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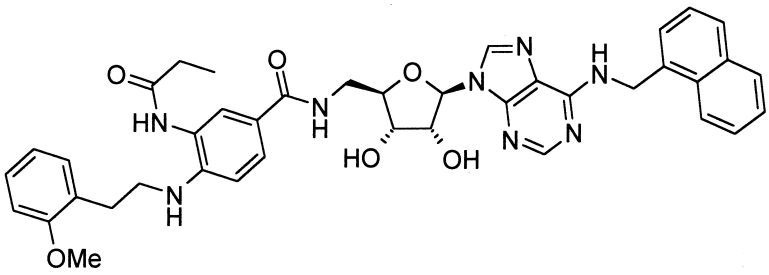

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Antimalarial Activity of N^6-Substituted Adenosine Derivatives (Part 2)[||]

Claudia Herforth,[†] Jochen Wiesner,[‡] Stephan Franke,[§] Abolfasl Golisade,[†] Hassan Jomaa,[‡] and Andreas Link*,[†]

Institut für Pharmazie, Fachbereich Chemie, Universität Hamburg, Bundesstrasse 45, D-20146 Hamburg, Germany, Jomaa Pharmaka GmbH, Frankfurter Strasse 50, D-35392 Giessen, Germany, and Institut für Organische Chemie, Fachbereich Chemie, Universität Hamburg, Martin-Luther-King-Platz 6, D-20146 Hamburg, Germany

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We have investigated the in vitro antimalarial activity of a new series of adenosine derivatives. The results show that N^6-(1-naphthylmethyl)-5′-deoxy-5′-(amido)adenosines as well as N^6-(4-phenylbenzyl)-5′-deoxy-5′-(amido)adenosines display significant activity against the malaria-causing parasites, with the sterically demanding bisubstituted species reported being active in most cases in the low-micromolar range. The novel compounds with unusual substitution pattern were obtained applying an efficient convergent polymer-assisted solution-phase (cPASP) synthesis protocol. Thus, we were able to prepare a series of substituted derivatives in parallel that would have been difficult to synthesize by standard techniques. The scope and limitations of the synthetic methodology are discussed.

Introduction

In the developing world, infectious diseases are the leading killers of young people.[1] According to estimations by the World Health Organization, 3.5 billion people suffer from one or more parasitic infections, with the greatest causes of morbidity being attributed to malaria.[2] Parasitic protozoan diseases must therefore be considered as one of the world's most extended health problems. The apicomplexan pathogen *Plasmodium falciparum*, the causative agent of malaria tropica, is a persistent scourge with new strains constantly developing which are resistant to available drugs. This pathogen infects approximately 400 million individuals each year, resulting in 1−2 million deaths annually. At the same time, vaccinations are still in development, and control of transmission vectors seems unfeasible. Consequently, the need for novel chemotherapeutic approaches in the fight against multiresistant *P. falciparum* is unquestionable.

In continuation of our efforts to contribute to the development of drugs for the treatment of malaria, we prepared novel substituted adenosines.[3] The underlying rationale of this approach is the fact that *P. falciparum* is incapable of de novo purine synthesis and that substituted adenosine derivatives are consequently prone to selective uptake by the parasite.[4] On account of supposed interactions with diverse adenosine binding motifs and the unique importance of the purine transport systems to parasite survival, the biological evaluation of substituted adenosine derivatives as possible antimalarial agents was considered rewarding.

Synthesis

The construction of desired 5′-amido-N^6-arylalkyl-5′-deoxyadenosines was divided into two independent parts. The nucleoside templates were obtained by conventional synthesis in solution, whereas the 5′-amido substituents were constructed on a solid support in up to five subsequent steps without purification other than washing of resin beads with appropriate solvents. For the final convergent connection, the polymer-supported carboxylic acid equivalents were transformed into acylating reagents by activation of the safety-catch linker used.[5,6] Chemoselective acylation of the unprotected nucleoside templates with the reactive species obtained yielded the 5′-amido-N^6-arylalkyl-5′-deoxyadenosines **7**−**40** intended for biological evaluation.

The synthesis of 5′-deoxy-N^6-(1-naphthylmethyl)-5′-phthalimidoadenosine (**4a**) and 5′-amino-5′-deoxy-N^6-(1-naphthylmethyl)adenosine (**5a**) has most recently been described by Bressi et al. (Scheme 1, path A).[7] For the preparation of novel derivatives **4b** and **5b** we followed a different path (Scheme 1, path B). Amination of commercially available 6-chloropurine-9-riboside (**1**) by aminolysis of the attached chlorine substituent at C6 with an excess of the appropriate primary amine yields N^6-(4-phenylbenzyl)adenosine (**3b**). Conversion with di-*tert*-butylazodicarboxylate and triphenylphosphin applying standard Mitsunobu condensation conditions results in the formation of 5′-deoxy-N^6-(4-phenylbenzyl)-5′-(phthalimido)adenosine **4b**. Subsequent hydrazine-mediated cleavage of the phthal-

[||] Dedicated Prof. Dr. Detlef Geffken on the occasion of his 60th birthday.

* To whom correspondence should be addressed. Phone: +49 40-42838-3467. Fax: +49 40 42838 6573; +49 40 42838 3467. E-mail: Andreas.Link@chemie.uni-hamburg.de.

[†] Institut für Pharmazie, Fachbereich Chemie, Universität Hamburg.

[‡] Jomaa Pharmaka GmbH. Fax: +49 641 99 47 529. E-mail: info@jomaa.de.

[§] Institut für Organische Chemie, Fachbereich Chemie, Universität Hamburg. Fax: +49 40 42838 2893. E-mail: franke@chemie.uni-hamburg.de.

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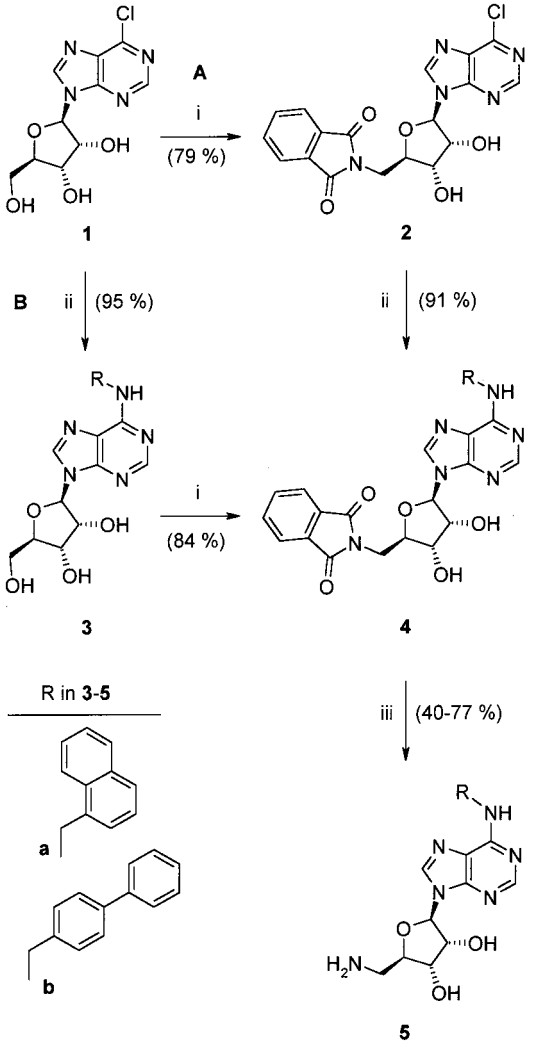
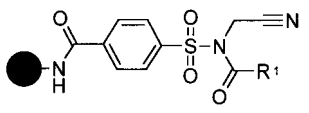
Scheme 1. Synthetic Sequence Leading to 5′-Amino-5′-deoxy-N^6-(1-naphthylmethyl)adenosine (**5a**) and 5′-Amino-5′-deoxy-N^6-(4-phenylbenzyl)adenosine (**5b**)[a]



[a] (i) $P(Ph)_3$, di-*tert*-butylazodicarboxylate, phthalimide, dry THF, 48 h; (ii) arylmethylamine derivative, EtOH or *n*-propanol, 50 °C, 72 h; (iii) hydrazine hydrate, EtOH, reflux, 1 h.



6

Figure 1. Polymer-bound carboxlic acid equivalent on activated Kenner safety-catch linker **6**.

imide group in **4b** as described for **4a** by Bressi et al. is the final step of the solution-phase synthesis part and leads to the required 5′-amino-N^6-(arylalkyl)-5′-deoxyadenosine scaffolds **5a** and **5b** in sufficient amounts for further derivatization.

Currently, two strategies for the introduction of amide substituents to the 5′-amino group of 5′-amino-5′-deoxyadenosines can be distinguished: (a) carbodiimide-mediated acylation in solution and (b) polymer-assisted solution-phase (PASP) acylation with the appropriately acylated safety-catch resin **6** (Figure 1; for R^1, see Figures 2 and 3). Both approaches have proven to be suitable for the much more challenging acylation of 2′-amino-2′-deoxyadenosine derivatives in high yield and purity and also furnish the desired N^6-(arylalkyl)-5′-deoxy-5′-(amido)adenosines **7**−**40** (Scheme 2; for R groups, see Figures 2 and 3).[7−9]

For the following reasons, we selected method b to access arrays of adenosine analogues for biological evaluation: Despite the additional steps needed to prepare the resins of type **6**, employing the safety-catch acylating agent has the added benefit of merely filtering off the solid support to obtain the desired product in nearly quantitative yield and in typically greater than 95% purity as determined by HPLC, according to our earlier findings and confirmed by Bressi et al. recently.[7−9]

In addition, the chemoselective acylation with activated carboxylic acid equivalents attached to the Kenner safety-catch linker (**6**) has shown high potential for the discrimination between two primary amino functions in multifunctional templates.[7] The chemoselectivity achievable is markedly superior to the results hitherto reported on enzymatically catalyzed transformations of similar diaminodideoxy nucleosides to the corresponding monoamides.[10]

The full potential of the acylating species of type **6** can be exploited when modifications of the carboxylic acid prior to activation are envisioned. The option to synthesize diverse carboxylic acid equivalents directly on the linker, which ensures good acylating properties after cyano methylation, is the most striking advantage of this concept. The additional steps needed to prepare safety-catch acylating agents such as **6a** therefore pay off because the degree of diversity obtainable increases significantly. This *convergent* polymer-assisted solution-phase synthesis has been termed cPASP synthesis by our group.[11]

On-bead modification of 4-fluoro-3-nitrobenzoic acid opens the way to sterically demanding 4-aminobenzoic acid derivatives as well as heterocyclic ring systems. This route has been shown to be an especially attractive instrument to achieve diverse carboxylic acid equivalents on conventional linkers in solid-phase synthesis by many groups.[12−14] Thus, 4-fluoro-3-nitrobenzoic acid was initially attached to the sulfamoyl linker (not shown) via in situ anhydride formation yielding intermediate **41**. Subsequent treatment with excess amine converted **41** to the corresponding nitroaniline analogue **42** by nucleophilic substitution. Reduction of the nitro moiety in **42** proceeded under established conditions with excess tin(II) chloride in DMF.[15] The following acylation with propionic anhydride and final alkylation with bromoacetonitrile led to the activated building block **6a** ready for the chemoselective transfer to the amino function of the scaffold **5a**. Since alkylation with bromoacetonitrile as an activation step for aromatic building blocks often displays suboptimal results, prolonged reaction times (48 h) for this activation protocol were employed (Scheme 3).[16] In a similar fashion, analogues of **6** were effectively prepared using different primary and secondary amines and different carboxylic acids for the acylation of the aniline nitrogen atoms formed upon reduction (for R groups in structures **18**−**36** and **39**, see Figures 2 and 3).

