14.1°, v_4 = C-3'−C-4'−O-4'−C-1' = 11.0°

$$\tan P = [(v_4 + v_1) - (v_3 + v_0)]/2v_2(\sin 36 + \sin 72) \quad (1)$$

From eq 1,[17] one can extract a P value of 145° or a ^2_1T puckering, *i.e.*, a twist with C(1')-*exo*/C(2')-*endo* conformation.

Molecule A of **1** exhibits a torsion angle γ (O-5'−C-5'−C-4'−C-3') of −166°, illustrating the *gauche*−*trans* conformation of the C-5'−O-5' bond with respect to the O-4'−C-1' bond and the C-3'−C-4' bond (t-rotamer). In molecule B the γ value of 42° demonstrates a *gauche*−*gauche* conformation (g^+) about the exocyclic C-4'−C-5' bond, which, again, agrees with the predominant solution state conformation as it was derived from the $J_{4',5'}$ coupling constants.[5] As the docking experiments of the modeling consisted of modifying the adenosine moiety of the crystallographically observed NAD, it is obvious that the 5'-OH in the modeled conformation is turned away from the ribose ring (excluding the g^+-conformation). However, the exact conformation of the exocyclic C-4'−C-5' bond seems less important as favorable interactions of the 5'-OH with the enzyme are not possible.

Considering all data (^{1}H NMR, X-ray, and modeled conformation), we can conclude that the conformational preferences of **1** in solid phase (*i.e.*, type S ribose with *anti* conformation of the base) find their parallel in solution and agree readily with the modeled conformation.

It is apparent from Table 1 that compouds **3a**−**d** are more potent than **1** as inhibitors of trypanosomal gGAPDH but are somewhat less selective, especially **3a**,**c**. On the other hand, compound **3e** only shows moderate inhibition, and **3f** is a poor inhibitor. The high IC_{50} of **3g** reveals that the secondary amine function is not a suitable hydrogen bond partner for Asp 37, probably because the second proton cannot be desolvated. Apparently the initial choice of replacing the 2'-hydroxyl of adenosine by an amide function as a hydrogen-bonding partner for Asp 37 was a good one.

Attempted simplification of the nucleoside **1** into its carbocyclic analogs demonstrated exceptional sensitivity toward binding to the adenosine site of the NAD cofactor of gGAPDH. Although the *trans* orientational requirement of the benzamido group relative to the base is conserved in the carbocyclic analogs **10a**−**c**, replacement of the typical C-2'-*endo* puckering of the ribose ring by a cylopentane ring is accompanied by a total loss of inhibitory activity. Analog **10d** had relatively good potency for gGAPDH, but it lacks selectivity properties.

Table 1. Inhibitory Activities of Adenosine Derivatives toward Parasite and Human GAPDH (IC_{50}, mM)

no.	g *T.b.*[a]	g *L.m.*[b]	human[c]
adenosine	100	50	35
1	2.2	0.3	>10 (84%)[d]
3a	0.2	0.2	0.4
3b	0.5	0.2	>2 (80%)
3c	0.5	0.4	0.6
3d	1	0.5	>2 (53%)
3e	3	3	>10 (97%)
3f	>10 (54%)	>10 (64%)	>10 (100%)
3g	>10 (98%)	>10 (70%)	>10 (100%)
10a	>4 (67%)	>4 (96%)	ND[e]
10b	>4 (55%)	>5 (92%)	ND
10c	>4(90%)	>2 (100%)	ND
10d	1.5	0.7	1.5
13a	>2 (94%)	>4 (96%)	ND
13b	>4 (100%)	>4 (78%)	ND
13c	>4 (83%)	>4 (83%)	ND
15	1.8	1.6	1.8
16	0.5	0.4	0.6
18	6.3	3.0	>10 (90%)
8-(thien-2-yl)adenosine	0.6	0.5	1.3
19a	1.2	0.5	1.2
19b	9	9	>10 (100%)
2-methyladenine	8	6	>10 (58%)
23	>10 (100%)	>10 (98%)	>10 (80%)
25a	>1 (100%)	>2 (94%)	>2 (92%)
25b	2	4	8
27a	0.25	0.25	0.25
27b	>1 (100%)	0.75	>2 (70%)

[a] g *T.b.* = glycosomal *T. brucei*. [b] g *L.m.* = glycosomal *L. mexicana*. [c] Human erythrocyte. [d] Not tested above the stated level due to insolubility, with the remaining activity at that level given in parentheses. [e] ND = not determined.

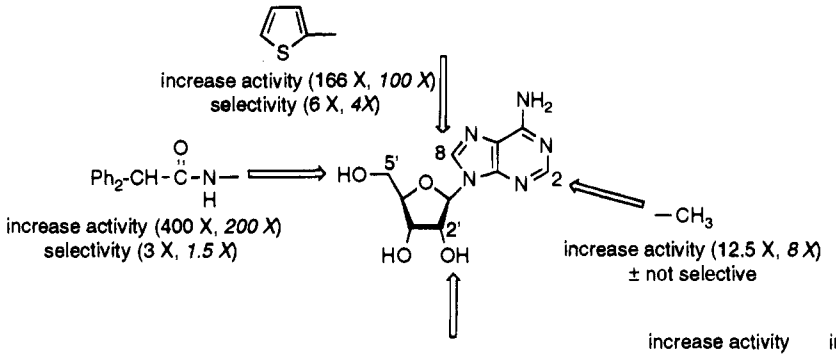
The acyclic nucleosides (**13a**−**c**) of **1** were inhibitory at 4 mM, suggesting that it is indeed possible to simplify the original structures. However, despite the fact that the number of bonds between the heteroaromatic moiety and the phenyl ring is retained in these structures, the higher entropy changes required to form the complex are likely to be unfavorable for binding.

As predicted, the affinity-enhancing properties of a 8-(2-thienyl) substituent and the selectivity-enhancing properties of a 2'-benzamido group did not seem to be additive when combined in the same molecule: compound **19a** had similar potency as 8-(thien-2-yl)adenosine against parasite and mammalian GAPDH and thus has only modest selectivity. The data of the 2D-NOESY experiment provide an additional[4] argument for assuming that **19a** binds in the *anti* conformation to *T. brucei* GAPDH. Such a mode of binding could explain the lack of selectivity of **19a**.

To our surprise, introduction of the relatively small methyl group on C-2 of compound **1** yielded a compound (**23**) that was completely devoid of affinity for the glycosomal enzymes. Compound **16** showed good affinity for the glycosomal enzymes, but the benzyl moiety did not improve selectivity. The 8-substituted adenosines **25a**,**b**, designed to bind to Leu 112 near N-7 and C-8 of the adenine base, were not as active as the 8-(2-thienyl) analog. With 5'-substituted adenosine derivatives **27a**,**b**, the affinity for *L. mexicana* gGAPDH could be increased drastically, but the gain in selectivity was marginal.

Conclusions

In summary, some new 2'-amido-2'-deoxyadenosines, *i.e.*, **3a**−**d**, the acyclic nucleoside **16**, and the 5'-amido-5'-deoxyadenosine **27a** displayed improved affinity for



		increase activity	increase selectivity
-NH-C(=O)-Ph(*m*MeO)	(1)	45 X *170 X*	>> 13 X *> 48 X*
-NH-C(=O)-Ph(*p*Ph)	(3a)	500 X *250 X*	6 X *3 X*
-NH-C(=O)-Ph(*m*Cl)	(3b)	200 X *250 X*	> 12 X *> 15 X*
-NH-C(=O)-Ph(*m*EtO)	(3c)	200 X *125 X*	3 X *2 X*
-NH-C(=O)-(7-quinoline)	(3d)	100 X *100 X*	> 6 X *> 6 X*

Figure 3. Influence of the different modifications of the adenosine lead structure on the activity and selectivity of gGAPDH of *T. brucei* and *L. mexicana* (in italic font) compared to adenosine itself.

gGAPDH of *T. brucei* when compared with the lead compound **1**. However, these compounds did not have the same selectivity as **1**. Simplification of the nucleoside structure led to loss of affinity, proving the importance of the ribose ring for enzyme recognition. Combinations of a base and sugar substituent in one molecule (**19a** and **23**) did not improve selectivity. Figure 3 summarizes these results.

Experimental Section

Inhibition Studies. For all final compounds synthesized, IC_{50} values for the inhibition of glycosomal *T. brucei*, glycosomal *L. mexicana*, and human GAPDH were determined as in ref 4 and are reported in Table 1.

Structure Determination of 1 by X-ray Crystallography. 1: $C_{18}H_{20}N_6O_5$, $M_r = 400.40$; orthorhombic, $P2_12_12_1$; $a = 6.900(4)$ Å, $b = 18.047(9)$ Å, $c = 29.645(15)$ Å, $V = 3692(3)$ Å^3, $Z = 8$, $D_c = 1.441$ mg m^{-3}; graphite monochromated Mo Kα radiation, $\lambda = 0.71069$ Å; 2245 observed reflections [$I > 2\sigma(I)$], 4250 weak reflections; $\mu = 0.108$ mm^{-1}, $F(000) = 1680$, $T = 293(2)$ K, final $R = 0.051$, $\Delta\varrho_{max} = 0.25$e Å^{-3}, $\Delta\varrho_{min} = -0.24$ e Å^{-3}; structure solution using SHELXS86,[18] structure refinement using SHELXL93.[19]

Synthesis. General. Melting points were determined in capillary tubes with an Electrothermal (IA 9000 series) digital melting point apparatus and are uncorrected. Ultraviolet spectra were recorded in MeOH with a Perkin-Elmer UV/vis spectrophotometer. For ^{1}H NMR spectra the solvent signals were used as secondary references: DMSO-d_6 (2.50 ppm) or $CDCl_3$ (7.23 ppm). For ^{13}C NMR spectra the methyl resonance of DMSO-d_6 vs TMS (39.60 ppm) was used as secondary reference. ^{1}H NMR spectra at 19 °C were obtained with a Bruker WH 360 spectrometer. For the 2D-NOESY experiment we used the sequence proposed by Macura *et al.*:[20] 90°(^{1}H)–t_1–90°(^{1}H)–τ_m–χt_1–90°(^{1}H)–t_2. We used a relaxation delay of 1.2 s, a 90° (^{1}H) pulse of 5 μs, and a mixing time (τ_m) of 100 ms randomly varied by 10% in order to suppress the zero quantum J cross-peaks. A matrix of 0.5 × 1 K data points was obtained using 16 scans, zero-filled in the F_1 direction. A 45° shifted sine-bell function was used in each direction.

Electron impact (EI) and chemical ionization (CI) mass spectra (MS), liquid secondary-ion mass spectra (LSIMS), and high-resolution mass spectra (HRMS) were obtained using a Kratos concept 1H mass spectrometer.

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: benzene was dried by distillation after 48 h of refluxing over CaH_2; pyridine was refluxed overnight in the presence of KOH and distilled; CH_2Cl_2 was obtained by distillation after reflux overnight with CaH_2; tetrahydrofuran was refluxed overnight on lithium aluminum hydride and distilled; MeOH was obtained by distillation after refluxing overnight on CaH_2; water was removed from absolute ethanol and DMF (99%; Janssen Chimica) by storing on Linde type 4 Å molecular sieves followed by distillation under reduced pressure. *N*-Methylpyrrolidone (NMP) was purchased from Janssen Chimica.

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

2′-Deoxy-2′-(4-phenylbenzamido)adenosine (3a). To a solution of 1 g (1.97 mmol) of **2**[2] in 30 mL of dry CH_2Cl_2–pyridine (2:1) was added 0.51 g (2.36 mmol) of 4-phenylbenzoyl chloride. After 4 h of stirring at room temperature, H_2O (100 mL) was added and the mixture extracted twice with 100 mL of CH_2Cl_2. The combined organic layer was dried ($MgSO_4$) and evaporated. Removal of the TIPS group was carried out by heating the residue with 300 mg of NH_4F in 50 mL of MeOH at reflux for 6 h. The mixture was concentrated and purified over a Dowex 1 × 2 (OH^-) resin. Elution with MeOH–water (10:90, 50:50, and finally 90:10) yielded 330 mg (36% yield based upon **2**) of the title compound as a white solid. Crystallization from MeOH yielded a pure crop: mp 208–210 °C dec; UV (MeOH) λ_{max} 265 nm (log ε 4.58); ^{1}H NMR (DMSO-d_6) δ 3.63 (m, H-5B′), 3.75 (m, H-5A′), 4.12 (br s, H-4′), 4.37 (t, H-3′), 5.35 (m, H-2′, $J_{2',3'} = 5.1$ Hz), 5.69 (dd, 5′-OH), 5.78 (d, 3′-OH, $J_{3'\text{-OH},H\text{-}3'} = 4.0$ Hz), 6.24 (d, H-1′, $J = 8.6$ Hz), 7.38 (br s, NH_2), 7.40 (t, 1H), 7.48 (t, 2H), 7.71 (d, 2H), 7.75 (d, 2H), 7.92 (d, 2H, arom H), 8.15 (s, H-2), 8.28 (s, H-8), 8.45 (d, NHCO, $J =$ 8.4 Hz); ^{13}C NMR (DMSO-d_6) δ 55.57 (C-2′), 62.15 (C-5′),

70.61 (C-3'), 86.06 (C-1'), 87.53 (C-4'), 119.54 (C-5), 126.43, 126.91, 128.24 and 129.07 (C-2",3",5",6",8",9",11",12"), 128.13, 132.71, 139.15 and 142.99 (C-1",4",7",10"), 140.03 (C-8), 149.21 (C-4), 152.44 (C-2), 156.26 (C-6), 166.29 (C=O); MS (LSIMS, thioglycerol) m/z 469 (M + Na)$^+$, 447 (M + H)$^+$, 312 (M − B)$^+$, 181 (CO-C_6H_4-p-Ph)$^+$, 136 (B + 2H)$^+$. Anal. ($C_{23}H_{22}N_6O_4$) C, H, N.

2'-(3-Chlorobenzamido)-2'-deoxyadenosine (3b). This compound was prepared and purified as described for **3a** using 1.00 g (1.97 mmol) of **2**, 0.265 mL (2.07 mmol) of 3-chlorobenzoyl chloride and 450 mg of NH_4F. The yield obtained was 470 mg (37% based upon **2**) of a white solid, which was crystallized from MeOH: mp 211−214 °C slow dec; UV (MeOH) λ_{max} 258 nm (log ϵ 4.25); ^{1}H NMR (DMSO-d_6) δ 3.62 (m, H-5B'), 3.73 (m, H-5A', $J_{5A',5B'} = -12.0$ Hz), 4.10 (br s, H-4'), 4.35 (br s, H-3'), 5.31 (m, H-2', $J_{2',3'} = 5.1$ Hz), 5.65 (m, 5'-OH), 5.73 (br s, 3'-OH), 6.22 (d, H-1', $J = 8.5$ Hz), 7.35 (br s, NH_2), 7.47 (t, arom H-5), 7.59 (d), 7.76 (d, arom H-4,6), 7.89 (s, arom H-2), 8.14 (s, H-2), 8.26 (s, H-8), 8.60 (d, NHCO, J = 8.4 Hz); ^{13}C NMR (DMSO-d_6) δ 55.69 (C-2'), 62.08 (C-5'), 70.52 (C-3'), 85.81 (C-1'), 87.41 (C-4'), 119.52 (C-5), 126.37, 127.37, 130.22, 131.24 (C-2",4",5",6"), 133.05 (C-3"), 135.94 (C-1"), 139.96 (C-8), 149.20 (C-4), 152.43 (C-2), 156.24 (C-6), 165.34 (C=O); MS (LSIMS, thioglycerol) m/z 427 (M + Na)$^+$, 405 (M + H)$^+$, 270 (M − B)$^+$, 139 (CO-C_6H_4-m-Cl)$^+$, 136 (B + 2H)$^+$. Anal. ($C_{17}H_{17}N_6O_4Cl$) C, H, N.

3-Ethoxybenzoic Acid (4). A suspension of 6.9 g (50 mmol) of 3-hydroxybenzoic acid, 20 mL (250 mmol) of iodoethane, and 45 g (326 mmol) of K_2CO_3 in 100 mL of DMF was stirred at 60 °C. After 3 h the mixture was partioned between water and CH_2Cl_2. The organic layer was dried ($MgSO_4$) and the residue purified by column chromatography (hexane−CH_2Cl_2, 3:1) to yield 9.0 g (93%) of ethyl 3-ethoxybenzoate as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.38 (t, CH_3-CH_2-O-Ph), 1.42 (t, CH_3-CH_2-O-CO), 4.06 (q, CH_2-O-Ph), 4.36 (t, CH_2-O-CO), 7.07 (dd, H-4), 7.32 (t, H-5), 7.55 (H-2), 7.62 (d, H-6); MS (LSIMS, 4-nitrobenzyl alcohol) m/z 195 (M + H)$^+$.

The ester was treated with boiling aquous 0.1 N NaOH solution for 1 h; the solution was acidified with HCl and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and purified by column chromatography (CH_2Cl_2−MeOH, 97:3) to yield 6.93 g (90%) of the title compound as a white solid: mp 137 °C; UV (MeOH) λ_{max} 294 (log ϵ 3.40), 230 nm (log ϵ 3.84), λ_{min} 261 nm (log ϵ 2.67); ^{1}H NMR (DMSO-d_6) δ 1.33 (t, CH_3, J = 7.0 Hz), 4.06 (q, CH_2), 7.16 (dd, H-4), 7.39 (t, H-5), 7.42 (s, H-2), 7.52 (d, H-6); MS (LSIMS, thioglycerol doped with NaOAc) m/z 293 (M - H + 2Na + NaOAc)$^+$, 211 (M − H + 2Na)$^+$.