In general, the target compounds could be obtained in good yield and purity. However, only the simpler constructs such as **7**−**15** and **17** resulting from a short modification sequence could be obtained in excellent yield and as a result in high

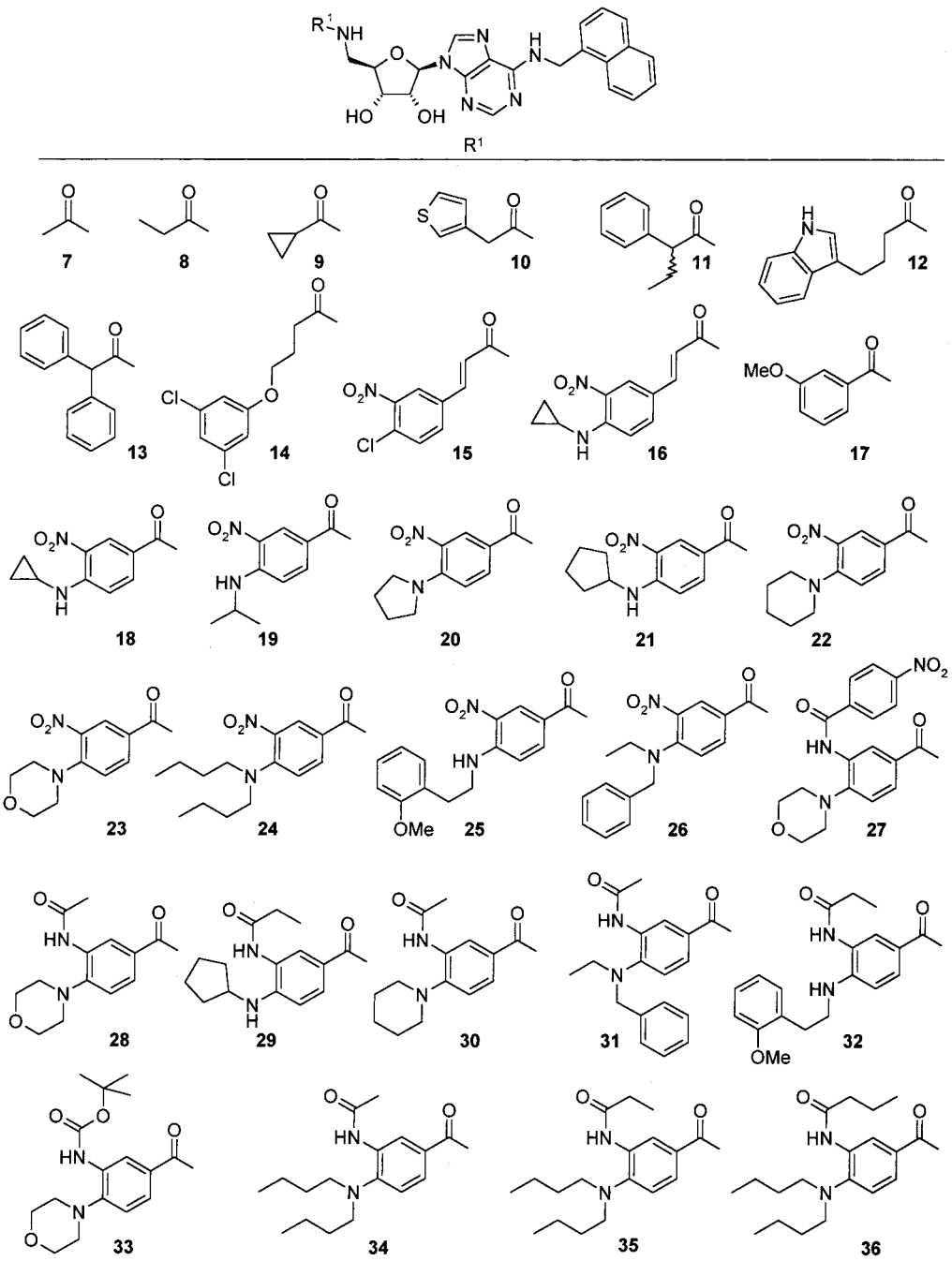


Figure 2. Structures of compounds **7**−**36**.

purity. These compounds could have been used for biological evaluation without resorting to chromatographic purification. Derivatives obtained from a multistep on-bead modification sequence in most cases did not meet the commonly accepted purity criterion of 80% purity prior to LC purification (see Table 1). In these cases, too, almost complete conversion of the starting material **5a** or **5b** could be deduced from TLC analysis, but because of incomplete formation of **41**, in the cases of **27**, **30**−**33**, and **39**, mixtures of two differently substituted 5′-amino-N^6-(arylalkyl)-5′-deoxyadenosines were obtained. This shared impurity resulted from the unintended formation of a second acylating species (e.g., **6** with $R^1 = CH_3$ or C_2H_5) by acylation of residual Kenner linker during amidation of the aniline nitrogen in polymer-bound intermediates such as **43**.

Another source for byproduct formation is the incomplete acylation of the aniline nitrogen formed upon reduction of the aromatic nitro group in compounds **27**−**36**, **39**, and **40**. As can be deduced from the results of the subset **34**−**36**, the increase of the size of the amide substituent adjacent to the secondary aniline nitrogen is unfavorable for a smooth conversion when the other aniline nitrogen is substituted with space-filling residues. The attempted synthesis of resin **44** failed because the homologue isovaleric acid residue could not be sufficiently introduced into resin **43** (Scheme 4). An attempt to use 4-chloro-3-nitro-*trans*-cinnamic acid attached to the Kenner safety-catch linker (**45**) for an analogous reaction was unsuccessful (Scheme 5). Treatment with primary aliphatic amines such as cyclopropylamine, subsequent activation of the linker, and transfer to scaffold **5a**

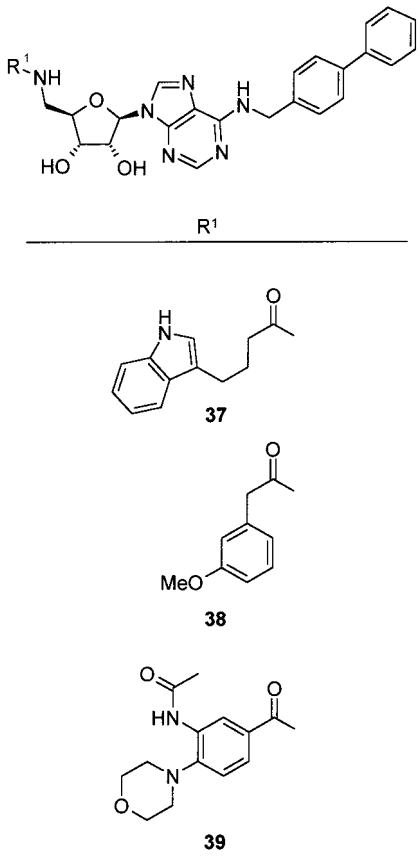
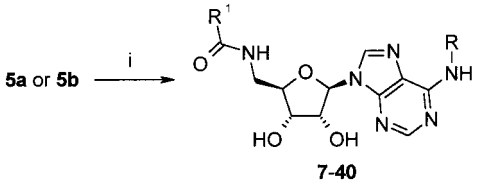


Figure 3. Structures of compounds **37**−**39**.

Scheme 2. Synthetic Approach Leading to 5′-Amido-5′-deoxy-N^6-(arylalkyl)adenosines **7**−**40** from templates **5a** and **5b**[a]



[a] (i) Carboxylic acid equivalents attached to the activated Kenner safety-catch linker (**6**), DMF or THF, room temperature.

did not produce the desired target compounds in sufficient purity. Regardless of these shortcomings, there is no superior preparation protocol for the more complex derivatives of this class of compounds to date.

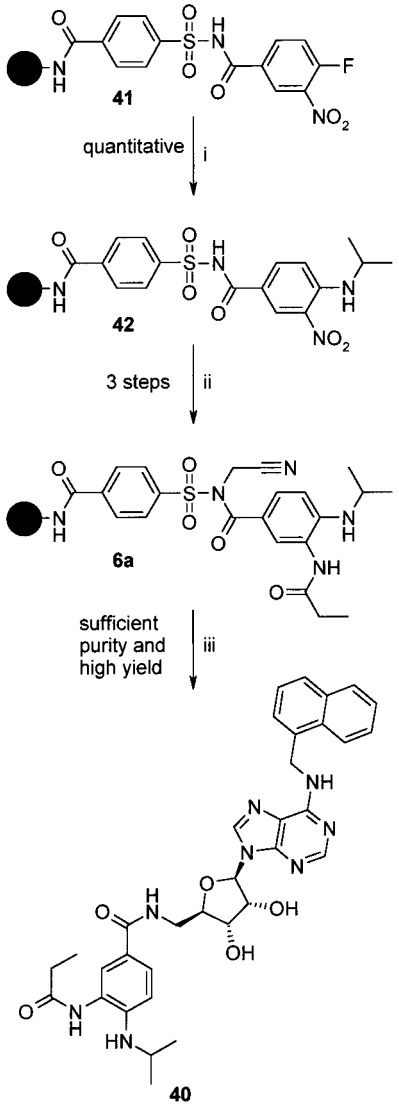
Biological Testing

Compounds **2**, **4**, **5**, **7**−**25**, **27**, **28**, **30**−**34**, and **36**−**40** were evaluated for their inhibitory activity against intraerythrocytic forms of *P. falciparum* using a semiautomated microdilution assay as described.[17−19] The growth of the parasites was monitored through the incorporation of tritium-labeled hypoxanthine. The results obtained are summarized below (Table 1).

Discussion

Only two especially attractive benzylic amines were selected for the synthesis of 33 novel and one known (**13**) N^6-5′-disubstituted adenosine derivatives. Using PASP and cPASP synthesis protocols, diversity fragments were introduced solely into the 5′-position of templates **5a** and **5b**,

Scheme 3. On-Bead Modification of a Polymer-Bound Building Block and Subsequent Chemoselective Transfer to Scaffold **5a**[a]



[a] (i) 1-Methylethylamine, DMF, 24 h; (ii) (a) $SnCl_2$, DMF, 48 h, (b) propionic anhydride, THF, DIEPA, DMAP, 24 h, (c) bromoacetonitrile, NMP, 48 h; (iii) **5a**, THF, 55 °C, 24 h.

leading to amidodeoxynucleosides **7**−**40** in fair to excellent yield. The reason for the selection of the 1-naphthyl and the biphenyl rings as fixed substituents in the N^6-position of the adenosine derivatives lies in the high probability of favorable lipophilic interactions with hydrophobic binding domains in biological systems, as discussed by Hajduk et al. recently.[20]

The second substituent, to be introduced into the 5′-postion of the modified adenosine scaffolds **5a** and **5b**, was chosen from a broad range of carboxylic acid residues. Because no information about a possible target-binding motif for the adenosine core was available, a considerable degree of diversity was regarded as necessary. The scope of the cPASP reaction applied for this purpose is considerable, but limitations were observed. When too large substituents on the aromatic ring adjacent the safety-catch linker are combined, the yield and the purity obtained are below the otherwise high standard and the products have to be purified by LC prior to biological evaluation. Generally speaking, the purity of the target compounds decreases with the extent of the

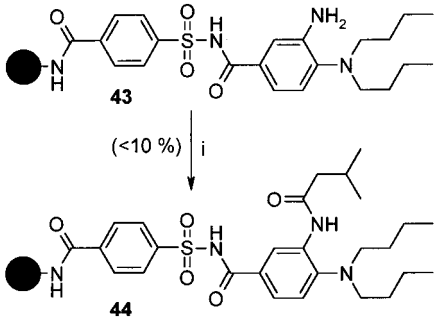
Table 1. Antimalarial Activity of Compounds **2**, **4**−**5**, **7**−**25**, **27**, **28**, **30**−**34**, and **36**−**40** and Yield and Indication of Sufficient Purity of Products **7**−**40** Originating from Polymer-Assisted Synthesis

compound	sufficient purity[a] (>80%)	yield,[a] %	IC_{50},[b] μM
2			42
4a			11
4b			4.3
5a			12
5b			2.1
7	prior to MPLC	97	23
8	prior to MPLC	87	15
9	prior to MPLC	97	11
10	prior to MPLC	86	11
11	prior to MPLC	92	6.2
12	prior to MPLC	97	8.5
13	prior to MPLC	92	6.2
14	prior to MPLC	91	10
15	prior to MPLC	95	5.3
16	not obtained	<10	4.8[c]
17	prior to MPLC	95	11
18	prior to MPLC	98	26[d]
19	after MPLC	67	4.1
20	after MPLC	79	15[d]
21	after MPLC	66	4.8
22	after MPLC	78	14[d]
23	after MPLC	66	4.8
24	after MPLC	64	4.2
25	prior to MPLC	92	1.3
26	prior to MPLC	91	nd
27	after MPLC	68	12
28	prior to MPLC	81	5.0
29	after MPLC	71	nd
30	prior to MPLC	54	4.2
31	after MPLC	59	3.3
32	after MPLC	58	2.7
33	after MPLC	47	3.1
34	after MPLC	72	3.7
35	after MPLC	52	nd
36	after MPLC	51	3.2
37	prior to MPLC	82	3.7
38	after MPLC	65	14
39	after MPLC	71	3.2
40	prior to MPLC	81	3.2

[a] All compounds were purified by a single semipreparative midpressure LC (MPLC) run under standard conditions that were not optimized for each individual compound. Product-containing fractions were collected and evaporated, and the yield of pure compounds obtained is reported above. Purity was estimated using the 100% method, UV detection at 254 nm. Sample **16** could not be purified sufficiently by a single MPLC run. [b] The *P. falciparum* strain Dd2 (Indochina) used in this study is resistant to most commonly used antimalarial drugs. When the resistance pattern was checked in our laboratory, the Dd2 strain was found to be highly resistant against chloroquine (IC_{50} = 170 nM), pyrimethamine (IC_{50} = 2500 nM), and cycloguanile (IC_{50} = 2200 nM) and was moderately resistant against quinine (IC_{50} = 380 nM) and mefloquine (IC_{50} = 57 nM). It was sensitive to halofantrine (IC_{50} = 18 nm), lumefantrine (IC_{50} = 30 nm), artemisinin (IC_{50} = 18 nm), and atovaquone (IC_{50} = 1 nm). [c] Mixture of compounds **15** and **16**. [d] *P. falciparum* strain 236.

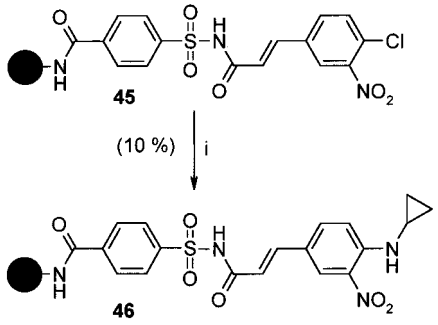
SPOS modification sequence. Further optimization of the individual transformation steps is necessary and should prevent time-consuming chromatographic purification in the future. The formation of the side products **7** and **8** in the cases of acylated aniline derivatives **30**−**32** and **39**, respectively, is reduced when no DMAP is added as the acylation catalyst during the introduction of the acetyl or propionyl group in **28**, **29**, and **34**−**36**. In the presence of DMAP, acetic anhydride or propionic anhydride acylates residual sulfamoyl groups of the linker that were not acylated by 4-fluoro-3-nitrobenzoic acid. Therefore, after cyano methylation, they form a second acylating species (e.g., **6** with $R^1 = CH_3$ or C_2H_5) and the byproducts **7** and **8** are formed along with the desired products and have to be removed by LC. A general solution to this problem is to ensure complete acylation during the first attachment by repeated immobilization of the first and desired carboxylic acid. In the case of expensive carboxylic acids, this might be undesirable. Alternatively, a capping step with bulky, sterically hindered acids is possible. The straightforward way already mentioned above is to avoid the strong acylation catalyst DMAP for further acylation steps. When a less powerful catalyst like 1-hydroxybenzotriazole (HOBt) was applied instead of DMAP in the cases of **28**, **29**, and **34**−**36**, practically no acylation of residual sulfamoyl groups of the linker is observed and consequently no byproducts **7** and **8** were formed.

Scheme 4[a]



[a] Acylation of **43** to **44** could not be driven to completion. (i) Isovaleric acid anhydride, DMAP, DIPEA, THF, 24 h.

Scheme 5[a]



[a] Because of poor conversion rates of the aminolysis (about 10%) of **45** to **46**, 4-chloro-3-nitro-*trans*-cinnamic acid did not prove to be suited for the on-bead modification depicted above. (i) Cyclopropylamine, DMF, 24 h.

By comparison of the purity obtained of N^6-naphthylmethyl- and N^6-biphenylmethyladenosine analogues, the use of N^6-biphenylmethyladenosine as a rule leads to a decrease of product purity of the derivatives obtained. This might partly be attributed to possible alteration of the polymer-bound building blocks during storage, but the small set of biphenyl derivatives **37**−**39** prepared so far does not allow drawing of a conclusion. More often than not, we were unable to detect a difference in conversion rate between different related amino deoxyadenosine derivatives in the final amidation step.

Despite considerable structural diversity, most of the N^6,5′-substituted adenosine derivatives displayed moderate but significant antimalarial activity. Obviously a small amide residue such as compound **7** is inferior to the parent amino compound or is in the same range of activity in the cases of slightly larger residues as seen in derivatives **8** and **9**. Large, lipophilic aniline-derived residues such as compounds **25**, **31**, **32**, and **36** lead to increased activity in the low micromolar range (1.3−3.3 μM). While the higher initial activity of scaffold **4b** suggested a possible increase in activity by replacing the naphthyl ring for a biphenyl moiety, this hope was not fulfilled in the in vitro experiments. Compounds **37** and **39** exhibit activity that is comparable to the activity of the compounds from the naphthyl series but are not superior to the parent compound **4b**, which displayed an IC_{50} value of 2.1 μM.

Conclusion

In addition to diverse N^6-monosubstituted adenosine derivatives discussed in part 1 of this investigation, the novel series of N^6,5′-disubstituted adenosine analogues displays significant activity versus the malaria-causing parasite in vitro. With respect to the different modification patterns of these different adenosines, it can be concluded that not a single molecular target is recognized, as we suggested earlier.[3] Potential targets include a variety of nucleotide-dependent enzymes, the parasite's nucleoside uptake machinery, and unrelated cell functions. To further explore their potential as antimalarial agents, selected N^6-substituted adenosine derivatives will be immobilized on biosensor chip surfaces via a biotin label in the 5′-position of 5′-amino-5′-deoxy derivatives. This approach seems feasible because the in vitro data from this study suggests that the biological activity is highly robust to alterations in this area of the molecule. The intended ligand fishing from different fractions from plasmodial proteins might become a valuable tool for the further understanding of the capability of nontoxic nucleoside derivatives to inhibit parasitic protozoa in humans.[21] A suitable method for the biotin labeling and immobilization of the chemical probes is under way. Preliminary results have been published recently.[22]

Experimental Section

The structures of all compounds were assigned by NMR spectroscopy. NMR spectra were recorded on a Bruker AMX 400 spectrometer, using tetramethylsilane as the internal standard. Identity and purity of compounds prepared on a larger (gram) scale were ascertained by combustion analysis, and test samples prepared in milligram quantities were evaluated by high-resolution MS. The purity of the latter compounds was deduced from ^{1}H NMR data as well as evaluated by LC. Elemental compositions were calculated on the basis of microanalysis results obtained on a Heraeus CHN−O rapid instrument. High-resolution MS data were obtained on a Finnigan MAT 95 XL (ESI, methanol/water (1/1, v/v) infusion at 2 μL/min with polypropylene glycol as reference) or a Micromass VG 70-250 S (FAB, *m*-nitrobenzylic alcohol as matrix with poly(ethylene glycol) as reference) instrument. Preparative column chromatography was performed using glass columns (4.5 cm × 15 cm) on silica gel 100−200 active, 60 A, from ICN or Dowex OH^- (1 × 2−200). TLC reaction control was performed on Macherey-Nagel Polygram Sil G/UV_{254} precoated microplates, and spots were visualized under UV illumination at 254 nm.

1-(6-Chloropurin-9-yl)-*β*-d-1,5-dideoxy-(5-phthalimido)-ribofuranose (2). To 1-(6-chloro-purin-9-yl)-β-D-1-deoxy-ribofuranose (**1**) (6.0 g, 21 mmol), phthalimide (7.70 g, 52 mmol, 2.5 equiv), and triphenylphosphin (13.72 g, 52 mmol, 2.5 equiv) freshly dried THF (150 mL) was added, and the resulting suspension was cooled to −20 °C. Then, di-*tert*-butyldiazocarboxylate (12.0 g, 52 mmol, 2.5 equiv) was added and the mixture was stirred first for 30 min at −20 °C and then at room temperature for 24 h. The dark-yellow suspension initially formed turned into a light-yellow solution after 5 min. After 24 h, the solution was evaporated in vacuo and the resulting brownish sticky residue was crystallized from CH_2Cl_2/MeOH (95:5) to give **2**, with ^{1}H NMR analytical data comparable to those reported and with convincing data from additional ^{13}C NMR and combustion analyses.[7] Yield: 79%. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.97 (s, 1H, 8H), 8.61 (s, 1H, 2H), 7.85 (s, 4H, phthalimido), 6.03 (d, 1H, 1′H, J = 5.1 Hz), 5.66 (d, 1H, 3′OH, J = 5.6 Hz), 5.45 (d, 1H, 2′OH, J = 5.6 Hz), 4.85−4.81 (m, 1H, 2′H), 4.33−4.30 (m, 1H, 3′H), 4.23−4.19 (m, 1H, 4′H), 4.02−3.91 (m, 2H, 5′CH_2). HRFAB-MS $[M + H]^+$: calcd 416.0762, found 416.0749. $C_{18}H_{14}ClN_5O_5$: calcd C 52.00, H 3.39, Cl 8.53, N 16.84; found C 51.93, H 3.51, Cl 8.74, N 16.44.

***N*^{6}-[(4-Phenyl)benzyl]adenosine (3).** To a solution of 1-(6-chloro-purin-9-yl)-β-D-1-deoxyribofuranose (**1**) in *n*-propanol was added 1.1 equiv of (4-phenyl)benzylamine and 1 equiv of Hünig's base. The reaction mixture was stirred at 60 °C. The reaction was monitored by TLC and was terminated when the starting material had disappeared (12−24 h). The resulting solid was crystallized from MeOH. ^{1}H NMR data are as reported.[3] HRFAB-MS $[M + H]^+$: calcd 434.1829, found 434.1848.

5′-Deoxy-*N*^{6}-(1-naphthylmethyl)-5′-phthalimidoadenosine (4a). To a suspension of 1-aminomethylnaphthalene (1.0 g, 6.38 mol, 1.1 equiv) in absolute ethanol (50 mL) **2** (2.41 g, 5.8 mol) was added, and the reaction mixture was stirred at 50 °C for 30 min. Hünig's base (0.374 g, 2.9 mmol, 0.5 equiv) was added, and the reaction mixture was further agitated at 50 °C for 24 h. Because the conversion of **2** to **4a** was incomplete, another equivalent of 1-aminomethylnaphthalene (0.91 g, 5.8 mmol) and of Hünig's base (0.75 g, 5.8 mmol) were added to the reaction mixture, and again, the mixture was stirred for 48 h at 50 °C. The mixture was evaporated in vacuo. The resulting material was crystallized from MeOH, and a white solid was obtained. Yield: 91%. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.42 (bs, 2H, N^6H overlapping 8H), 8.24 (m, 1H, naphthyl), 8.01 (s, 1H, 2H), 7.96−7.94 (m, 1H, naphthyl), 7.87−7.81 (m, 5H, 1H naphthyl overlapping 4H phthalimido), 7.59−7.53 (m, 2H, naphthyl), 7.45−7.41 (m, 2H, naphthyl), 5.90 (d, 1H, 1′H, J = 5.6 Hz), 5.53 (d, 1H, 3′OH, J = 6.1 Hz), 5.34 (d, 1H, 2′OH, J = 5.08 Hz), 5.17 (bs, 2H, CH_2, naphthylmethyl),

4.81−4.80 (m, 1H, 2′H), 4.28−4.27 (m, 1H, 3′H), 4.17−4.13 (m, 1H, 4′H), 4.01−3.96 (m, 1H, 5′CH_2), 3.89−3.84 (m, 1H, 5′CH_2). HRESI-MS $[M + H]^+$: calcd 537.1886, found 537.1890. $C_{29}H_{24}N_6O_5 \cdot {}^1/_2H_2O$: calcd C 63.83, H 4.58, N 15.40; found C 63.83, H 4.42, N 15.19.

***N*⁶-(1-Biphenylmethyl)-5′-deoxy-5′-phthalimidoadenosine (4b).** To **3** (0.78 g, 1.8 mmol), phthalimide (0.589 g, 4 mmol), and triphenylphosphin (1.048 g, 4 mmol) freshly dried THF (14 mL) was added, and the resulting suspension was cooled to −20 °C. Then, di-*tert*-butyldiazocarboxylate (0.92 g, 4 mmol) was added and the mixture was stirred first for 30 min at −20 °C and then at room temperature, resulting in a dark-yellow suspension, which turned into a light-yellow solution after 5 min. After 12 h the conversion of **3** to **4b** was completed. The solution was evaporated in vacuo, and the resulting solid residue was crystallized from MeOH to give pure **4b**. Yield: 84%. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.45 (bs, 1H, N⁶H), 8.41 (s, 1H, 8H), 8.01 (bs, 1H, 2H), 7.87−7.81 (m, 4H, phthalimido), 7.64−7.58 (m, 4H, biphenyl), 7.46−7.41 (m, 4H, biphenyl), 7.35−7.32 (m, 1H, biphenyl), 5.89 (d, 1H, 1′H, J = 5.3 Hz), 5.53 (d, 1H, 3′OH, J = 5.9 Hz), 5.34 (d, 1H, 2′OH, J = 5.1 Hz), 4.81−4.77 (m, 1H, 2′H), 4.73 (bs, 2H, CH_2, biphenylmethyl), 4.29−4.26 (m, 1H, 3′H), 4.17−4.12 (m, 1H, 4′H), 4.01−3.96 (m, 1H, 5′CH_2), 3.89−3.84 (m, 1H, 5′CH_2). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 167.75, 152.32, 139.95, 139.25, 138.52, 134.36, 131.45, 128.78, 127.65, 127.14, 126.47, 123.0, 87.78, 81.26, 72.53, 71.42. HRESI-MS $[M + H]^+$: calcd 563.2043, found 563.2028. $C_{31}H_{26}N_6O_5 \cdot {}^1/_2H_2O$: calcd C 65.14, H 4.76, N 14.70; found C 65.46, H 4.67, N 14.80.