2'-Deoxy-2'-(3-ethoxybenzamido)adenosine (3c). To a cooled (−20 °C), stirred suspension of 710 mg (1.4 mmol) of **2** and 332 mg (2.0 mmol) of 3-ethoxybenzoic acid (**4**) in 10 mL of DMF were added NHS (230 mg, 2.0 mmol) and DCC (410 mg, 2.0 mmol), and stirring was continued for 30 h at room temperature. The reaction mixture was filtered and the solid material washed with EtOAc. The combined filtrate and washings were evaporated, and the residue together with 500 mg of NH_4F in 30 mL of MeOH was heated at reflux for 5 h. The mixture was evaporated on Celite and purified by column chromatography (CH_2Cl_2−MeOH, 95:5 and then 90:10) to obtain 290 mg (50%) of the title compound, which was then crystallized from MeOH: mp 198−199 °C dec; UV (MeOH) λ_{max} 258 nm (log ϵ 4.23); ^{1}H NMR (DMSO-d_6) δ 1.33 (t, CH_3), 3.62 (m, H-5B'), 3.73 (m, H-5A', $J_{5A',5B'} = -12.1$ Hz), 4.05 (q, CH_2), 4.10 (H-4'), 4.34 (t, H-3'), 5.31 (m, H-2', $J_{2',3'} = 5.3$ Hz), 5.66 (dd, 5'-OH), 5.74 (d, 3'-OH), 6.21 (d, H-1', $J = 8.6$ Hz), 7.06 (d, H-4"), 7.29−7.40 (m, H-2", H-5", H-6", NH_2), 8.14 (s, H-2), 8.26 (s, H-8), 8.35 (d, NHCO, J = 8.3 Hz); ^{13}C NMR (DMSO-d_6) δ 14.63 (CH_3), 55.52 (C-2'), 62.12 (C-5'), 63.29 (CH_2), 70.57 (C-3'), 85.99 (C-1'), 87.50 (C-4'), 113.45 (C-5"), 117.53 (C-4"), 119.53 (C-5), 119.67 (C-6"), 129.39 (C-2"), 135.31 (C-1"), 139.99 (C-8), 149.19 (C-4), 152.42 (C-2), 156.26 (C-6), 158.37 (C-3"), 166.37 (C=O); MS (LSIMS, thioglycerol) m/z 829 (2M + H)$^+$, 437 (M + Na)$^+$, 415 (M + H)$^+$, 280 (M − B)$^+$, 149 (CO-C_6H_4-m-OEt)$^+$, 136 (B + 2H)$^+$. Anal. ($C_{19}H_{22}N_6O_5$) C, H, N.

2'-Deoxy-2'-quinoline-7-carboxamidoadenosine (3d). A stirred solution of 328 mg (1.89 mmol) of quinoline-7-carboxylic acid in 10 mL of CH_2Cl_2 (dry) containing 0.8 mL of TEA was cooled at −10 °C and treated with 0.250 mL (1.89 mmol) of isobutyl chloroformate. The mixture was stirred for 30 min at 0 °C, and a solution of 912 mg (1.79 mmol) of amino nucleoside **2** in 5 mL of CH_2Cl_2 and 0.3 mL of TEA was added dropwise. After stirring overnight at ambient temperature and protected from moisture, the mixture was diluted with 50 mL of saturated aquous $NaHCO_3$ solution and extracted twice with 50 mL of CH_2Cl_2. The combined organic layers were dried, the residue was taken up in 30 mL of MeOH, 500 mg of NH_4F was added, and the mixture was heated at reflux for 3 h. The reaction mixture was worked up and purified by silica gel column chromatography. Elution with CH_2Cl_2−CH_3OH (90:10) yielded 120 mg (18% yield based on **2**) of a compound which was identified as **3f**, and further elution with CH_2Cl_2−CH_3OH (80:20) gave 912 mg of **3d** (46% yield based on **2**). **3d** was crystallized from MeOH: mp 160 °C slow dec; UV (MeOH) λ_{max} 258 (log ϵ 4.27), 235 nm (log ϵ 4.56), λ_{min} 252 nm (log ϵ 4.26); ^{1}H NMR (DMSO-d_6) δ 3.64 (m, H-5B'), 3.76 (m, H-5A', $J_{5A',5B'} = -12.1$ Hz), 4.13 (br s, H-4'), 4.40 (br s, H-3'), 5.39 (m, H-2', $J_{2',3'} = 5.1$ Hz), 5.69 (q, 5'-OH), 5.79 (d, 3'-OH), 6.30 (d, H-1', $J = 8.5$ Hz), 7.38 (br s, NH_2), 7.61 (q), 7.95 (d), 8.03 (d), 8.41 (d), 8.75 (s), 8.99 (d) (quinoline H's), 8.15 (s, H-2), 8.29 (s, H-8), 8.77 (d, NHCO, J = 8.3 Hz); ^{13}C NMR (DMSO-d_6) δ 55.79 (C-2'), 62.15 (C-5'), 70.60 (C-3'), 85.97 (C-1'), 87.50 (C-4'), 119.57 (C-5), 122.77, 125.07, 128.22, 128.46, 129.41, 134.61, 135.91, 147.02, 151.56 (quinoline C's), 140.08 (C-8), 149.19 (C-4), 152.43 (C-2), 156.27 (C-6), 166.35 (C=O); MS (LSIMS, thioglycerol) m/z 444 (M + Na)$^+$, 422 (M + H)$^+$, 287 (M − B)$^+$, 156 (CO-7-quinoline)$^+$, 136 (B + 2H)$^+$. Anal. ($C_{20}H_{19}N_7O$·CH_3OH) C, H, N.

2'-Benzimidazole-5-carboxamido-2'-deoxyadenosine (3e). To a stirred solution (at −10 °C) of 0.85 g (2.10 mmol) of N^1-tritylbenzimidazole-5-carboxylic acid in 10 mL of anhydrous CH_2Cl_2 containing 0.8 mL of TEA was added 0.28 mL (2.16 mmol) of isobutyl chloroformate. The mixture was stirred for 30 min at 0 °C, and 1.0 g (1.97 mmol) of **2** dissolved in 5 mL of CH_2Cl_2 and 0.3 mL of TEA was added dropwise. After stirring overnight at room temperature, the reaction mixture was worked up, and the TIPS group was removed as for **3d**. TLC revealed the presence of two products: one contained a trityl function and the other (slightly more polar) had similar R_f as **3f**. Detritylation of the first compound was found to facilitate further separation. Therefore the residue was treated with 1 mL of CF_3COOH in 10 mL of CH_2Cl_2 for 1 h at 50 °C, neutralized with $NaHCO_3$, concentrated, and subjected to column chromatography. Elution with CH_2Cl_2−MeOH (90:10) yielded 120 mg of **3f**, and further elution with CH_2Cl_2−MeOH (80:20) gave 350 mg of crude **3e**. The latter was purified by elution over a Dowex 1 × 2 (OH^-) resin to give 286 mg (35% yield) of an analytically pure white solid: UV (MeOH) λ_{max} 259 nm (log ϵ 4.26); ^{1}H NMR (DMSO-d_6) δ 3.63 (m, H-5B', $J_{5A',5B'} = -12.0$ Hz), 3.75 (m, H-5A'), 4.12 (m, H-4'), 4.36 (t, H-3'), 5.34 (dt, H-2', $J_{2',3'} = 5.4$ Hz, $J_{2',NH} = 8.6$ Hz), 5.68 (br, 5'-OH), 5.75 (br, 3'-OH), 6.24 (d, H-1', $J = 8.5$ Hz), 7.36 (br s, NH_2), 7.67 (br, H-7", H-6"), 8.14 (s, H-8), 8.28 (s, H-2, H-2"), 8.32 (br, NHCO, H-4"); ^{13}C NMR (DMSO-d_6) δ 55.58 (C-2'), 62.18 (C-5'), 70.65 (C-3'), 86.17 (C-4'), 87.55 (C-1'), 118.46, 118.83 (C-4", C-7"), 119.56 (C-5), 121.03 (C-6"), 122.28 (C-5"), 140.07 (C-8), 143.98 (C-2"), 149.21 (C-4), 152.41 (C-2), 156.26 (C-6), 167.09 (C=O); MS (LSIMS, thioglycerol) m/z 433 (M + Na)$^+$, 411 (M + H)$^+$, 276 (M − B)$^+$, 145 (benzimidazole-5-CO)$^+$, 136 (B + 2H)$^+$. Anal. ($C_{18}H_{18}N_8O_4$·H_2O) C, H; N: calcd, 26.16; found, 25.18.

2'-Deoxy-2'-[(isobutoxycarbonyl)amino]adenosine (3f). This compound was prepared as described for **3a** using 600 mg (1.18 mmol) of **2**, 0.128 mL (0.98 mmol) of isobutyl chloroformate, and 300 mg of NH_4F. Chromatographic purification (CH_2Cl_2−CH_3OH, 95:5 and then 90:10) yielded 370 mg (86% based upon **2**) of **3f** as a white solid. This product was crystallized from MeOH: mp 193 °C dec; UV (MeOH) λ_{max} 259 nm (log ϵ 4.19); ^{1}H NMR (DMSO-d_6) δ 0.80 (t, 6H, CH-(CH_3)$_2$), 1.72 (m, CH(CH_3)$_2$), 3.55−3.64 (m, 3H, OCH_2, H-5B'), 3.68 (m, H-5A', $J_{5A',5B'} = -11.9$ Hz), 4.02 (br s, H-4'), 4.22 (br s, H-3'), 4.83 (m, H-2', $J_{2',3'} = 5.3$ Hz), 5.60 (m, 5'-OH), 5.67 (br s, 3'-OH), 5.95 (d, H-1', $J = 8.4$ Hz), 7.11 (d, NHCO, $J = 8.6$ Hz),

7.45 (br s, NH_2), 8.12 (s, H-2), 8.23 (s, H-8); ^{13}C NMR (DMSO-d_6) δ 18.84 ($2CH_3$), 27.53 ($CH(CH_3)_2$), 56.74 (C-2′), 62.04 (C-5′), 70.08, 70.35 (C-3′, CH_2-CH), 86.20 (C-1′), 87.32 (C-4′), 119.46 (C-5), 139.97 (C-8), 149.17 (C-4), 152.34 (C-2), 156.05, 156.23 (C-6, CO); MS (LSIMS, thioglycerol) m/z 389 (M + Na)$^+$, 367 (M + H)$^+$, 232 (M − B)$^+$, 136 (B + 2H)$^+$. Anal. ($C_{15}H_{22}N_6O_5$) C, H, N.