5′-Amino-5′-deoxy-*N*⁶-(1-naphthylmethyl)adenosine (5a). A suspension of **4a** (1 g, 1.86 mmol) and hydrazine hydrate (0.153 g, 3 mmol) in ethanol (150 mL) was stirred for 30 min at 50 °C and successively refluxed for 1 h, with the precipitate being dissolved completely after 5 min of refluxing. After the mixture was cooled to room temperature, one-half of the solvent of the reaction mixture was evaporated in vacuo. The resulting precipitate, phthalazid, was separated from the reaction mixture, which subsequently was further evaporated leading to a brownish, highly viscous liquid. The product was purified over Dowex OH^- (1 × 2−200) with MeOH/H_2O gradients as eluent and gave ^{1}H NMR analytical data comparable to those reported and convincing data from additional ^{13}C NMR and combustion analyses.[7] Yield: 77%. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.45 (bs, 1H, N⁶H), 8.42 (bs, 1H, 8H), 8.25 (m, 1H, naphthyl), 8.22 (s, 1H, 2H), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.80 (m, 1H, naphthyl), 7.59−7.52 (m, 2H, naphthyl), 7.46−7.40 (m, 2H, naphthyl), 5.88 (d, 1H, 1′H, J = 6.3 Hz), 5.42 (bs, 1H, 3′OH), 5.18 (bs, 3H, 1H, 2′OH overlapping CH_2 naphthylmethyl), 4.71 (m, 1H, 2′H), 4.17−4.15 (m, 1H, 3′H), 3.89−3.86 (m, 1H, 4′H), 2.85−2.81 (m, 1H, 5′CH_2), 2.77−2.72 (m, 1H, 5′CH_2), 2.32−1.43 (bs, 2H, NH_2). HRESI-MS $[2M + H]^+$: calcd 813.3585, found 813.3587. $C_{21}H_{22}N_6O_3 \cdot {}^1/_2H_2O$: calcd C 60.65, H 5.54, N 20.22; found C 60.33, H 5.45, N 19.98.

5′-Amino-*N*⁶-(1-biphenylmethyl)-5′-deoxyadenosine (5b). A suspension of **4b** (1 g, 1.8 mmol) and hydrazine hydrate (0.180 g, 3.6 mmol) in ethanol/THF 1:1 (150 mL) was stirred for 30 min at 50 °C, successively refluxed for 4 h, and then stirred at room temperature over the weekend. Because the conversion was incomplete, hydrazine hydrate (0.18 g, 3 mmol) was added again, and the mixture was stirred at 50 °C and subsequently refluxed for 6 h. One-half of the solvent of the reaction mixture was evaporated in vacuo. The resulting precipitate, phthalazid, was separated from the reaction mixture, which subsequently was further evaporated leading to a brownish, highly viscous liquid. The product was purified over Dowex OH^- (1 × 2−200) with MeOH/H_2O gradients as eluent. Yield: 40%. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.44 (bs, 1H, N⁶H), 8.41 (s, 1H, 8H), 8.22 (s, 1H, 2H), 7.63−7.58 (m, 4H, biphenyl), 7.46−7.42 (m, 4H, biphenyl), 7.35−7.31 (m, 1H, biphenyl), 5.86 (d, 1H, 1′H, J = 6.1 Hz), 5.39 (d, 1H, 3′OH, J = 5.9 Hz), 5.10 (bs, 1H, 2′OH), 4.75 (bs, 2H, CH_2, biphenylmethyl), 4.71−4.69 (m, 1H, 2′H), 4.15−4.12 (m, 1H, 3′H), 3.88−3.85 (m, 1H, 4′H), 2.85−2.80 (m, 1H, 5′CH_2), 2.76−2.72 (m, 1H, 5′CH_2), 1.69−1.41 (bs, 2H, NH_2). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 152.40, 140.05, 139.95, 139.25, 138.47, 128.77, 127.60, 127.14, 126.44, 87.36, 86.15, 72.91, 70.69, 43.10. HRESI-MS $[M + H]^+$: calcd 433.1989, found 433.1968. $C_{23}H_{24}N_6O_3$: calcd C 63.88, H 5.59, N 19.43; found C 63.63, H 5.63, N 19.04.

General Procedure A for the Synthesis of Simple Polymer-Supported Acids. To a flask containing 2.0 g of dry 4-sulfamoylbenzoylaminomethylpolystyrene with an initial loading level of 1.24 mmol/g as determined by elemental analysis (prepared from very high load aminomethylated polystyrene, purchased from Novabiochem, Switzerland, batch number A20540) was added 20 mL of THF. The resin was allowed to swell at room temperature for 2 h. In another flask, 10 mmol of the appropriate acid was dissolved in 10−20 mL of dry THF and was preactivated via in situ anhydride formation by adding 780 μL (5 mmol) of *N*,*N*-diisopropylcarbodiimide. *CAUTION*: *N*,*N*-Diisopropylcarbodiimide may lead to severe allergic reactions. Strictly avoid skin contact. After addition of 580 μL of Hünig's base (3.4 mmol) and 15 mg (0.12 mmol) of 4-(dimethylamino)-pyridine (DMAP) as catalyst to the swollen resin, the coupling mixture was added. The resulting reaction mixture was agitated at room temperature for 24 h. The resin beads were filtered off and washed exhaustively with DMF (three times 5 mL), dichloromethane (three times 5 mL), and methanol (three times 5 mL). After careful drying, the increase in weight was determined. The success of the reaction could be followed by IR spectroscopy, too: the acylation of the sulfonamide linker leads to a decrease of the intensity of the sulfonamide absorption at 3340 cm^{-1}, while a new carbonyl stretch at 1718 cm^{-1} is formed.

General Procedure B for the Synthesis of the On-Bead-Modified Polymer-Supported Acids Resulting in Final Compounds 18−36, 39, and 40. To a flask containing 52.0 g of dry 4-sulfamoylbenzoylaminomethylpolystyrene with an initial loading level of 1.24 mmol/g as determined by elemental analysis (prepared from very high load aminomethylated polystyrene, purchased from Novabiochem, Switzerland, batch number A20540) was added 500 mL of THF. The resin was allowed to swell at room temperature

for 2 h. In another flask, 44.4 g (240 mmol) of 4-fluoro-3-nitrobenzoic acid was dissolved in 500 mL of dry THF and was preactivated via in situ anhydride formation by adding 18.6 mL (120 mmol) of *N*,*N*-diisopropylcarbodiimide overnight. After addition of 15 mL of Hünig's base (88 mmol) and 500 mg (4.1 mmol) of DMAP as catalyst to the swollen resin, the coupling mixture was added. The resulting reaction mixture was agitated at room temperature for 48 h. The resin beads were filtered off and washed exhaustively with DMF (three times), CH_2Cl_2 (three times), and methanol (three times), resulting in 53.48 g of resin after careful drying in vacuo. This weight increase of 11.48 g corresponds to a practically quantitative conversion of 4-sulfamylbenzamidomethylpolystyrene to [(4-fluoro-3-nitrobenzoyl)-4-sulfamyl]-benzamidomethylpolystyrene **41**, resulting in a loading level of 1.00 mmol/g. For the derivatization of **41** to the appropriate resins to subsequently give final compounds **18**−**26**, 2.0 g of **41** (2.0 mmol) was treated with 20 mmol of the appropriate amine in 25 mL of DMF overnight, and the mixture was subsequently washed with DMF (3 × 5 mL) and methanol (3 × 5 mL). The color of the resin beads changed from white to dark-orange. To each 2.0 g of the appropriate nitroaniline resins thus obtained, 40 mL of a 2 M tin(II) chloride solution in DMF was added. The resin suspensions were agitated for 48 h at room temperature and subsequently washed with DMF (3 × 5 mL) and MeOH (3 × 5 mL). The color of the resin beads changed from orange to yellow. The resulting dianiline resins were agitated with 40 mL of THF, Hünig's base (0.580 mL, 3.4 mmol), DMAP (0.02 g, 0.15 mmol) as catalyst, and the appropriate anhydride (5 mmol) for 24 h, leading to target compounds **27**, **30**−**33**, and **39**. The resin beads were filtered off and washed exhaustively with DMF (3 × 5 mL), CH_2Cl_2 (3 × 5 mL), and MeOH (3 × 5 mL). To reduce unwanted byproduct formation caused by acylation of uncapped sulfamoyl linker groups, these experiments were repeated by replacing DMAP by HOBt (0.80 g, 5.9 mmol) as catalyst for the acylation of the dianiline resins, resulting in final compounds **28**, **29**, and **34**−**36**.

General Procedure C for the Activation of Polymer-Supported Acids Leading to 6. The sulfonamide linker of the appropriate resins (approximately 0.4 mmol) was activated for cleavage by alkylation with 640 μL (9 mmol) of bromoacetonitrile (*CAUTION*: alkylating agent; strictly avoid skin contact) and 340 μL (2 mmol) of Hünig's base in 4 mL of 1-methylpyrrolidone for 12−48 h. The dark-brown slurry was washed with dry dimethyl sulfoxide (5 × 5 mL) and THF (3 × 10 mL), leading to white, yellow, and orange resin particles, respectively.

General Procedure D for the Synthesis of Compounds 7−**40.** The activated polymer-supported acids resulting from the alkylation of appropriate resins (approximately 0.4 mmol) described above were transferred to the amino groups of 10 μmol of the appropriate amino template **5a** dissolved in 1 mL of THF and of **5b** dissolved in 1 mL of NMP, respectively, by shaking at 55 °C in 4 mL of THF. The reaction was monitored by TLC and terminated when the starting material was quenched (12−48 h). Polymer beads and particulates were removed by filtration, the beads where extracted exhaustively with dry THF and methanol, and the combined fractions were evaporated to furnish the target compounds.

5′-Acetamido-5′-deoxy-N^6-(1-naphthylmethyl)adenosine (7). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.51 (bs, 1H, N^6H), 8.39 (bs, 1H, 8H), 8.25−8.23 (m, 3H, naphthyl overlapping NH amide overlapping 2H), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.81 (m, 1H, naphthyl), 7.59−7.52 (m, 2H, naphthyl), 7.44−7.41 (m, 2H, naphthyl), 5.88 (d, 1H, 1′H, J = 6.1 Hz), 5.47 (d, 1H, 3′OH, J = 6.1 Hz), 5.27 (d, 1H, 2′OH, J = 5.1 Hz), 5.19 (bs, 2H, CH_2, naphthylmethyl), 4.71−4.70 (m, 1H, 2′H), 4.06−4.03 (m, 1H, 3′H), 3.96−3.93 (m, 1H, 4′H), 1.85 (s, 3H, CH_3, acetamido). HRESI-MS $[M + Na]^+$: calcd 471.1757, found 471.1764.

5′-Deoxy-N^6-(1-naphthylmethyl)-5′-propanamidoadenosine (8). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.48 (bs, 1H, N^6H), 8.37 (bs, 1H, 8H), 8.24−8.23 (m, 2H, 2H overlapping naphthyl), 8.11 (t, 1H, NH, amide, J = 5.5 Hz), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.80 (m, 1H, naphthyl), 7.59−7.52 (m, 2H, naphthyl), 7.47−7.41 (m, 2H, naphthyl), 5.87 (d, 1H, 1′H, J = 6.4 Hz), 5.44 (d, 1H, 3′OH, J = 5.9 Hz), 5.24 (d, 1H, 2′OH, J = 4.3 Hz), 5.19 (bs, 2H, CH_2, naphthylmethyl), 4.71−4.67 (m, 1H, 2′H), 4.06−4.03 (m, 1H, 3′H), 3.97−3.94 (m, 1H, 4′H), 3.41−3.36 (m, 2H, 5′CH_2), 2.15−2.09 (m, 2H, CH_2, propanamido), 0.99 (t, 3H, CH_3, propanamido, J = 7.6 Hz). HRESI-MS $[M + Na]^+$: calcd 485.1913, found 485.1913.

5′-Cyclopropanamido-5′-deoxy-N^6-(1-naphthylmethyl)-adenosine (9). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.51 (s, 1H, N^6H), 8.44 (t, 1H, NH, amide, J = 5.2 Hz), 8.39 (bs, 1H, 8H), 8.25−8.23 (m, 2H, 2H overlapping naphthyl), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.81 (m, 1H, naphthyl), 7.59−7.53 (m, 2H, naphthyl), 7.44−7.41 (m, 2H, naphthyl), 5.89 (d, 1H, 1′H, J = 6.6 Hz), 5.49 (d, 1H, 3′OH, J = 6.6 Hz), 5.29 (d, 1H, 2′OH, J = 5.1 Hz), 5.18 (bs, 2H, CH_2, naphthylmethyl), 4.72−4.71 (m, 1H, 2′H), 4.06−4.04 (m, 1H, 3′H), 3.96−3.94 (m, 1H, 4′H), 1.62−1.56 (m, 1H, cyclopropyl), 0.67−0.63 (m, 4H, CH_2, cyclopropyl). HR-FAB-MS $[M + H]^+$: calcd 475.2095, found 475.2112.

5′-Deoxy-N^6-(1-naphthylmethyl)-5′-[(3-thienyl)acetamido]adenosine (10). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.46 (bs, 1H, N^6H), 8.36 (bs, 1H, 8H), 8.31 (t, 1H, amide, J = 5.7 Hz), 8.25−8.24 (m, 2H, naphthyl overlapping 2H), 7.96−7.94 (m, 1H, naphthyl), 7.82−7.80 (m, 1H, naphthyl), 7.59−7.52 (m, 2H, naphthyl), 7.47−7.40 (m, 3H, 2H naphthyl overlapping 1H thienyl), 7.21 (m, 1H, thienyl), 7.00−6.99 (m, 1H, thienyl), 5.88 (d, 1H, 1′H, J = 6.1 Hz), 5.44 (bs, 1H, 3′OH), 5.25 (bs, 1H, 2′OH), 5.18 (bs, 2H, CH_2, naphthylmethyl), 4.71−4.67 (m, 1H, 2′H), 4.08−4.05 (m, 1H, 3′H), 3.98−3.94 (m, 1H, 4′H), 3.47 (s, 2H, CH_2, 3-thienylacetamido). HRESI-MS $[M + H]^+$: calcd 531.1815, found 531.1824.

5′-Deoxy-N^6-(1-naphthylmethyl)-5′-(2-phenylbutanamido)adenosine (11) (Mixture of Two Diastereomers). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.48 (bs, 1H, N^6H), 8.36−8.30 (m, 2H, NH amide overlapping 8H), 8.26−8.24 (m, 2H, naphthyl overlapping 2H), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.81 (m, 1H, naphthyl), 7.59−7.52 (m, 2H, naphthyl), 7.47−7.41 (m, 2H, naphthyl), 7.32 (m, 5H,

benzene), 5.85 (t, 1H, 1′H, $J = 5.6$ Hz), 5.45 (bs, 1H, 3′OH), 5.19 (bs, 3H, 2′OH overlapping CH_2 naphthylmethyl), 4.71−4.68 (m, 0.5 H, 2′H), 4.57−4.54 (m, 0.5H, 2′H), 4.06−4.04 (m, 0.5H, 3′H), 3.95−3.92 (m, 1.5 H, 4′H overlapping 3′H), 1.97−1.89 (m, 1H, CH_2, 2-phenylbutanamido), 1.64−1.55 (m, 1H, CH_2, 2-phenylbutanamido), 0.78 (m, 3H, CH_3). HRESI-MS $[M + H]^+$: calcd 553.2564, found 553.2579.

5′-Deoxy-5′-[4-(3-indolyl)butanamido]-*N*^{6}-(1-naphthylmethyl)adenosine (12). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.73 (s, 1H, NH, indolyl), 8.50 (bs, 1H, N^{6}H), 8.39 (bs, 1H, 8H), 8.25−8.23 (m, 1H, naphthyl), 8.21 (s, 1H, 2H), 8.20−8.18 (m, 1H, NH, amide), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.81 (m, 1H, naphthyl), 7.59−7.52 (m, 2H, naphthyl), 7.49−7.40 (m, 3H, 1H indolyl overlapping 2H naphthyl), 7.32 (d, 1H, indolyl, $J = 8.1$ Hz), 7.08 (m, 1H, indolyl), 7.05−7.01 (m, 1H, indolyl), 6.95−6.91 (m, 1H, indolyl), 5.87 (d, 1H, 1′H, $J = 6.6$ Hz), 5.46 (d, 1H, 3′OH, $J = 6.6$ Hz), 5.27 (d, 1H, 2′OH, $J = 4.6$ Hz), 5.19 (bs, 2H, CH_2, naphthylmethyl), 4.73−4.68 (m, 1H, 2′H), 4.07−4.04 (m, 1H, 3′H), 3.99−3.95 (m, 1H, 4′H), 2.65 (t, 2H, CH_2, butyryl, $J = 7.6$ Hz), 2.20 (t, 2H, CH2, butyryl, $J = 7.5$ Hz), 1.90−1.83 (m, 2H, CH_2, butyryl). HRESI-MS $[M + H]^+$: calcd 592.2673, found 592.2666.

5′-Deoxy-5′-diphenylacetamido-*N*^{6}-(1-naphthylmethyl)-adenosine (13). Analytical data as reported.[7] ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.54 (t, 1H, NH, amide, $J = 5.6$ Hz), 8.46 (bs, 1H, N^{6}H), 8.33 (bs, 1H, 8H), 8.25−8.22 (m, 2H, naphthyl overlapping 2H), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.80 (m, 1H, naphthyl), 7.59−7.52 (m, 2H, naphthyl), 7.47−7.40 (m, 2H, naphthyl), 7.29−7.25 (m, 8H, phenyl), 7.23−7.16 (m, 2H, phenyl), 5.87 (d, 1H, 1′H, $J = 6.1$ Hz), 5.43 (bs, 1H, 3′OH), 5.27 (bs, 1H, 2′OH), 5.19 (bs, 2H, CH_2, naphthylmethyl), 4.98 (s, 1H, CH, diphenylmethyl), 4.65 (bs, 1H, 2′H), 4.06−4.03 (m, 1H, 3′H), 3.98−3.94 (m, 1H, 4′H), 3.53−3.36 (m, 2H, 5′CH_2). HRESI-MS $[M + H]^+$: calcd 601.2564, found 601.2562.

5′-[4-(2,4-Dichlorphenoxy)butanamido]-5′-deoxy-*N*^{6}-(1-naphthylmethyl)adenosine (14). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.49 (bs, 1H, N^{6}H), 8.35 (bs, 1H, 8H), 8.26 (s, 1H, 2H), 8.24−8.22 (m, 1H, naphthyl), 7.83−7.80 (m, 1H, naphthyl), 7.59−7.52 (m, 2H, naphthyl), 7.51 (d, 1H, aromatic, $J = 2.5$ Hz), 7.46−7.40 (m, 2H, naphthyl), 7.38−7.35 (m, 2H, aromatic), 7.13 (d, 1H, naphthyl, $J = 8.9$ Hz), 5.90 (d, 1H, 1′H, $J = 6.1$ Hz), 5.45 (d, 1H, 3′OH, $J = 6.4$ Hz), 5.26 (d, 1H, 2′OH, $J = 4.8$ Hz), 5.18 (bs, 2H, 2H, CH_2 naphthylmethyl), 4.80−4.75 (m, 1H, 2′H), 4.17−4.15 (m, 1H, 3′H), 3.89−3.86 (m, 1H, 4′H), 2.35−2.32 (m, 2H, CH_2 butanamido), 2.00−1.92 (m, 2H, CH_2 butanamido). HRESI-MS $[M + Na]^+$ calcd 659.1552, found 659.1540.

5′-{*trans*-3-[(4-Chloro-3-nitro)phenyl]prop-2-enamido}-5′-deoxy-*N*^{6}-(1-naphthylmethyl)adenosine (15). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.47−8.40 (m, 3H, NH amide overlapping N^{6}H overlapping 8H), 8.27−8.23 (m, 3H, naphthyl overlapping 2H overlapping cinnamoyl), 7.96−7.94 (m, 1H, naphthyl), 7.89−7.86 (m, 1H, cinnamoyl), 7.83−7.78 (m, 2H, naphthyl overlapping cinnamoyl), 7.59−7.41 (m, 5H, 4H naphthyl, 1H cinnamoyl), 6.83 (d, 1H, cinnamoyl, $J = 16.0$ Hz), 5.91 (d, 1H, 1′H, $J = 6.1$ Hz), 5.48 (d, 1H, 3′OH, $J = 6.1$ Hz), 5.30 (d, 1H, 2′OH, $J = 4.83$ Hz), 5.19 (bs, 2H, CH_2, naphthylmethyl), 4.74−4.72 (m, 1H, 2′H), 4.15−4.11 (m, 1H, 3′H), 4.04−4.00 (m, 1H, 4′H). HRESI-MS $[M + H]^+$: calcd 617.1712, found 617.1711.

5′-Deoxy-5′-{*trans*-3-[(3-nitro-4-propylamino)phenyl]-prop-2-enamido}-*N*^{6}-(1-naphthylmethyl)adenosine (16). Mixture of compounds **15** and **16**. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.46 (t, 1H, NH, amide, $J = 6.1$, 5.9 Hz), 8.40 (bs, 2H, N^{6}H overlapping 8H), 8.27−8.23 (m, 3H, naphthyl overlapping 2H overlapping cinnamic acid), 7.96−7.94 (m, 1H, naphthyl), 7.89−7.86 (m, 1H, cinnamic acid), 7.83−7.78 (m, 2H, naphthyl overlapping cinnamic acid), 7.59−7.40 (m, 5H, 4H naphthyl, 1H cinnamic acid), 6.83 (d, 1H, cinnamic acid, $J = 15.8$ Hz), 5.91 (d, 1H, 1′H, $J = 6.1$ Hz), 5.47 (d, 1H, 3′OH, $J = 6.1$ Hz), 5.29 (d, 1H, 2′OH, $J = 4.8$ Hz), 5.19 (bs, 2H, CH_2, naphthylmethyl), 4.75−4.71 (m, 1H, 2′H), 4.15−4.12 (m, 1H, 3′H), 4.04−4.00 (m, 1H, 4′H), 3.62−3.51 (m, 2H, 5′H), 0.89−0.86 (m, 0.2H, CH_2, cyclopropyl), 0.65 (m, 0.2H, CH_2, cyclopropyl). HRESI-MS $[M + Na]^+$: calcd 659.2342, found 659.2326.

5′-(3-Methoxybenzamido)-5′-deoxy-*N*^{6}-(1-naphthylmethyl)adenosine (17). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.70 (t, 1H, NH, amide, $J = 5.6$ Hz), 8.48 (bs, 1H, N^{6}H), 8.40 (bs, 1H, 8H), 8.24 (m, 1H, naphthyl), 8.14 (s, 1H, 2H), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.81 (m, 1H, naphthyl), 7.59−7.53 (m, 2H, naphthyl), 7.44−7.35 (m, 5H, 3H benzyl overlapping 2H naphthyl), 7.10−7.07 (m, 1H, benzoyl), 5.90 (d, 1H, 1′H, $J = 6.6$ Hz), 5.50 (d, 1H, 3′OH, $J = 6.1$ Hz), 5.31 (d, 1H, 2′OH, $J = 4.6$ Hz), 5.18 (bs, 2H, CH_2, naphthylmethyl), 4.79−4.78 (m, 1H, 2′H), 4.19−4.17 (m, 1H, 3′H), 4.11−4.07 (m, 1H, 4′H), 3.78 (s, 3H, CH_3, methoxy). HRESI-MS $[M + H]^+$: calcd 541.2200, found 541.2185.

5′-[(4-Cyclopropylamino-3-nitro)benzamido]-5′-deoxy-*N*^{6}-(1-naphthylmethyl)adenosine (18). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.75 (t, 1H, NH, amide, $J = 5.6$ Hz), 8.65 (m, 1H, aromatic), 8.46 (bs, 1H, N^{6}H), 8.41 (bs, 1H, 8H), 8.25 (bs, 1H, NH), 8.22 (m, 1H, naphthyl), 8.18 (s, 1H, 2H), 8.08−8.05 (m, 1H, aromatic), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.80 (m, 1H, naphthyl), 7.59−7.52 (m, 2H, naphthyl), 7.44−7.39 (m, 3H, 2H naphthyl overlapping 1H aromatic), 5.90 (d, 1H, 1′H, $J = 6.1$ Hz), 5.51 (d, 1H, 3′OH, $J = 5.6$ Hz), 5.32 (d, 1H, 2′OH, $J = 4.6$ Hz), 5.17 (bs, 2H, CH_2, naphthylmethyl), 4.79−4.77 (m, 1H, 2′H), 4.21−4.19 (m, 1H, 3′H), 4.09−4.06 (m, 1H, 4′H), 1.94−1.86 (m, 1H, cyclopropyl), 0.91−0.86 (m, 2H, CH_2, cyclopropyl), 0.68−0.64 (m, 2H, CH_2, cyclopropyl). HRFAB-MS $[M + H]^+$: calcd 611.2367, found 611.2379.

5′-Deoxy-5′-[4-(1-methylethyl)amino-3-nitro]benzamido-*N*^{6}-(1-naphthylmethyl)adenosine (19). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.70 (t, 1H, NH, amide, $J = 5.9$ Hz), 8.66 (d, 1H, aromatic, $J = 2.29$ Hz), 8.43 (bs, 1H, N^{6}H), 8.39 (bs, 1H, 8H), 8.24 (d, 1H, naphthyl, $J = 8.0$ Hz), 8.18 (s, 1H, 2H), 8.08 (d, 1H, NH, isopropylamino, $J = 7.6$ Hz), 8.01−7.99 (m, 1H, aromatic), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.80 (m, 1H, naphthyl), 7.59−7.52 (m, 2H, naphthyl), 7.46−7.40 (m, 2H, naphthyl), 7.15 (d, 1H, aromatic, $J = 9.4$ Hz), 5.90 (d, 1H, 1′H, $J = 6.1$ Hz), 5.45 (d, 1H, 3′OH, $J = 6.35$ Hz), 5.26 (d, 1H, 2′OH, $J = 4.8$ Hz), 5.18 (bs, 2H, CH_2, naphthylmethyl), 4.80−4.75 (m, 1H, 2′H), 4.21−4.18

(m, 1H, 3′H), 4.09−4.05 (m, 1H, 4′H), 3.84−3.74 (m, 1H, CH, isopropylamino), 1.27 (d, 6H, CH_3, isopropylamino, $J = 6.4$ Hz). HRESI-MS $[M + H]^+$: calcd 613.2523, found 613.2533.