2′-(Benzylamino)-2′-deoxyadenosine (3g). To a solution of 540 mg of **2** (1.06 mmol) in 20 mL of anhydrous benzene were added 2 g of $CuSO_4$ and 130 μL (1.3 mmol) of benzaldehyde. The mixture was stirred for 1 h at 50 °C and filtered, and the solids were washed with CH_2Cl_2. The combined filtrate and washings were evaporated to yield an oily residue, which was coevaporated twice with toluene. To an ice-bath-cooled solution of the residue in 12 mL of dry MeOH were added two 100 mg portions of $NaBH_4$ with 1 h of stirring after each addition. The reaction was quenched with 30 mL of H_2O and the mixture extracted twice with 30 mL of EtOAc. The combined organic layer was dried and evaporated to yield crude TIPS-protected **3g**: MS (LSIMS, thioglycerol) m/z 599 (M + H)$^+$, 462 (M − B)$^+$, 136 (B + 2H)$^+$, 91 (CH_2-Ph)$^+$.

The obtained syrup was dissolved in 30 mL of MeOH, 300 mg of NH_4F was added, and the mixture was heated at reflux for 4 h. Chromatographic purification (CH_2Cl_2–MeOH, 85:15) of the residue (obtained after evaporation) yielded 158 mg (42%) of the title compound as a white foam. The product was taken up in MeOH and precipitated as its hydrochloride salt by addition of 1.0 M HCl solution in Et_2O: mp 171–174 °C slow dec; UV (MeOH) λ_{max} 259 nm (log ϵ 4.17); ^1H NMR (DMSO-d_6, free base) δ 3.35–3.68 (m, H-5′, 2′-NH), 4.15 (A of AB, $J_{A,B}$ = 12.3 Hz, 1H, CH_2), 4.19 (H-4′), 4.27 (B of AB, 1H, CH_2), 4.62 (m, H-2′), 4.68 (br, H-3′), 5.70 (br, 5′-OH), 5.78 (br, 3′-OH), 5.87 (d, H-1′, J = 7.5 Hz), 7.03–7.14 (m, arom H), 7.38 (br, NH_2), 8.07 (s), 8.27 (s, H-2, H-8); ^{13}C NMR (DMSO-d_6, free base) δ 49.42 (CH_2), 60.43 (C-2′), 61.42 (C-5′), 68.91 (C-3′), 83.95 (C-1′), 87.35 (C-4′), 119.19 (C-5), 128.53 (C-3″,5″), 128.98 (C-4″), 130.02 (C-2″,6″), 131.69 (C-1″), 140.48 (C-8), 149.12 (C-4), 151.01 (C-2), 155.03 (C-6); MS (LSIMS, thioglycerol) m/z 379 (M + Na)$^+$, 357 (M + H)$^+$, 222 (M − B)$^+$, 136 (B + 2H)$^+$, 91 (CH_2-Ph)$^+$. Anal. ($C_{17}H_{20}N_6O_3$·HCl·H_2O) C, H, N.

***trans*-1-(Adenin-9-yl)-2-hydroxycyclopentane (5).** A mixture of 7.02 g (52.0 mmol) of adenine and 412 mg (51.8 mmol) of LiH in 150 mL of DMF under N_2 was heated for 1 h at 60 °C, after which time 4.0 mL (3.86 g, 45.8 mmol) of cyclopentane epoxide was added. The mixture was heated for another 4 h at 120 °C. The dark brown reaction mixture was evaporated and coevaporated with xylene and the residue purified by column chromatography (CH_2Cl_2–MeOH, 95:5, and then CH_2Cl_2–MeOH, 90:10) to yield 7.15 g (32.6 mmol, 71%) of the alcohol **5** as a white foam: UV (MeOH) λ_{max} 261 nm (log ϵ 4.18); ^1H NMR (DMSO-d_6) δ 1.55–2.22 (m, 6H, H-3′,3″,4′,4″,5′,5″), 4.49 (t, 2H, H-1′,2′), 5.20 (br s, 2′-OH), 7.21 (br s, NH_2), 8.14 (s), 8.18 (s, H-2, H-8); ^{13}C NMR (DMSO-d_6) δ 20.78 (C-4′), 29.70 (C-5′), 32.93 (C-3′), 63.74 (C-1′), 75.91 (C-2′), 120.20 (C-5), 140.91 (C-8), 150.53 (C-4), 152.97 (C-2), 156.93 (C-6); HRMS (LSIMS, glycerol) m/z 220.1211 [MH$^+$ ($C_{10}H_{14}N_5O$) 220.1198].

***cis*-1-(Adenin-9-yl)-2-hydroxycyclopentane (6).** To a solution of 5.34 g (24.4 mmol) of **5** and 8.5 g (32.4 mmol) of triphenylphosphine in 50 mL of THF (dry) were added (30 min) 5.1 mL (5.64 g, 32.4 mmol) of DEAD and 2.65 g (21.7 mmol) of benzoic acid dissolved in 15 mL of THF. The mixture became clear, and a precipitate formed upon further stirring at room temperature. After 3 h, the solvent was evaporated and the residue was roughly purified by flash chromatography (CH_2Cl_2–MeOH, 95:5). Fractions containing the benzoic ester where collected and evaporated to yield a white residue which was disolved in 200 mL of MeOH containing 1 g of NaOMe. The mixture was kept at room temperature for 48 h; the mixture was neutralized with AcOH, evaporated, and purified by column chromatography (CH_2Cl_2–MeOH, 95:5, and then CH_2Cl_2–MeOH, 85:15) to yield 2.82 g (12.9 mmol, 59%) of the *cis*-alcohol **6** as a white solid: UV (MeOH) λ_{max} 260 nm (log ϵ 4.16); ^1H NMR (DMSO-d_6) δ 1.64–2.33 (m, 6H, H-3′,3″,4′,4″,5′,5″), 4.16 (nr, H-2′), 4.69 (ddd, H-1′, J = 11.6, ≈7, ≈4 Hz), 4.96 (d, 2′-OH, J = 4.7 Hz), 7.18 (br s, NH_2), 8.14 (s), 8.16 (s, H-2, H-8); ^{13}C NMR (DMSO-d_6) δ 20.61 (C-4′), 28.22 (C-5′), 33.42 (C-3′), 58.68 (C-1′), 71.23 (C-2′), 119.46 (C-5), 141.20 (C-8), 150.75 (C-4), 152.94 (C-2), 156.76 (C-6); HRMS (LSIMS, glycerol) m/z 220.1182 [MH$^+$ ($C_{10}H_{14}N_5O$) 220.1198].

***cis*-1-(Adenin-9-yl)-2-(*O*-methylsulfonyl)cyclopentane (7).** To a cooled (ice bath) suspension of 1.20 g (5.5 mmol) of the *cis*-alcohol **6** in 30 mL of CH_2Cl_2 and 10 mL of pyridine was added 0.47 mL (6.1 mmol) of methanesulfonyl chloride. After the mixture was stirred for 2 h, the reaction was quenched by addition of 50 mL of H_2O. The mixture was extracted twice with 30 mL of CH_2Cl_2. The organic layers were dried ($MgSO_4$) and evaporated. Purification of the residue by column chromatography (CH_2Cl_2–MeOH, 95:5) yielded 1.51 g (5.08 mmol, 92% yield) of **7** as a white solid: UV (MeOH) λ_{max} 260 nm (log ϵ 4.16); ^1H NMR (DMSO-d_6) δ 1.79–2.47 (m, 6H, H-3′,3″,4′,4″,5′,5″), 2.82 (s, 3H, CH_3SO_2), 5.00 (ddd, H-1′, J = 4.5, 8.1, and 11.0 Hz), 5.18 (br, H-2′), 7.26 (br s, NH_2), 8.17 (s), 8.24 (s, H-2, H-8); ^{13}C NMR (DMSO-d_6) δ 20.21 (C-4′), 27.43 (C-5′), 31.24 (C-3′), 38.16 (CH_3SO_2), 56.96 (C-1′), 82.71 (C-2′), 119.50 (C-5), 140.50 (C-8), 149.66 (C-4), 153.23 (C-2), 156.80 (C-6); HRMS (LSIMS, thioglycerol) m/z 298.0961 [MH$^+$ ($C_{11}H_{16}N_5O_3S$) 298.0974].

***trans*-1-(Adenin-9-yl)-2-azidocyclopentane (8).** **7** (1.4 g, 4.71 mmol) was taken up in 20 mL of DMF, 1.5 g (23.0 mmol) of NaN_3 was added, and the mixture was stirred for 8 h at 80 °C. The solvent was evaporated; the residue was adsorbed on Celite and purified by column chromatography (CH_2Cl_2–MeOH, 95:5) yielding 1.0 g (4.10 mmol, 87% yield) of **8** as a white solid: UV (MeOH) λ_{max} 260 nm; ^1H NMR (DMSO-d_6) δ 1.67–2.29 (m, 6H, H-3′,3″,4′,4″,5′,5″), 4.55 (q), 4.74 (q, H-1′, H-2′), 7.33 (br s, NH_2), 8.17 (s), 8.30 (s, H-2, H-8); ^{13}C NMR (DMSO-d_6) δ 21.12 (C-4′), 29.78, 29.89 (C-3′, C-5′), 61.22 (C-1′), 65.77 (C-2′), 120.13 (C-5), 140.72 (C-8), 150.31 (C-4), 153.12 (C-2), 156.84 (C-6); HRMS (LSIMS, glycerol) m/z 245.1257 [MH$^+$ ($C_{10}H_{13}N_8$) 245.1263].

***trans*-1-(Adenin-9-yl)-2-aminocyclopentane (9).** A solution of 4.80 g (19.65 mmol) of azide **8** in MeOH (80 mL) was hydrogenated at room temperature and 1100 psi of pressure in the presence of 10% Pd/C (700 mg) for 3 h. The mixture was filtered and evaporated to yield 3.85 g (90%) of **9**: UV (MeOH) λ_{max} 260 nm; ^1H NMR (DMSO-d_6) δ 1.41–1.52 (m, 1H), 1.70–1.88 (m, 2H), 1.98–2.22 (m, 3H, H-3′,3″,4′,4″,5′,5″), 2.95 (br s, NH_2), 3.64 (q), 4.38 (q, H-1′, H-2′), 7.18 (br s, aliphatic NH_2), 8.11(s), 8.18 (s, H-2, H-8); ^{13}C NMR (DMSO-d_6) δ 20.42 (C-4′), 29.83, 32.88 (C-3′, C-5′), 57.08 (C-1′), 63.13 (C-2′), 119.43 (C-5), 139.98 (C-8), 149.80 (C-4), 152.13 (C-2), 156.07 (C-6); HRMS (LSIMS, glycerol) m/z 219.1358 [MH$^+$ ($C_{10}H_{15}N_6$) 219.1358].

***trans*-1-(Adenin-9-yl)-2-benzamidocyclopentane (10a).** To a solution of 1.40 g (6.4 mmol) amine **9** in 50 mL of CH_2Cl_2–pyridine (3:2) was added 1.60 g (7.1 mmol) of benzoic anhydride. The mixture was stirred for 2 h at room temperature. After addition of 5 mL of water, the mixture was evaporated and purified by column chromatography (CH_2Cl_2 and then CH_2Cl_2–MeOH, 95:5) yielding 1.15 g (3.6 mmol, 56%) of **10a** as a white foam: mp (MeOH) 256 °C; UV (MeOH) λ_{max} 259 nm (log ϵ 4.19); ^1H NMR (DMSO-d_6) δ 1.73–2.01 (m, 3H), 2.14–2.27 (m, 3H, H-3′,3″,4′,4″,5′,5″), 4.86 (m, 2H, H-1′,2′), 7.17 (br s, NH_2), 7.40–7.50 (m, 3H, arom H-3,5,4), 7.72 (d, 2H, arom H-2,6), 8.12 (s), 8.20 (s, H-2, H-8), 8.56 (d, NHCO); ^{13}C NMR (DMSO-d_6) δ 20.73 (C-4′), 29.65, 29.90 (C-3′, C-5′), 54.76 (C-1′), 60.06 (C-2′), 119.28 (C-5), 127.24, 128.28 (C-2″,6″,3″,5″), 131.27 (C-4″), 134.29 (C-1″), 139.91 (C-8), 149.82 (C-4), 152.23 (C-2), 156.06 (C-6), 166.30 (C=O); HRMS (EI) m/z 322.1531 [M$^+$ ($C_{17}H_{18}N_6O$) 322.1542]. Anal. ($C_{17}H_{18}N_6O$) C, H, N.

***trans*-1-(Adenin-9-yl)-2-(*m*-methoxybenzamido)cyclopentane (10b).** A suspension of 1.05 g (4.8 mmol) of amine **9** and 760 mg (5.0 mmol) of *m*-anisic acid in 25 mL of dry DMF was cooled to −20 °C. Then 550 mg (4.78 mmol) of NHS and 1.00 g (4.85 mmol) of DCC were added. The mixture was allowed to come to room temperature and stirred for 24 h. Then it was filtered, the solid material was washed with EtOAc, and the combined filtrates were evaporated. Purification of the residue by column chromatography (CH_2Cl_2 and then CH_2Cl_2–MeOH, 95:5) yielded 840 mg (2.4 mmol, 50%) of **10b** as a white foam: mp (MeOH) 244 °C; UV (MeOH) λ_{max} 260 nm (log ϵ 4.20);

^{1}H NMR (DMSO-d_6) δ 1.73–2.02 (m, 3H), 2.12–2.26 (m, 3H, H-3',3'',4',4'',5',5''), 3.76 (s, 3H, OCH_3), 4.79–4.92 (m, 2H, H-1',2'), 7.05 (m, arom H-4), 7.16 (br s, NH_2), 7.23 (s, arom H-2), 7.30 (m, 2H, arom H-5,6), 8.10 (s), 8.18 (s, H-2, H-8), 8.53 (d, NHCO); ^{13}C NMR (DMSO-d_6) δ 20.72 (C-4'), 29.64, 29.85 (C-3', C-5'), 54.80 (C-1'), 55.33 (MeO), 60.02 (C-2'), 112.53 (C-5''), 117.02 (C-4''), 119.26 (C-6''), 119.43 (C-5), 129.43 (C-2''), 135.82 (C-1''), 139.90 (C-8), 149.79 (C-4), 152.20 (C-2), 156.04 (C-6), 159.16 (C-3''), 166.01 (C=O); HRMS (EI) m/z 352.1648 [M$^+$ ($C_{18}H_{20}N_6O_2$) 352.1648]. Anal. ($C_{18}H_{20}N_6O_2$) C, H, N.

***trans*-1-(Adenin-9-yl)-2-(*m*-chlorobenzamido)cyclopentane (10c).** To an ice-cold suspension of 400 mg (1.83 mmol) of the amine **9** in 20 mL of CH_2Cl_2–pyridine (3:2) was added 0.25 mL (1.95 mmol) of *m*-chlorobenzoyl chloride. After the mixture was stirred for 2 h, the reaction was quenched with water; the mixture was evaporated and purified by column chromatography (CH_2Cl_2–MeOH, 95:5) to yield 514 mg (1.44 mmol, 78% yield) of **10c** as a white solid: mp (MeOH) 252 °C dec; UV (MeOH) λ_{max} 260 nm (log ϵ 4.20); ^{1}H NMR (DMSO-d_6) δ 1.74–2.01 (m, 3H), 2.13–2.30 (m, 3H, H-3',3'',4',4'',5',5''), 4.83 (m, 2H, H-1',2'), 7.16 (br s, NH_2), 7.47 (t, arom H-5), 7.57 (d), 7.68 (d, arom H-4,6), 7.77 (s, arom H-2), 8.10 (s), 8.22 (s, H-2, H-8), 8.70 (d, NHCO); ^{13}C NMR (DMSO-d_6) δ 20.75 (C-4'), 29.55, 29.75 (C-3', C-5'), 55.01 (C-1'), 60.07 (C-2'), 119.23 (C-5), 126.02, 126.96, 130.28, 131.03 (C-2'',4'',5'',6''), 133.11 (C-3''), 136.34 (C-1''), 139.81 (C-8), 149.77 (C-4), 152.14 (C-2), 156.01 (C-6), 164.79 (C=O); HRMS (EI) m/z 356.1142 [M$^+$ ($C_{17}H_{17}N_6OCl$) 356.1152]. Anal. ($C_{17}H_{17}N_6OCl$) C, H, N.

***trans*-1-(Adenin-9-yl)-2-(*m*-bromobenzamido)cyclopentane (10d).** This compound was prepared as described for **10b**, using 600 mg (2.75 mmol) of the amine **9**, 600 mg (2.99 mmol) of *m*-bromobenzoic acid, 315 mg (2.74 mmol) of NHS, and 575 mg (2.79 mmol) of DCC. The title compound was obtained as a white solid: 600 mg (1.50 mmol, 54% yield); mp (EtOH) 249 °C; UV (MeOH) λ_{max} 261 nm (log ϵ 4.21); ^{1}H NMR (DMSO-d_6) δ 1.75–2.03 (m, 3H), 2.13–2.26 (m, 3H, H-3',3'',4',4'',5',5''), 4.84 (m, 2H, H-1',2'), 7.38 (t, arom H-5), 7.50 (br s, NH_2), 7.69 (d, 2H, arom H-4,6), 7.89 (s, arom H-2), 8.16 (s), 8.29 (s, H-2, H-8), 8.71 (d, NHCO, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6) δ 20.79 (C-4'), 29.62, 29.70 (C-3', C-5'), 55.10 (C-1'), 60.27 (C-2'), 119.12 (C-5), 121.59, 126.41, 129.81, 130.55 (C-2'',4'',5'',6''), 133.96 (C-3''), 136.49 (C-1''), 140.38 (C-8), 149.60 (C-4), 150.85 (C-2), 155.01 (C-6), 164.72 (C=O); HRMS (LSIMS, thioglycerol) m/z 401.0733 [MH$^+$ ($C_{17}H_{18}N_6O$-Br) 401.0725]. Anal. ($C_{17}H_{17}N_6OBr{\cdot}C_2H_5OH$) C, H, N.

2-(Adenin-9-yl)-*N*-[(*tert*-butyloxy)carbonyl]-ethylamine (11). A solution of 10 g of *N*-[(*tert*-butyloxy)-carbonyl]ethanolamine (62.0 mmol) and 10.6 mL (67.3 mmol) of diethyl azodicarboxylate in 80 mL of THF was added dropwise to a suspension of 8.4 g (62.2 mmol) of adenine and 17.5 g (66.7 mmol) of triphenylphosphine in 100 mL of THF over a period of 1 h. The mixture was stirred for 4 h at room temperature and evaporated. Chromatographic purification (CH_2Cl_2–MeOH, 9:1) afforded 13.5 g (48.5 mmol, 78% yield) of 11 as a white solid: UV (MeOH) λ_{max} 261 nm (log ϵ 4.19); ^{1}H NMR (DMSO-d_6) δ 1.30 (3CH_3), 3.35 (CH_2-NH), 4.17 (t, CH_2-N-9, J = 5.6 Hz), 6.95 (t, NHCO, J = 5.1 Hz), 7.18 (br s, NH_2), 8.01 (s), 8.13 (s, H-2, H-8); HRMS (LSIMS, thioglycerol) m/z 279.1562 [MH$^+$ ($C_{12}H_{19}N_6O_2$) 279.1569].