5′-Deoxy-N^6-(1-naphthylmethyl)-5′-[3-nitro-4-(pyrrolid-1-yl)benzamido]adenosine (20). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.62 (t, 1H, NH, amide, $J = 5.7$ Hz), 8.43 (bs, 1H, N^6H), 8.39 (bs, 1H, 8H), 8.29 (d, 1H, aromatic, $J = 2.3$ Hz), 8.24−8.21 (m, 1H, naphthyl), 8.19 (s, 1H, 2H), 7.96−7.92 (m, 2H, naphthyl overlapping aromatic), 7.83−7.80 (m, 1H, naphthyl), 7.59−7.52 (m, 2H, naphthyl), 7.46−7.40 (m, 2H, naphthyl), 7.08 (d, 1H, aromatic, $J = 8.9$ Hz), 5.90 (d, 1H, 1′H, $J = 6.1$ Hz), 5.45 (d, 1H, 3′OH, $J = 6.4$ Hz), 5.26 (d, 1H, 2′H, $J = 4.8$ Hz), 5.19 (bs, 2H, CH_2, naphthylmethyl), 4.78−4.75 (m, 1H, 2′H), 4.20−4.17 (m, 1H, 3′H), 4.10−4.05 (m, 1H, 4′H), 3.20−3.16 (m, 4H, CH_2, pyrrolidyl), 1.93−1.90 (m, 4H, CH_2, pyrrolidyl). HRESI-MS $[M + Na]^+$: calcd 647.2342, found 647.2345.

5′-[(4-Cyclopentylamino-3-nitro)benzamido]-5′-deoxy-N^6-(1-naphthylmethyl)adenosine (21). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.70 (t, 1H, NH, amide, $J = 5.9$ Hz), 8.66 (d, 1H, aromatic, $J = 2.0$ Hz), 8.42 (bs, 1H, N^6H), 8.39 (bs, 1H, 8H), 8.24 (d, 1H, naphthyl, $J = 8.1$ Hz), 8.18 (s, 1H, 2H), 8.17−8.15 (m, 1H, NH, cyclopentylamino), 8.02−7.99 (m, 1H, aromatic), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.80 (m, 1H, naphthyl), 7.59−7.52 (m, 2H, naphthyl), 7.46−7.40 (m, 2H, naphthyl), 7.16 (d, 1H, aromatic, $J = 9.4$ Hz), 5.90 (d, 1H, 1′H, $J = 6.1$ Hz), 5.46 (d, 1H, 3′OH, $J = 6.1$ Hz), 5.26 (d, 1H, 2′OH, $J = 4.8$ Hz), 5.18 (bs, 2H, CH_2, naphthylmethyl), 4.80−4.76 (m, 1H, 2′H), 4.22−4.18 (m, 1H, 3′H), 4.07−4.05 (m, 1H, 4′H), 3.84−3.74 (m, 1H, CH, cyclopentylamino), 2.11−2.04 (m, 2H, CH_2, cyclopentylamino), 1.77−1.51 (m, 6H, CH_2, cyclopentylamino). HRESI-MS $[M + H]^+$: calcd 639.2680, found 639.2699.

5′-Deoxy-N^6-(1-naphthylmethyl)-5′-[3-nitro-4-(piperid-1-yl)benzamido]adenosine (22). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.73 (m, 1H, NH, amide), 8.47 (bs, 1H, N^6H), 8.40 (bs, 1H, 8H), 8.30 (d, 1H, aromatic, $J = 2.0$ Hz), 8.24 (m, 1H, naphthyl), 8.17 (s, 1H, 2H), 8.00−7.99 (m, 1H, aromatic), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.80 (m, 1H, naphthyl), 7.59−7.52 (m, 2H, naphthyl), 7.45−7.40 (m, 2H, naphthyl), 7.29 (d, 1H, aromatic, $J = 9.2$ Hz), 5.90 (d, 1H, 1′H, $J = 6.1$ Hz), 5.50 (d, 1H, 3′OH, $J = 6.6$ Hz), 5.32 (d, 1H, 2′OH, $J = 4.6$ Hz), 5.18 (bs, 2H, CH_2, naphthylmethyl), 4.79−4.75 (m, 1H, 2′H), 4.21−4.17 (m, 1H, 3′H), 4.08−4.04 (m, 1H, 4′H), 3.61 (m, 4H, CH_2, piperidyl), 1.64−1.51 (m, 6H, CH_2, piperidyl). HRESI-MS $[M + H]^+$: calcd 639.2679, found 639.2687.

5′-Deoxy-5′-[4-(morphol-1-yl)-3-nitro]benzamido-N^6-(1-naphthylmethyl)adenosine (23). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.78 (t, 1H, NH, amide, $J = 5.5$ Hz), 8.47 (bs, 1H, N^6H), 8.40 (bs, 1H, 8H), 8.33 (m, 1H, aromatic), 8.24−8.22 (m, 1H, naphthyl), 8.17 (s, 1H, 2H), 8.05−8.03 (m, 1H, aromatic), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.81 (m, 1H, naphthyl), 7.59−7.53 (m, 2H, naphthyl), 7.44−7.40 (m, 2H, naphthyl), 7.34 (d, 1H, aromatic, $J = 8.6$ Hz), 5.90 (d, 1H, 1′H, $J = 6.1$ Hz), 5.51 (bs, 1H, 3′OH), 5.32 (bs, 1H, 2′OH), 5.18 (bs, 2H, CH_2, naphthylmethyl), 4.80−4.76 (m, 1H, 2′H), 4.19 (m, 1H, 3′H), 4.08−4.05 (m, 1H, 4′H), 3.68 (t, 4H, CH_2, morpholyl, $J = 4.5$ Hz), 3.07 (t, 4H, CH_2, morpholyl, $J = 4.6$). HRESI-MS $[M + Na]^+$ calcd 663.2292, found 663.2293.

5′-Deoxy-5′-[(4-dibutylamino-3-nitro)benzamido]-N^6-(1-naphthylmethyl)adenosine (24). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.67 (t, 1H, NH, amide, $J = 5.9$ Hz), 8.42−8.39 (bs, 2H, N^6H overlapping 8H), 8.24−8.22 (m, 2H, naphthyl overlapping aromatic), 8.16 (s, 1H, 2H), 7.96−7.91 (m, 2H, naphthyl overlapping aromatic), 7.82−7.80 (m, 1H, naphthyl), 7.59−7.52 (m, 2H, naphthyl), 7.46−7.40 (m, 2H, naphthyl), 7.31 (d, 1H, aromatic, $J = 9.2$ Hz), 5.90 (d, 1H, 1′H, $J = 6.1$ Hz), 5.45 (d, 1H, 3′OH, $J = 6.1$ Hz), 5.26 (d, 1H, 2′OH, $J = 4.8$ Hz), 5.18 (bs, 2H, CH_2, naphthylmethyl), 4.79−4.75 (m, 1H, 2′H), 4.20−4.17 (m, 1H, 3′H), 4.08−4.04 (m, 1H, 4′H), 3.18−3.13 (m, 4H, CH_2, dibutylamino), 1.48−1.40 (m, 4H, CH_2, dibutylamino), 1.25−1.18 (m, 4H, CH_2, dibutylamino), 0.81 (t, 6H, CH_3, dibutylamino, $J = 7.3$ Hz). HRESI-MS $[M + H]^+$: calcd 683.3305, found 683.3294.

5′-Deoxy-5′-{[4-(2-(2-methoxyphenyl)ethlylamino)-3-nitro]benzamido}-N^6-(1-naphthylmethyl)adenosine (25). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.69 (t, 1H, NH, amide, $J = 5.6$ Hz), 8.65 (d, 1H, aromatic, $J = 2.03$ Hz), 8.43−8.39 (m, 3H, N^6H overlapping 8H overlapping NH), 8.24 (d, 1H, naphthyl, $J = 7.9$ Hz), 8.18 (s, 1H, 2H), 8.04−8.01 (m, 1H, aromatic), 7.96−7.94 (m, 1H, naphthyl), 7.82−7.80 (m, 1H, naphthyl), 7.59−7.52 (m, 2H, naphthyl), 7.46−7.40 (m, 2H, naphthyl), 7.24−7.20 (m, 2H, aromatic), 7.17 (d, 1H, aromatic, $J = 9.2$ Hz), 6.98 (d, 1H, aromatic, $J = 8.1$ Hz), 6.89 (t, 1H, aromatic, $J = 7.3$ Hz), 5.90 (d, 1H, 1′H, $J = 6.1$ Hz), 5.45 (d, 1H, 3′OH, $J = 6.1$ Hz), 5.27 (d, 1H, 2′OH, $J = 4.8$ Hz), 5.18 (bs, 2H, CH_2, naphthylmethyl), 4.78−4.76 (m, 1H, 2′H), 4.20−4.18 (m, 1H, 3′H), 4.09−4.06 (m, 1H, 4′H), 3.81 (s, 3H, CH_3, methoxy), 2.93 (t, 2H, CH_2, ethylamino, $J = 7.0$ Hz). HRESI-MS $[M + H]^+$: calcd 705.2785, found 705.2797.

5′-[4-(*N*-Benzyl-*N*-ethyl)amino-3-nitrobenzamido]-5′-deoxy-N^6-(1-naphthylmethyl)adenosine (26). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.71 (t, 1H, NH, amide, $J = 6.1$ Hz), 8.46 (bs, 1H, N^6H), 8.40 (bs, 1H, 8H), 8.25−8.23 (m, 2H, naphthyl overlapping 2H), 8.15 (s, 1H, aromatic), 7.96−7.94 (m, 1H, naphthyl), 7.92−7.89 (m, 1H, aromatic), 7.83−7.81 (m, 1H, naphthyl), 7.59−7.52 (m, 2H, naphthyl), 7.44−7.40 (m, 2H, naphthyl), 7.32−7.26 (m, 4H, aromatic), 7.23−7.19 (m, 1H, aromatic), 5.89 (d, 1H, 1′H, $J = 6.1$ Hz), 5.48 (d, 1H, 3′OH, $J = 6.1$ Hz), 5.29 (d, 1H, 2′OH, $J = 4.6$ Hz), 5.18 (bs, 2H, CH_2, naphthylmethyl), 4.79−4.76 (m, 1H, 2′H), 4.44 (s, 2H, CH_2, benzyl), 4.18−4.16 (m, 1H, 3′H), 4.06−4.03 (m, 1H, 4′H), 1.06 (t, 3H, CH_3, $J = 7.1$ Hz). HRESI-MS $[M + Na]^+$: calcd 711.2655, found 711.2662.

5′-Deoxy-5′-{[4-(morphol-1-yl)-3-(4-nitrobenzamido)]-benzamido}-N^6-(1-naphthylmethyl)adenosine (27). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.97 (s, 1H, NH, amide), 8.62 (m, 1H, NH, amide), 8.40−8.38 (m, 4H, N^6H overlapping 8H overlapping 2H aromatic), 8.31 (m, 1H, naphthyl), 8.21−8.17 (m, 4H, 2H overlapping 3H aromatic), 7.96−7.93 (m, 1H, naphthyl), 7.82−7.80 (m, 1H, naphthyl), 7.76−7.70 (m, 1H, aromatic), 7.57−7.53 (m, 2H, naphthyl), 7.45−7.41 (m, 2H, naphthyl), 7.27−7.23 (m, 1H, aromatic), 5.90 (d,

1H, 1′H, J = 6.1 Hz), 5.44 (m, 1H, 3′OH), 5.29 (m, 1H, 2′OH), 5.17 (bs, 2H, CH_2, naphthylmethyl), 4.79−4.77 (m, 1H, 2′H), 4.20−4.18 (m, 1H, 3′H), 4.11−4.07 (m, 1H, 4′H), 3.74−3.72 (m, 4H, CH_2 morpholyl), 2.95−2.92 (m, 4H, CH_2 morpholyl). HRESI-MS $[M + H]^+$: calcd 760.2843, found 760.2845.

5′-{[3-Acetamido-4-(morphol-1-yl)]benzamido}-5′-deoxy-*N*^{6}-(1-naphthylmethyl)adenosine (28). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.01 (s, 1H, NH, amide), 8.57 (t, 1H, NH, amide, J = 5.7 Hz), 8.47 (bs, 1H, N^{6}H), 8.41 (bs, 1H, 8H), 8.25−8.22 (m, 2H, aromatic overlapping naphthyl), 8.16 (s, 1H, 2H), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.81 (m, 1H, naphthyl), 7.61−7.53 (m, 3H, 1H aromatic overlapping 2H naphthyl), 7.44−7.40 (m, 2H, naphthyl), 7.14 (d, 1H, aromatic, J = 8.1 Hz), 5.89 (d, 1H, 1′H, J = 6.6 Hz), 5.46 (d, 1H, 3′OH, J = 6.1 Hz), 5.29 (d, 1H, 2′OH, J = 4.6 Hz), 5.19 (bs, 2H, CH_2, naphthylmethyl), 4.78−4.77 (m, 1H, 2′H), 4.17 (m, 1H, 3′H), 4.08 (m, 1H, 4′H), 3.78 (t, 4H, CH_2, morpholyl, J = 4.1 Hz), 2.85 (t, 4H, CH_2, morpholyl, J = 4.1 Hz), 2.10 (s, 3H, CH_3, acetamido). HRESI-MS $[M + Na]^+$ calcd 675.2655, found 675.2670.