2-(Adenin-9-yl)ethylamine (12). Deprotection of 5.6 g (20 mmol) of 11 was accomplished in a few minutes by treatment with 8 mL (104 mmol) of trifluoroacetic acid in 50 mL of CH_2Cl_2. The trifluoroacetate salt of **12** was extracted with water (3 × 75 mL). Concentration of the combined aqueous layer and treatment with Dowex 1 × 2 (OH^-) resin yielded the free base: 3.4 g (95% yield); UV (MeOH) λ_{max} 261 nm (log ϵ 4.11); ^{1}H NMR (DMSO-d_6) δ 2.93 (t, CH_2-NH_2), 4.11 (t, CH_2-N-9, J = 6.2 Hz), 7.20 (br s, 6-NH_2), 8.10 (s, H-2), 8.13 (s, H-8); HRMS (LSIMS, thioglycerol) m/z 179.1025 [MH$^+$ ($C_7H_{11}N_6$) 179.1045].

***N*-(2-Ethyladenin-9-yl)-*p*-methylbenzamide (13a).** A solution of the amine **12** (0.66 g, 3.7 mmol) and 0.60 mL (4.54 mmol) of *p*-toluoyl chloride in 40 mL of CH_2Cl_2–pyridine (1:1) was stirred for 3 h at room temperature. The solvents were evaporated, and the residue purified by column chromatography (EtOAc and then EtOAc–MeOH, 85:15) yielded 0.78 g (2.6 mmol, 71% yield) of the title compound: UV (MeOH) λ_{max} 243 nm; ^{1}H NMR (DMSO-d_6) δ 2.32 (s, CH_3), 3.66 (q, CH_2-NH), 4.34 (t, CH_2-N-9), 7.14 (s, NH_2), 7.23 (d, 2 arom H-3,5), 7.66 (d, 2 arom H-2,4), 8.04 (s), 8.12 (s, H-2, H-8), 8.58 (t, NHCO); MS (CI, isobutane) m/z 297 (M + H)$^+$, 136 (B + 2H)$^+$. Anal. ($C_{15}H_{16}N_6O$) C, H, N.

***N*-(2-Ethyladenin-9-yl)-*m*-fluorobenzamide (13b).** A solution of the amine **12** (0.47 g, 3.7 mmol) and 0.35 mL (2.88 mmol) of *m*-fluorobenzoyl chloride in 30 mL of CH_2Cl_2–pyridine (1:1) was stirred for 3 h at room temperature Workup and purification as for **13a** yielded 0.61 g (2.0 mmol, 77% yield) of the title compound: UV (MeOH) λ_{max} 261 nm; ^{1}H NMR (DMSO-d_6) δ 3.68 (q, CH_2-NH), 4.36 (t, CH_2-N-9), 7.17 (s, NH_2), 7.36 (t, arom H-5), 7.47–7.57 (m, arom H-2,6), 7.62 (d, arom H-4), 8.09 (s), 8.12 (s, H-2, H-8), 8.82 (t, NHCO); MS (CI, isobutane) m/z 301 (M + H)$^+$, 136 (B + 2H)$^+$. Anal. ($C_{14}H_{13}N_6OF$) C, H, N.

***N*-(2-Ethyladenin-9-yl)-*m*-chlorobenzamide (13c).** To a solution of the amine **12** (0.70 g, 3.9 mmol) in 40 mL of CH_2Cl_2–pyridine (1:1) was added 0.50 mL (3.91 mmol) of *m*-chlorobenzoyl chloride. This solution was stirred for 3 h at room temperature, after which time TLC (EtOAc–MeOH, 85:15) proved the reaction was complete. Workup and purification as for **13a** yielded 0.84 g (2.7 mmol, 68% yield) of the title compound: UV (MeOH) λ_{max} 260 nm; ^{1}H NMR (DMSO-d_6) δ 3.67 (q, CH_2-NH), 4.35 (t, CH_2-N-9), 7.17 (br s, NH_2), 7.47 (t, arom H-5), 7.57 (d), 7.72 (d, arom H-4,6), 7.78 (t, arom H-2), 8.09 (s), 8.11 (s, H-2, H-8), 8.82 (t, NHCO); MS (CI, isobutane) m/z 317 (M + H)$^+$, 136 (B + 2H)$^+$. Anal. ($C_{14}H_{13}N_6OCl$) C, H, N.

2-(8-Bromoadenin-9-yl)-*N*-[(*tert*-butyloxy)carbonyl]-ethylamine (14). To a solution of 4.33 g (15.6 mmol) of 11 in 120 mL of MeOH–1 M NaOAc buffer, pH 4.3, was added dropwise 1.50 mL of bromine. After being stirred for 7 h at room temperature, the solution was decolorized by addition of saturated sodium metabisulfite solution and extracted three times with 100 mL of CH_2Cl_2. The organic layers were dried ($MgSO_4$) and evaporated to yield a slightly yellow solid. Purification by column chromatography (CH_2Cl_2–MeOH, 90:10) yielded 3.97 g (71%) of **14** as a white solid: UV (MeOH) λ_{max} 266 nm (log ϵ 4.20); ^{1}H NMR (DMSO-d_6) δ 1.30 (3CH_3), 3.30 (CH_2-NH), 4.16 (t, CH_2-N-9, J = 5.3 Hz), 6.95 (t, NHCO, J = 5.9 Hz), 7.30 (br s, NH_2), 8.12 (s, H-2); HRMS (LSIMS, thioglycerol) m/z 357.0652 [MH$^+$ ($C_{12}H_{18}N_6O_2Br$) 357.0675].

2-[8-(2-Thienyl)adenin-9-yl]ethylamine (15). To a solution of 2.7 g (7.6 mmol) of **14**, 180 mg (0.8 mmol) of palladium(II) acetate, and 500 mg (1.6 mmol) of triphenylarsine in 25 mL of dry THF containining 1.2 mL (9 mmol) of TEA, stirred for 10 min at room temperature under N_2, was added 3 g (8 mmol) of 2-(tributylstannyl)thiophene,[7] and the mixture was heated at reflux for 15 h. At that time TLC analysis (CH_2Cl_2–MeOH, 90:10) indicated the reaction to be almost complete. The mixture was diluted with 150 mL of CH_2Cl_2 and washed with water (2 × 100 mL). The organic layer was dried ($MgSO_4$), concentrated, and subjected to flash chromatography (CH_2Cl_2–MeOH, 95:5) to yield crude *N*-*t*-BOC-protected **15**. Deprotection of the amino function and purification was performed as described for **12**. **15**: overall yield 1.5 g (76%); UV (MeOH) λ_{max} 246 (log ϵ 4.19), 308 nm (log ϵ 4.18), λ_{min} 272 nm (log ϵ 3.91); ^{1}H NMR (DMSO-d_6) δ 3.09 (t, CH_2-CH_2-NH_2, J = 6.8 Hz), 3.67 (br, CH_2-NH_2), 4.48 (t, CH_2-N-9), 7.27 (t, H-4''), 7.34 (br s, 6-NH_2), 7.78 (d, H-3'', J = 3.7 Hz), 7.81 (d, H-5'', J = 5.1 Hz), 8.18 (s, H-2); HRMS (LSIMS, thioglycerol) m/z 261.0929 [MH$^+$ ($C_{11}H_{13}N_6S$) 261.0922]. Anal. ($C_{11}H_{12}N_6S{\cdot}^1/_2H_2O$) C, H, N.

2-[8-(2-Thienyl)adenin-9-yl]-*N*-benzylethylamine (16). To a solution of 250 mg (0.96 mmol) of **15** in 20 mL of EtOH containing 5 g of molecular sieves (4 Å, $^1/_{16}$ in. beads, 8–12 mesh) was added 110 μL (1.08 mmol) of benzaldehyde. The mixture was stirred for 1 h at 50 °C, the mixture was cooled in an ice bath, and three 15 mg portions of $NaBH_4$ (1.19 mmol) were added at 15 min intervals. Thirty minutes after the last addition, the mixture was filtered and the solvent removed. Chromatographic purification (CH_2Cl_2–MeOH, 98:2–95:5) provided 245 mg (73% yield) of the title compound. The

product was taken up in acetone and precipitated by addition of petroleum ether: mp 107 °C; UV (MeOH) λ_{max} 246 (4.22), 308 nm (log ϵ 4.18), λ_{min} 271 nm (log ϵ 3.87); ^{1}H NMR (DMSO-d_6) δ 2.89 (t, CH_2-NH), 3.30 (br s, NH-Bz), 3.67 (s, CH_2-Ph), 4.46 (t, CH_2-N-9, J = 6.7 Hz), 7.14–7.27 (m, 6H, arom H, thienyl H-4), 7.30 (br s, NH_2), 7.74 (d, thienyl H-3, J = 3.7 Hz), 7.78 (d, thienyl H-5, J = 5.1 Hz), 8.16 (s, H-2); MS (LSIMS, thioglycerol) m/z 351 (M + H)$^+$, 218 (B + 2H)$^+$, 91 (CH$_2$-Ph)$^+$. Anal. ($C_{18}H_{18}N_6S\cdot{}^1/_4CH_3COCH_3$) C, H, N.

8-Bromo-2′-benzamido-2′-deoxyadenosine (18). A solution of 400 mg (1.08 mmol) of 2′-benzamido-2′-deoxyadenosine (**17**) and 0.120 mL (2.3 mmol) of bromine in MeOH (10 mL)–1 M acetate buffer, pH 4.3 (10 mL), was stirred at room temperature for 8 h (after 10 min the reaction mixture became slightly turbid). The mixture was diluted with 50 mL of saturated sodium metabisulfite solution and extracted three times with 50 mL of EtOAc. The combined organic layers were dried over $MgSO_4$, and the product was purified by column chromatography (CH_2Cl_2–MeOH, 95:5) to yield 400 mg (0.89 mmol, 82% yield) of **18** as a white solid: mp (MeOH) 163 °C; UV (MeOH) λ_{max} 264 nm (log ϵ 4.26); ^{1}H NMR (DMSO-d_6) δ 3.60 (H-5B′), 3.79 (H-5A′, $J_{5A',5B'}$ = −12.1 Hz), 4.12 (H-4′), 4.42 (H-3′), 5.65 (5′-OH), 5.76 (H-2′, $J_{2',3'}$= 5.9 Hz), 5.86 (OH-3′, $J_{3',OH\text{-}3'}$ = 4.2 Hz), 6.14 (H-1′, J = 7.8 Hz), 7.44 (arom H-3,5), 7.52 (arom H-4), 7.55 (NH_2), 7.82 (arom H-2,6), 8.15 (H-2), 8.37 (NH, J = 8.3 Hz); ^{13}C NMR (DMSO-d_6) δ 53.58 (C-2′), 62.06 (C-5′), 70.20 (C-3′), 87.59 (C-1′), 89.04 (C-4′), 119.73 (C-5), 126.76 (C-8, being 140.02 in the nonbrominated analog **17**,[5] 127.50, 128.29 (arom C-2,6, C-3,5), 131.50 (arom C-4), 133.90 (arom C-1), 150.13 (C-4), 152.48 (C-2), 155.18 (C-6), 166.72 (C=O); HRMS (LSIMS, glycerol) m/z 449.0575 [MH$^+$ ($C_{17}H_{18}N_6O_4Br$) 449.0573]. Anal. ($C_{17}H_{17}N_6O_4Br\cdot H_2O$) C, H, N.

8-(2-Thienyl)-2′-benzamido-2′-deoxyadenosine (19a). To a mixture of 380 mg (0.85 mmol) of **18**, 22 mg of palladium(II) acetate, and 60 mg of triphenylarsine in 5 mL of NMP under N_2 atmosphere was added 0.14 mL of triethylamine. After stirring for 10 min at room temperature, 0.75 mL of 2-(tributylstannyl)thiophene was added and the mixture stirred overnight at 60 °C. Rough purification by column chromatography (CH_2Cl_2–MeOH, 95:5) and removal of remaining traces of NMP by elution (MeOH–H_2O, 50:50) over a Dowex 1 × 2 (OH$^-$) resin gave 270 mg (0.60 mmol, 71% yield) of **19a** as a white solid: mp (MeOH) 161 °C; UV (MeOH) λ_{max} 301 (log ϵ 4.11), 241 nm (log ϵ 4.26), λ_{min} 269 nm (log ϵ 3.95); ^{1}H NMR (DMSO-d_6) δ 3.61 (m, H-5B′), 3.80 (m, H-5A′), 4.10 (br, H-4′), 4.46 (dd, H-3′, $J_{2',3'} \approx$ 5.5 Hz, $J_{3',4'}$ = 2.3 Hz), 5.54 (br, 5′-OH), 5.78 (br, 3′-OH), 6.06 (m, H-2′), 6.25 (d, H-1′, J = 7.7 Hz), 7.28 (t, thienyl H-4), 7.41 (t, arom H-3,5), 7.45 (br s, NH_2), 7.49 (t, arom H-4), 7.62 (d, thienyl H-3, J = 3.6 Hz), 7.78 (d, arom H-2,6), 7.85 (d, thienyl H-5, J = 5.1), 8.38 (d, NH, J = 8.0 Hz); ^{13}C NMR (DMSO-d_6) δ 53.06 (C-2′), 62.01 (C-5′), 70.02 (C-3′), 87.02, 87.69 (C-1′, C-4′), 119.12 (C-5), 127.50, 128.22 (arom C-2,6, C-3,5), 129.48, 129.93 (2 thienyl C's), 130.93 (thienyl C-2), 131.41 (arom C-4), 133.97 (arom C-1), 145.01 (C-8), 150.13 (C-4), 152.30 (C-2), 155.99 (C-6), 166.69 (C=O); MS (LSIMS, thioglycerol), m/z 905 (2M + H)$^+$, 453 (M + H)$^+$, 236 (S + H)$^+$, 218 (B + 2H)$^+$. Anal. ($C_{21}H_{20}N_6O_4S\cdot 1^1/_2H_2O$) C, H, N.

8-Methoxy-2′-benzamido-2′-deoxyadenosine (19b). A methanolic solution of 200 mg (0.45 mmol) of **18** was eluted with MeOH over a column of Dowex 1 × 2 (OH$^-$) resin to afford 163 mg (95%) of the title compound as a pure white solid: mp 231 °C; UV (MeOH) λ_{max} 257 nm (log ϵ 4.16); ^{1}H NMR (DMSO-d_6) δ 3.55 (m, H-5B′), 3.72 (m, H-5A′, $J_{5A',5B'}$ = −12.0 Hz), 4.03 (q, H-4′), 4.10 (s, CH_3O), 4.34 (br, H-3′), 5.49 (dd, 5′-OH), 5.63 (m, H-2′, $J_{2',3'}$ = 5.7 Hz), 5.70 (d, 3′-OH, J = 4.5 Hz), 6.05 (d, H-1′, J = 7.9 Hz), 6.97 (br s, NH_2), 7.44 (t, H-3″,5″), 7.52 (t, H-4″), 7.82 (d, H-2″,6″), 8.05 (s, H-2), 8.36 (d, NH, J = 8.4 Hz); ^{13}C NMR (DMSO-d_6) δ 53.17 (C-2′), 57.31 (CH_3O), 62.12 (C-5′), 70.16 (C-3′), 85.07, 86.83 (C-1′, C-4′), 114.92 (C-5), 127.53, 128.22 (C-2″,6″, C-3″,5″), 131.40 (C-4″), 133.99 (C-1″), 148.95 (C-4), 150.64 (C-2), 154.04 (C-6), 154.45 (C-8), 166.65 (C=O); MS (LSIMS, thioglycerol) m/z 423 (M + Na)$^+$, 401 (M + H)$^+$, 236 (M − B)$^+$, 166 (B + 2H)$^+$, 105 (COPh)$^+$. Anal. ($C_{18}H_{20}N_6O_5$) C, H, N.

2′-Amino-2′-deoxyuridine (20). A solution of 2′-azido-2′-deoxyuridine (1.50 g, 5.57 mmol) in MeOH (80 mL) was hydrogenated at room temperature and at 200 psi of pressure in the presence of Pd/C (1.00 g) for 3 h. The mixture was filtered over a Celite pad and evaporated to yield 1.25 g (92%) of **20** as a white solid, which was sufficiently pure for the next step. The ^{1}H NMR (DMSO-d_6) and UV spectra of a pure crop, obtained by crystallization from EtOH, were identical with those reported in ref 8.

2′-Deoxy-2′-(3-methoxybenzamido)uridine (21). Method A. To a solution of **20** (5 g, 20.6 mmol) in pyridine (75 mL) and CH_2Cl_2 (25 mL) was added 10 mL (71 mmol) of m-anisoyl chloride. The mixture was stirred for 3 h and partioned between 150 mL of CH_2Cl_2 and 150 mL of $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and evaporated. The residue was treated with methanolic ammonia for 2 days to yield two main products. They were separated by column chromatography (CH_2Cl_2–MeOH, 95:5 and then 90:10). The less polar one was identified as compound **21** (3.21 g 41% yield).

Method B. To a suspension of **20** (930 mg, 3.82 mmol) and m-anisic acid (761 mg, 5 mmol) in DMF (20 mL) at −20 °C were added NHS (575 mg, 5 mmol) and DCC (1.03 g, 5 mmol). After being stirred at room temperature for 24 h, the mixture was filtered, the solid material was washed with EtOAc, and the combined filtrate was evaporated. The residue was purified by column chromatography (CH_2Cl_2–MeOH, 90:10) to yield 981 mg (68%) of the title compound: mp (MeOH) 199 °C; UV (MeOH) λ_{max} 257 nm (log ϵ 4.02); ^{1}H NMR (DMSO-d_6) δ 3.63 (m, H-5A′, B′), 3.80 (s, OCH_3), 3.99 (m, H-4′), 4.19 (m, H-3′), 4.71 (m, H-2′), 5.21 (t, 5′-OH), 5.71 (d, H-1′, J = 7.5 Hz), 5.72 (br s, 2′-OH), 6.08 (d, H-5, J = 8.2 Hz), 7.10 (d, H-4″), 7.35–7.42 (m, 3H, H-2″,5″,6″), 7.96 (d, H-6), 8.15 (d, NH, J = 8.5 Hz), 11.28 (br s, H-3); ^{13}C NMR (DMSO-d_6) δ 55.35, 55.39 (C-2′, CH_3O), 61.67 (C-5′), 70.43 (C-3′), 86.01, 86.62 (C-1′, C-4′), 102.23 (C-5), 112.86 (C-5″), 117.33 (C-4″), 119.75 (C-6″), 129.49 (C-2″), 135.44 (C-1″), 140.92 (C-6), 150.89 (C-2), 159.20 (C-3″), 163.14 (C-4), 166.54 (C=O); MS (LSIMS, thioglycerol) m/z 400 (M + Na)$^+$, 378 (M + H)$^+$, 266 (M − B)$^+$, 135 (3-MeOC$_6$H$_4$-CO)$^+$.