5′-[(4-Cyclopentylamino-3-propanamido)benzamido]-5′-deoxy-*N*^{6}-(1-naphthylmethyl)adenosine (29). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.10 (s, 1H, NH, amide), 8.44 (bs, 1H, N^{6}H), 8.38 (bs, 1H, 8H), 8.30 (t, 1H, NH, amide, J = 5.8 Hz), 8.24 (d, 1H, naphthyl, J = 7.63 Hz), 8.20 (s, 1H, 2H), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.80 (m, 1H, naphthyl), 7.70 (d, 1H, aromatic, J = 1.5 Hz), 7.61−7.52 (m, 3H, 2H naphthyl overlapping 1H aromatic), 7.46−7.41 (m, 2H, naphthyl), 6.67 (d, 1H, aromatic, J = 8.9 Hz), 5.88 (d, 1H, 1′H, J = 6.6 Hz), 5.42 (d, 1H, 3′OH, J = 6.4 Hz), 5.25 (d, 1H, 2′OH, J = 4.6 Hz), 5.19 (bs, 2H, CH_2, naphthylmethyl), 5.10 (d, 1H, NH, amine, J = 6.4 Hz), 4.78−4.74 (m, 1H, 2′H), 4.16−4.14 (m, 1H, 3′H), 4.08−4.05 (m, 1H, 4′H), 3.82−3.75 (m, 1H, CH, cyclopentylamino), 2.36−2.30 (m, 2H, CH_2, propanamido), 2.01−1.93 (m, 2H, CH_2, cyclopentylamino), 1.70−1.63 (m, 2H, CH_2, cyclopentylamino), 1.60−1.52 (m, 2H, CH_2, cyclopentylamino), 1.47−1.39 (m, 2H, CH_2, cyclopentylamino), 1.09−1.06 (m, 3H, CH_3, propanamido). HRESI-MS $[M + Na]^+$: calcd 687.3019, found 687.3040.

5′-[3-Acetamido-4-(piperid-1-yl)benzamido]-5′-deoxy-*N*^{6}-(1-naphthylmethyl)adenosine (30). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.86 (s, 1H, NH, amide), 8.54 (t, 1H, NH, amide, J = 5.8 Hz), 8.47 (bs, 1H, N^{6}H), 8.40 (bs, 1H, 8H), 8.24−8.22 (m, 2H, aromatic H overlapping naphthyl), 8.15 (s, 1H, 2H), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.81 (m, 1H, naphthyl), 7.59−7.53 (m, 3H, 2H naphthyl overlapping 1H aromatic), 7.44−7.41 (m, 2H, naphthyl), 7.10 (d, 1H, aromatic, J = 8.6 Hz), 5.89 (d, 1H, 1′H, J = 6.1 Hz), 5.45 (d, 1H, 3′OH, J = 6.1 Hz), 5.28 (d, 1H, 2′OH, J = 4.6 Hz), 5.19 (bs, 2H, CH_2, naphthylmethyl), 4.78−4.75 (m, 1H, 2′H), 4.17−4.15 (m, 1H, 3′H), 4.09−4.06 (m, 1H, 4′H), 2.79 (m, 4H, CH_2, piperidyl), 2.10 (s, 3H, CH_3, acetamido), 1.69−1.68 (m, 4H, CH_2, piperidyl), 1.56−1.51 (m, 2H, CH_2, piperidyl). HRFAB-MS $[M + H]^+$: calcd 651.3043, found 651.3062.

5′-[3-Acetamido-4-(*N*-benzyl-*N*-ethylamino)benzamido]-5′-deoxy-*N*^{6}-(1-naphthylmethyl)adenosine (31). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.02 (s, 1H, NH, amide), 8.53 (t, 1H, NH, amide, J = 5.9 Hz), 8.47 (bs, 1H, N^{6}H), 8.40 (bs, 1H, 8H), 8.24−8.22 (m, 2H, aromatic overlapping naphthyl), 8.13 (s, 1H, 2H), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.80 (m, 1H, naphthyl), 7.59−7.40 (m, 5H, 4H naphthyl overlapping 1H aromatic), 7.33−7.31 (d, 2H, aromatic, J = 7.12 Hz), 7.27−7.12 (m, 4H, aromatic), 5.88 (d, 1H, 1′H, J = 6.6 Hz), 5.45 (d, 1H, 3′OH, J = 6.6 Hz), 5.29 (d, 1H, 2′OH, J = 4.6 Hz), 5.19 (bs, 2H, CH_2 naphthylmethyl), 4.78−4.77 (m, 1H, 2′H), 4.16−4.13 (m, 3H, 3′H overlapping CH_2 benzylamine), 4.08−4.05 (m, 1H, 4′H), 3.03−2.97 (m, 2H, CH_2, ethylamino), 2.05 (s, 3H, CH_3, acetamido), 1.00−0.93 (m, 3H, CH_3, ethylamine). HRESI-MS $[M + H]^+$: calcd 701.3200, found 701.3196.

5′-Deoxy-5′-{4-[2-(2-Methoxyphenyl)ethylamino]-3-propanamido}benzamido-*N*^{6}-(1-naphthylmethyl)adenosine (32). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.03 (s, 1H, NH, amide), 8.45 (bs, 1H, N^{6}H), 8.39 (bs, 1H, 8H), 8.31 (t, 1H, NH, amide, J = 5.9 Hz), 8.24−0.8.22 (m, 2H, naphthyl overlapping 2H), 7.96−7.94 (m, 1H, naphthyl), 7.82−7.80 (m, 1H, naphthyl), 7.67−7.64 (m, 2H, aromatic), 7.59−7.52 (m, 2H, naphthyl), 7.46−7.37 (m, 2H, naphthyl), 7.23−7.18 (m, 2H, aromatic), 6.97−6.86 (m, 2H, aromatic), 6.75 (d, 1H, aromatic, J = 8.7 Hz), 5.88 (d, 1H, 1′H, J = 6.6 Hz), 5.48−5.46 (m, 1H, NH, amine), 5.42 (d, 1H, 3′OH, J = 6.4 Hz), 5.25 (d, 1H, 2′OH, J = 4.6 Hz), 5.19 (bs, 2H, CH_2, naphthylmethyl), 4.81−4.74 (m, 1H, 2′H), 4.16−4.13 (m, 1H, 3′H), 4.11−4.06 (m, 1H, 4′H), 3.80 (s, 3H, CH_3, methoxy), 2.83 (t, 2H, CH_2, ethylamino, J = 7.4 Hz), 2.36−2.27 (m, 2H, CH_2, propanamido), 1.10−1.02 (m, 3H, CH_3, propanamido). HRESI-MS $[M + Na]^+$: calcd 753.3125, found 753.3132.

5′-[3-*tert*-Butyloxycarbonamido-4-(morphol-1-yl)]benzamido-5′-deoxy-*N*^{6}-(1-naphthylmethyl)adenosine (33). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.56 (t, 1H, NH, amide, J = 5.9 Hz), 8.44 (bs, 1H, N^{6}H), 8.39 (bs, 1H, 8H), 8.24 (m, 1H, naphthyl), 8.18 (d, 1H, aromatic, J = 2.0 Hz), 8.16 (s, 1H, 2H), 7.97 (s, 1H, NH, amide), 7.96−7.94 (m, 1H, naphthyl), 7.82−7.80 (m, 1H, naphthyl), 7.59−7.52 (m, 3H, 2H naphthyl overlapping 1H aromatic), 7.46−7.40 (m, 2H, naphthyl), 7.19 (d, 1H, aromatic, J = 8.1 Hz), 5.89 (d, 1H, 1′H, J = 6.4 Hz), 5.44 (d, 1H, 3′OH, J = 5.6 Hz), 5.27 (d, 1H, 2′OH, J = 4.3 Hz), 5.18 (bs, 2H, CH_2, naphthylmethyl), 4.77 (bs, 1H, 2′H), 4.18−4.15 (m, 1H, 3′H), 4.10−4.07 (m, 1H, 4′H), 3.74 (t, 4H, CH_2, morpholyl, J = 4.5 Hz), 2.83 (t, 4H, CH_2, morpholyl, J = 4.6 Hz), 1.45 (s, 9H, CH_3, BOC). HRESI-MS $[M + H]^+$: calcd 711.3255, found 711.3252.

5′-[(3-Acetamido-4-dibut-1-ylamino)benzamido]-5′-deoxy-*N*^{6}-(1-naphthylmethyl)adenosine (34). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.91 (bs, 1H, NH, amide), 8.54 (t, 1H, NH, amide, J = 5.6 Hz), 8.45−8.36 (m, 3H, N^{6}H overlapping 8H overlapping aromatic), 8.24 (d, 1H, naphthyl, J = 7.9 Hz), 8.11 (s, 1H, 2H), 7.96−7.94 (m, 1H, naphthyl), 7.82−7.80 (m, 1H, naphthyl), 7.59−7.52 (m, 3H, 2H naphthyl overlapping 1H aromatic), 7.44−7.40 (m, 2H, naphthyl), 7.21 (d, 1H, aromatic, J = 8.4 Hz), 5.89 (d, 1H, 1′H, J = 6.4 Hz), 5.44 (d, 1H, 3′OH, J = 6.4 Hz), 5.27 (d, 1H, 2′OH, J = 4.8 Hz), 5.18 (bs, 2H, CH_2, naphthylmethyl), 4.80−

4.74 (m, 1H, 2′H), 4.20−4.17 (m, 1H, 3′H), 4.11−4.07 (m, 1H, 4′H), 2.90 (t, 4H, CH_2, dibutylamino, $J = 7.1$, 7.4 Hz), 2.09 (s, 3H, CH_3, acetamido), 1.37−1.29 (m, 4H, CH_2, dibut-1-ylamino), 1.25−1.20 (m, 4H, CH_2, dibut-1-ylamino), 0.81 (t, 6H, CH_3, dibutylamino, $J = 7.2$ Hz). HRESI-MS $[M + Na]^+$: calcd 717.3489, found 717.3491.

5′-[(4-Dibut-1-ylamino-3-propanamido)benzamido]-5′-deoxy-*N*^{6}-(1-naphthylmethyl)adenosine (35). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.86 (s, 1H, NH, amide), 8.56 (t, 1H, NH, amide, $J = 5.6$ Hz), 8.43−8.40 (m, 3H, N^{6}H overlapping 8H overlapping aromatic), 8.24 (d, 1H, naphthyl, $J = 7.9$ Hz), 8.11 (s, 1H, 2H), 7.96−7.94 (m, 1H, naphthyl), 7.82−7.80 (m, 1H, naphthyl), 7.59−7.51 (m, 3H, 2H naphthyl overlapping 1H aromatic), 7.46−7.40 (m, 2H, naphthyl), 7.23 (d, 1H, aromatic, $J = 8.4$ Hz), 5.89 (d, 1H, 1′H, $J = 6.4$ Hz), 5.44 (d, 1H, 3′OH, $J = 6.4$ Hz), 5.27 (d, 1H, 2′OH, $J = 4.6$ Hz), 5.18 (bs, 2H, CH_2, naphthylmethyl), 4.80−4.77 (m, 1H, 2′H), 4.18−4.16 (m, 1H, 3′H), 4.10−4.08 (m, 1H, 4′H), 2.89 (t, 4H, CH_2, dibut-1-ylamino, $J = 7.8$ Hz), 2.41−2.35 (m, 2H, CH_2, propanamido), 1.36−1.28 (m, 4H, CH_2, dibut-1-ylamino), 1.25−1.19 (m, 4H, CH_2, dibut-1-ylamino), 1.09 (t, 3H, CH_3, propanamido, $J = 7.5$ Hz), 0.81 (t, 6H, CH_3, dibutylamino, $J = 7.3$ Hz). HRESI-MS $[M + Na]^+$: calcd 731.3645, found 731.3645.

5′-[(4-Dibut-1-ylamino-3-butanamido)benzamido]-5′-deoxy-*N*^{6}-(1-naphthylmethyl)adenosine (36). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.87 (s, 1H, NH, amide), 8.56 (t, 1H, NH, amide, $J = 5.7$ Hz), 8.44−8.37 (m, 3H, N^{6}H overlapping 8H overlapping aromatic), 8.23 (d, 1H, naphthyl, $J = 7.9$ Hz), 8.11 (s, 1H, 2H), 7.96−7.94 (m, 1H, naphthyl), 7.82−7.80 (m, 1H, naphthyl), 7.59−7.51 (m, 3H, 2H naphthyl overlapping 1H aromatic), 7.46−7.40 (m, 2H, naphthyl), 7.24 (d, 1H, aromatic, $J = 8.39$ Hz), 5.89 (d, 1H, 1′H, $J = 6.6$ Hz), 5.44 (d, 1H, 3′OH, $J = 6.1$ Hz), 5.28 (d, 1H, 2′OH, $J = 4.3$ Hz), 5.18 (bs, 2H, CH_2, naphthylmethyl), 4.79−4.74 (m, 1H, 2′H), 4.17 (m, 1H, 3′H), 4.11−4.08 (m, 1H, 4′H), 2.89 (t, 4H, CH_2, dibutylamino, $J = 7.2$ Hz), 2.35 (t, 2H, CH_2, butanamido, $J = 7.3$ Hz), 1.64−1.59 (m, 2H, butanamido), 1.35−1.28 (m, 4H, CH_2, dibut-1-ylamino), 1.24−1.17 (m, 4H, CH_2, dibutylamino), 0.92 (t, 3H, CH_3, butanamido, $J = 7.4$, 7.4 Hz), 0.80 (t, 6H, CH_3, dibut-1-ylamino, $J = 7.3$ Hz). HRESI-MS $[M + H]^+$: calcd 723.3983, found 723.3960.