***N*^{6}-Decanoyl-2-methyladenine (22).** A suspension of 730 mg of 2-methyladenine hemisulfate salt (1.5H$_2$O) (3.24 mmol) and 3 g (9.19 mmol) of decanoic anhydride in 15 mL of pyridine was refluxed for 3 h. H_2O was added, and the mixture was evaporated. Column chromatography (CH_2Cl_2–MeOH, 95:5) yielded 850 mg (84%) of the title compound as a white solid: UV (MeOH) λ_{max} 273 nm; ^{1}H NMR (DMSO-d_6) δ 0.85 (t, CH$_2$-CH_3), 1.24 (br s, 7CH$_2$), 2.18 (t, CH$_2$-CO), 2.54 (s, 2-Me), 8.30 (s, H-8), 11.10 (br s, NHCO), 12.05 (br, N-9H); MS (LSIMS, 4-nitrobenzyl alcohol) m/z 607 (2M + H)$^+$, 326 (M + Na)$^+$, 304 (M + H)$^+$, 150 (M − dodecanoyl + 2H)$^+$.

2′-Deoxy-2′-(3-methoxybenzamido)-2-methyladenosine (23). To a suspension of 405 mg (1.33 mmol) of *N*^{6}-decanoyl-2-methyladenine (**22**) and 275 mg (0.73 mmol) of **21** in 5 mL of anhydrous acetonitrile was added 1.25 mL (5 mmol) of BSA. After refluxing for 20 min, 160 μL of TMSTF was added to the clear solution. Refluxing was continued for another 2 h, and the mixture was partioned between CH_2Cl_2 and H_2O. The organic layer was evaporated and the residue treated with 100 mL of 1 N NaOMe in MeOH. The residue was roughly purified by elution (CH_2Cl_2–MeOH, 90:10) over a silica gel column. Crude **23** was further purified on a column of Dowex 1 × 2 (OH$^-$) resin. Elution with 40% MeOH–H_2O afforded 100 mg of the title compound as a white foam: mp 162 °C; UV (MeOH) λ_{max} 262 nm (log ϵ 4.14); ^{1}H NMR (DMSO-d_6) δ 2.40 (s, 2-CH_3), 3.63 (m, H-5B′, $J_{5A',5B'}$ = −11.8 Hz), 3.73 (m, H-5A′), 3.78 (s, OCH_3), 4.12 (br, H-4′), 4.34 (t, H-3′), 5.28 (H-2′, $J_{2',3'}$ = 5.1 Hz), 5.76 (d, OH-5′), 6.07 (d, OH-3′), 6.19 (d, H-1′, J = 8.8 Hz), 7.08 (d, H-4″), 7.29 (br s, NH_2), 7.35 (t, H-5″), 7.37 (s, H-2″), 7.40 (d, H-6″), 8.13 (s, H-8), 8.34 (d, NHCO, J = 8.2 Hz); ^{13}C NMR (DMSO-d_6) δ 25.15 (CH_3-C-2), 55.35 (OMe), 55.58 (C-2′), 62.35 (C-5′), 70.78 (C-3′), 86.34 (C-1′), 87.83 (C-4′), 112.88 (C-5″), 117.23 (C-4″), 119.75 (C-5, C-6″), 129.40 (C-2″), 135.37 (C-1″), 139.63 (C-8), 149.67 (C-4), 155.95 (C-6), 159.15 (C-3″), 161.13 (C-2, being 152.45 in the nonmethylated analog 1[5]), 166.37 (C=O); MS (LSIMS, thioglycerol) m/z 415

(M + H)$^+$, 266 (M − B)$^+$, 150 (B + 2H)$^+$, 135 (3-MeOC$_6$H$_4$-CO)$^+$. Anal. ($C_{19}H_{22}N_6O_5 \cdot {}^1/_4H_2O$) C, H, N.

8-(Cyclohexylthio)adenosine (25a). A solution of cyclohexanethiol (3.25 g, 28 mmol) and NaOMe (756 mg, 14 mmol) in 30 mL of anhydrous EtOH was stirred for 10 min. 8-Bromoadenosine (**24**) (1 g, 2.8 mmol) was added and the clear solution refluxed for 3 h. The precipitate was filtered, and the filtrate was neutralized to pH 7−8 with CH_3COOH−MeOH (1:9). The suspension was filtered again and the filtrate evaporated to dryness. Purification of the residue by chromatography (CH_2Cl_2 and CH_2Cl_2−MeOH, 95:5 and then 90:10) yielded a white solid. Recrystallization from anhydrous EtOH yielded 523 mg (49%) of the title compound: mp 207−208 °C; UV (MeOH) λ_{max} 282 nm (log ϵ 4.28); ^{1}H NMR (DMSO-d_6) δ 1.20−1.60 (br m, 6H), 1.70 (m, 2H), 2.00 (m, 2H, cyclohexyl H), 3.51 (m, H-5'B), 3.67 (m, H-5'A), 3.79 (m, S-CH), 3.95 (q, H-4'), 4.25 (q, H-3'), 5.00 (q, H-2'), 5.20 (d, 3'-OH), 5.40 (d, 2'-OH), 5.68 (q, 5'-OH), 5.83 (d, H-1'), 7.33 (br s, NH_2), 8.07 (s, H-2). Anal. ($C_{16}H_{23}N_5O_4S$) C, H, N.

8-(2-Pyrimidinylthio)adenosine (25b). The procedure for the synthesis of **25a** was followed, using 3.14 g (28 mmol) of 2-pyrimidinethiol, 756 mg (14 mmol) of NaOMe, and 1 g (2.8 mmol) of 8-bromoadenosine (**24**). The pure title compound was obtained as a yellow solid: 924 mg (87%); mp 117 °C; UV (MeOH) λ_{max} 282 nm (log ϵ 4.04); ^{1}H NMR (DMSO-d_6) δ 3.50 (m, H-5'B), 3.70 (d, H-5'A), 3.90 (br s, H-4'), 4.19 (br s, H-3'), 4.88 (br s, H-2'), 5.12 (br s, 3'-OH), 5.23 (br s, 2'-OH), 5.18 (d, 5'-OH), 5.95 (d, H-1'), 7.36 (m, H-4''), 7.70 (br s, NH_2), 8.20 (s, H-2), 8.65 (d, H-3'',5''). Anal. ($C_{14}H_{15}N_7O_4S \cdot CH_3CH_2OH$) C, H, N.

5'-Deoxy-5'-(diphenylacetamido)adenosine (27a). The procedure for the synthesis of **3c** was followed, using 400 mg (1.5 mmol) of **26**, 320 mg (1.5 mmol) of diphenylacetic acid, 172 mg (1.5 mmol) of NHS, and 309 mg (1.5 mmol) of DCC. The pure title compound was obtained as a white solid: 650 mg (94%); UV (MeOH) λ_{max} 260 nm (log ϵ 4.13); ^{1}H NMR (DMSO-d_6) δ 3.50 (m, H-5'), 3.97 (t, H-4'), 4.08 (q, H-3'), 4.63 (q, H-2'), 5.00 (s, COCH), 5.30 (d, 3'-OH), 5.48 (d, 2'-OH), 5.84 (d, H-1'), 7.15−7.30 (br m, 10H, arom H), 7.35 (br s, NH_2), 8.15 (s, H-2), 8.30 (s, H-8), 8.64 (t, 5'-NH). Anal. ($C_{24}H_{24}N_6O_4 \cdot CH_3CH_2OH$) C, H, N.

5'-Deoxy-5'-(4-ethylbiphenyl-4'-carboxamido)adenosine (27b). The procedure for the synthesis of **3c** was followed, using 868 mg (3.26 mmol) of **26**, 737 mg (3.26 mmol) of 4-ethylbiphenyl-4'-carboxylic acid, 450 mg (3.91 mmol) of NHS, and 806 mg (3.91 mmol) of DCC. The pure title compound was obtained as a white solid: 368 mg (24%); mp 180 °C dec; UV (MeOH) λ_{max} 264 nm (log ϵ 4.00); ^{1}H NMR (DMSO-d_6) δ 1.20 (t, CH_3-CH_2), 2.65 (q, CH_3-CH_2), 3.62 (m, H-5'), 4.10 (t, H-4'), 4.20 (q, H-3'), 4.79 (q, H-3'), 4.79 (q, H-2'), 5.30 (br s, 3'-OH), 5.48 (br s, 2'-OH), 5.90 (d, H-1'), 7.32 (d, H-9'',11''), 7.45 (s, NH_2), 7.65 (d, H-8'',12''), 7.75 (d, H-2'',6''), 7.94 (d, H-3'',5''), 8.13 (s, H-2), 8.40 (s, H-8), 8.75 (t, 5'-NH). Anal. ($C_{25}H_{26}N_6O_4 \cdot {}^1/_2CH_3CH_2OH$) C, H, N.

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Supporting Information Available: All further information concerning the X-ray analysis (atomic coordinates, equivalent isotropic displacement parameters, anisotropic displacement parameters, bond lengths, bond angles, torsion angles, and geometry of the hydrogen bonds) (12 pages). Ordering information is given on any current masthead page.

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