5′-Deoxy-5′-[4-(3-indolyl)butanamido]-*N*^{6}-(4-phenyl)-benzyladenosine (37). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.71 (bs, 1H, NH, indolyl), 8.48 (bs, 1H, N^{6}H), 8.38 (s, 1H, 8H), 8.22 (s, 1H, 2H), 8.18 (t, 1H, NH, amide, $J = 5.6$ Hz), 7.62−7.57 (m, 4H, biphenyl), 7.49−7.42 (m, 5H, 4H biphenyl overlapping 1H indolyl), 7.35−7.30 (m, 2H, biphenyl overlapping indolyl), 7.08 (d, 1H, indolyl, $J = 2.3$ Hz), 7.05−7.01 (m, 1H, indolyl), 6.95−6.91 (m, 1H, indolyl), 5.88 (d, 1H, 1′H, $J = 6.4$ Hz), 5.44 (d, 1H, 3′OH, $J = 6.4$ Hz), 5.25 (d, 1H, 2′OH, $J = 4.6$ Hz), 4.76 (bs, 2H, CH_2, biphenylmethyl), 4.73−4.69 (m, 1H, 2′H), 4.08−4.05 (m, 1H, 3′H), 3.99−3.96 (m, 1H, 4′H), 2.66 (t, 2H, CH_2, butyryl, $J = 7.5$ Hz), 2.21 (t, 2H, CH_2, butyryl, $J = 7.4$ Hz), 1.89 (t, 2H, CH_2, butyryl, $J = 7.62$ Hz). HRESI-MS $[M + H]^+$: calcd 618.2830, found 618.2815.

5′-Deoxy-5′-(3-methoxyphenylacetamido)-*N*^{6}-(4-phenyl)benzyladenosine (38). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.48 (bs, 1H, N^{6}H), 8.36 (s, 1H, 8H), 8.35−8.32 (m, 1H, NH, amide), 8.25 (s, 1H, 2H), 7.63−7.58 (m, 4H, biphenyl), 7.46−7.42 (m, 4H, biphenyl), 7.35−7.32 (m, 1H, biphenyl), 7.17 (t, 1H, aromatic, $J = 7.7$ Hz), 6.81−6.78 (m, 3H, aromatic), 5.88 (d, 1H, 1′H, $J = 6.1$ Hz), 5.45 (d, 1H, 3′OH, $J = 6.1$ Hz), 5.26 (d, 1H, 2′OH, $J = 4.6$ Hz), 4.76 (bs, 2H, CH_2, biphenylmethyl), 4.71−4.65 (m, 1H, 2′H), 4.10−4.05 (m, 1H, 3′H), 3.97−3.96 (m, 1H, 4′H), 3.82−3.76 (m, 2H, 5′CH_2), 3.69 (s, 3H, CH_3, methoxy). HRESI-MS $[M + H]^+$: calcd 581.2513, found 581.2524.

5′-[3-Acetamido-4-(morphol-1-yl)]benzamido-5′-deoxy-*N*^{6}-(4-phenyl)benzyladenosine (39). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.99 (s, 1H, NH, amide), 8.55 (t, 1H, NH, amide, $J = 5.8$ Hz), 8.46 (bs, 1H, N^{6}H), 8.39 (s, 1H, 8H), 8.25 (bs, 1H, aromatic), 8.17 (s, 1H, 2H), 7.63−7.58 (m, 5H, 4H biphenyl overlapping 1H aromatic), 7.46−7.42 (m, 4H, biphenyl), 7.35−7.32 (m, 1H, biphenyl), 7.14 (d, 1H, aromatic, $J = 8.7$ Hz), 5.89 (d, 1H, 1′H, $J = 6.4$ Hz), 5.44 (d, 1H, 3′OH, $J = 6.1$ Hz), 5.27 (d, 1H, 2′OH, $J = 4.8$ Hz), 4.79−4.74 (m, 3H, CH_2 biphenylmethyl overlapping 2′H), 4.19−4.16 (m, 1H, 3′H), 4.10−4.07 (m, 1H, 4′H), 3.82−3.74 (m, 4H, CH_2, morpholyl), 2.87−2.85 (m, 4H, CH_2, morpholyl), 2.10 (s, 3H, CH_3, acetamido). HRESI-MS $[M + H]^+$: calcd 679.2993, found 679.2990.

5′-Deoxy-5′-{[4-(1-methylethyl)amino-3-propanamido]-benzamido}-*N*^{6}-(1-naphthylmethyl)adenosine (40). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.05 (s, 1H, NH, amide), 8.44 (bs, 1H, N^{6}H), 8.39 (bs, 1H, 8H), 8.30 (t, NH, amide, $J = 5.6$ Hz), 8.25 (d, 1H, naphthyl, $J = 7.9$ Hz), 8.20 (s, 1H, 2H), 7.96−7.94 (m, 1H, naphthyl), 7.83−7.80 (m, 1H, naphthyl), 7.70 (s, 1H, aromatic), 7.61−7.52 (m, 3H, 2H naphthyl overlapping 1H aromatic), 7.46−7.41 (m, 2H, naphthyl), 6.66 (d, 1H, aromatic, $J = 8.7$ Hz), 5.88 (d, 1H, 1′H, $J = 6.4$ Hz), 5.42 (d, 1H, 3′OH, $J = 6.4$ Hz), 5.25 (d, 1H, 2′OH, $J = 4.6$ Hz), 5.19 (bs, 2H, CH_2, naphthylmethyl), 4.95 (d, 1H, NH, isopropylamino, $J = 7.6$ Hz), 4.77−4.74 (m, 1H, 2′H), 4.16−4.14 (m, 1H, 3′H), 4.10−4.05 (m, 1H, 4′H), 3.68−3.61 (m, 1H, CH, isopropylamino), 2.37−2.31 (m, 2H, CH_2, propanamido), 1.16 (d, 6H, CH_3, isopropylamino, $J = 6.1$ Hz), 1.11−1.04 (m, 3H, CH_3, propanamido). HRESI-MS $[M + H]^+$: calcd 639.3043, found 639.3040.

In Vitro Measurement of *P. falciparum* Growth Inhibition.[17−19] The *P. falciparum* strain Dd2 was cultivated by a modification of the method described by Trager and Jensen. The culture medium consisted of RPMI 1640 supplemented with 10% human type 0$^+$ serum and 25 mM HEPES. Human type 0$^+$ erythrocytes served as host cells. The cultures were kept at 37 °C in an atmosphere of 5% O_2, 3% CO_2, and 92% N_2. Testing of compounds was carried out in 96-well microtiter plates. The compounds were dissolved in DMSO (10 mM) and prediluted in complete culture medium. Infected erythrocytes (200 μL per well, with 2% hematocrit and 0.4% parasitemia) were incubated in duplicate with a serial dilution of the compounds for 48 h. After the addition of 0.8 μCi [^{3}H]-hypoxanthine in 50 μL of medium per well, the plates were further incubated for 24 h. Cells were collected on glass fiber filters with a cell

harvester (Micromate 196, Packard), and incorporated radioactivity was measured using a β-counter (Matrix 9600, Packard).

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References and Notes

(1) WHO Information Office. HIV, TB, and malaria—three major infectious diseases threats. *Fact Sheet WHO/Bg/01* (http://www.who.int/inf-fs/en/back001.html); WHO: Geneva, 2000.
(2) Hirst, S. I.; Stapley, L. A. Parasitology: the dawn of a new millennium. *Parasitol. Today* **2000**, *16*, 1−3.
(3) Golisade, A.; Wiesner, J.; Herforth, C.; Jomaa, H.; Link, A. Anti-malarial Activity of N^6-substituted Adenosine Derivatives. Part I. *Bioorg. Med. Chem.* **2002**, *10*, 769−777.
(4) Carter, N.; Ben Mamoun, C.; Liu, W.; Silva, E.; Landfear, S.; et al. Isolation and functional characterization of the PfNT1 nucleoside transporter gene from Plasmodium falciparum. *J. Biol. Chem.* **2000**, *275*, 10683−10691.
(5) Kenner, G. W.; McDermott, J. R.; Sheppard, R. C. The Safety Catch Principle in Solid Phase Peptide Synthesis. *J. Chem. Soc., Chem. Commun.* **1971**, 636−637.
(6) Backes, B. J.; Ellman, J. A. Carbon−Carbon Bond-Forming Methods on Solid Support. Utilization of Kenner's "Safety-Catch" Linker. *J. Am. Chem. Soc.* **1994**, *116*, 11171−11172.
(7) Bressi, J. C.; Verlinde, C. L.; Aronov, A. M.; Shaw, M. L.; Shin, S. S.; et al. Adenosine Analogues as Selective Inhibitors of Glyceraldehyde-3-phosphate Dehydrogenase of *Trypanosomatidae* via Structure-Based Drug Design. *J. Med. Chem.* **2001**, *44*, 2080−2093.
(8) Link, A.; Van Calenbergh, S.; Herdewijn, P. Practical method for the parallel synthesis of 2′-amido-2′-deoxyadenosines. *Tetrahedron Lett.* **1998**, *39*, 5175−5176.
(9) Golisade, A.; Bressi, J. C.; Van Calenbergh, S.; Gelb, M. H.; Link, A. Polymer-Assisted Solution-Phase Synthesis of 2′-Amido-2′-deoxyadenosine Derivatives Targeted at the NAD^+-Binding Sites of Parasite Enzymes. *J. Comb. Chem.* **2000**, *2*, 537−544.
(10) Lavandera, I.; Fernández, S.; Ferrero, M.; Gotor, V. First Regioselective Enzymatic Acylation of Amino Groups Applied to Pyrimidine 3′,5′-Diaminonucleoside Derivatives. Improved Synthesis of Pyrimidine 3′,5′-Diamino-2′,3′,5′-trideoxynucleosides. *J. Org. Chem.* **2001**, *66*, 4079−4082.
(11) Golisade, A.; Van Calenbergh, S.; Link, A. 2′-Amino-2′-deoxy-N^6-(1-naphthylmethyl)adenosine as novel scaffold for a polymer-assisted amidation protocol. *Tetrahedron* **2000**, *56*, 3167−3172.
(12) Dankwardt, S.; Newman, S.; Krstenansky, J. Solid phase synthesis of aryl and benzylpiperazines and their application in combinatorial chemistry. *Tetrahedron Lett.* **1995**, *36*, 4923−4926.
(13) Tumelty, D.; Schwarz, M.; Needels, M. Solid-phase synthesis of substituted 1-phenyl-2-aminomethyl-benzimidazoles and 1-phenyl-2-thiomethyl-benzimidazoles. *Tetrahedron Lett.* **1998**, *39*, 7467−7470.
(14) Morales, G.; Corbett, J.; DeGrado, W. Solid-Phase Synthesis of Benzopiperazinones. *J. Org. Chem.* **1998**, *63*, 1172−1177.
(15) Meyers, H.; Dilley, G.; Durgin, T.; Powers, T.; Winssinger, N.; et al. Multiple simultaneous synthesis of phenolic libraries. *Mol. Diversity* **1995**, *1*, 13−20.
(16) Backes, B. J.; Virgilio, A. A.; Ellman, J. A. Activation Method To Prepare a Highly Reactive Acylsulfonamide "Safety-Catch" Linker for Solid-Phase Synthesis. *J. Am. Chem. Soc.* **1996**, *118*, 3055−3056.
(17) Ancelin, M. L.; Calas, M.; Bompart, J.; Cordina, G.; Martin, D.; et al. Antimalarial activity of 77 phospholipid polar head analogs: close correlation between inhibition of phospholipid metabolism and in vitro *Plasmodium falciparum* growth. *Blood* **1998**, *91*, 1426−1437.
(18) Desjardins, R. E.; Canfield, C. J.; Haynes, J. D.; Chulay, J. D. Quantitative assessment of antimalarial activity in vitro by a semiautomated microdilution technique. *Antimicrob. Agents Chemother.* **1979**, *16*, 710−718.
(19) Trager, W.; Jensen, J. B. Human malaria parasites in continuous culture. *Science* **1976**, *193*, 673−675.
(20) Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. Privileged molecules for protein binding identified from NMR-based screening. *J. Med. Chem.* **2000**, *43*, 3443−3447.
(21) Seok, Y. J.; Sondej, M.; Badawi, P.; Lewis, M. S.; Briggs, M. C.; et al. High affinity binding and allosteric regulation of *Escherichia coli* glycogen phosphorylase by the histidine phosphocarrier protein, HPr. *J. Biol. Chem.* **1997**, *272*, 26511−26521.
(22) Golisade, A.; Herforth, C.; Wieking, K.; Kunick, C.; Link, A. Biotin labelling of amines by polymer-assisted solution-phase synthesis. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1783−1786.

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