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Anti-Malarial Activity of N^6-Substituted Adenosine Derivatives. Part I

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Abstract—The synthesis and biological evaluation of novel N^6-substituted adenosine derivatives is reported. The first series of compounds was obtained using an established procedure for the nucleophilic substitution of a 1-(6-chloro-purin-9-yl)-β-D-1-deoxy-ribofuranose with various amines. In addition, attachment of two different amino-functionalised spacer arms at the N^6-position of adenosine enabled derivatisation by an innovative polymer-assisted protocol. Thus, we were able to prepare three series of substituted derivatives that displayed activity versus the multiresistant *Plasmodium falciparum* strain Dd2 in cell culture experiments.

Introduction

Safe and cost-effective drugs for the treatment of malaria caused by multidrug-resistant *Plasmodium falciparum* strains are urgently needed. Because *P. falciparum* is incapable of de novo purine synthesis, purine acquisition from the host is an indispensable nutritional requirement. Unlike the mammalian nucleoside transporters, those of the parasite exhibit broad substrate specificity for purine nucleosides.[1] Substituted adenosine derivatives are therefore prone to selective uptake by the parasite. The adenosine scaffold itself is relatively small and hydrophilic. Therefore, it may be regarded as a "lead-like lead structure", according to Teague et al.[2] Consequently, the synthetic attachment of lipophilic substituents to the adenosine scaffold will result in drug-like compounds with balanced physico-chemical properties.

Owing to putative interactions with various adenosine binding motifs and the special importance of the purine transport systems to parasite survival, the biological evaluation of substituted adenosine derivatives as potential anti-malarial drugs seems promising. The development of novel techniques for the combinatorial or massive parallel synthesis of arrays of adenosine analogues is therefore highly demanded.

Suitable primary aliphatic amines were selected for the synthesis of 24 novel and two known N^6-substituted adenosine derivatives. The 26 compounds prepared were evaluated for their inhibitory activity on a multidrug-resistant *P. falciparum* strain in vitro. Some of the compounds showed promising activity justifying future investigation of additional derivatives.

Chemistry

The novel amine **5** containing an ethylene glycol bridge with three ethylene units was synthesized as outlined below. Triethyleneglycol ditosylate (**1**) was thus refluxed with an equimolar amount of the sodium salt of 1-naphthol resulting in a mixture of the known compound 2-[2-(2-naphth-1-yloxy-ethoxy)-ethoxy]-ethyl-naphth-1-yl ether (**2**), unchanged triethylene glycol ditosylate (**1**) and **3**. The latter compound was transformed to the phthalimido derivative **4** and subsequently deprotected to target amine **5**. Because we were not able to obtain sufficient combustion analysis of the amine **5** or its corresponding hydrochloric acid salt, the amide **6** was prepared by treatment of **5** with succinic anhydride as a derivative for analytical purposes. Succinamic acid **6**

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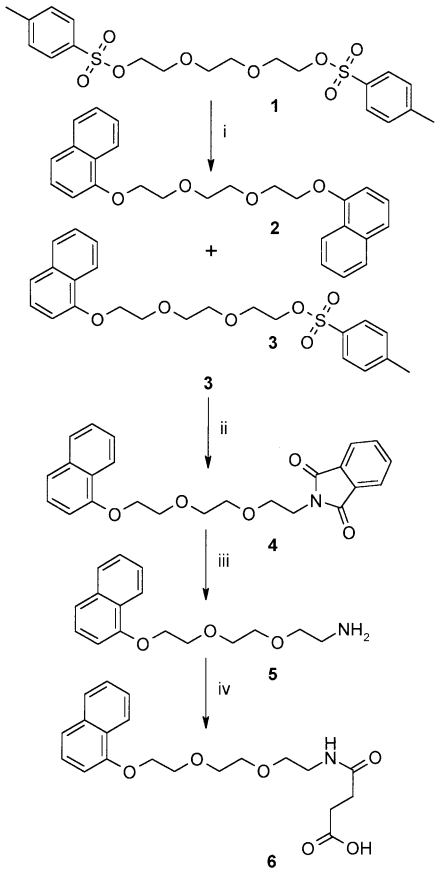
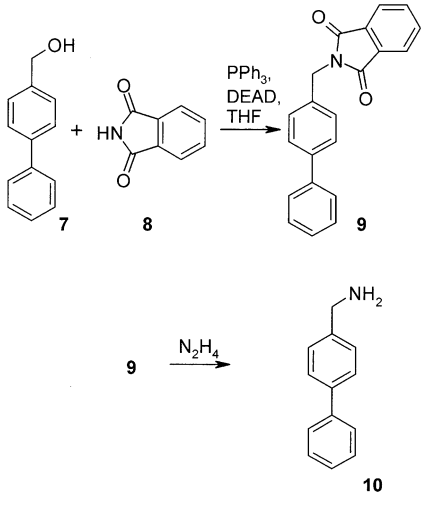


Scheme 1. Synthesis of 2-[2-(2-Naphth-1-yloxy-ethoxy)-ethoxy]-ethylamine (**5**) and succinamic acid derivative **6:** (i): 1-naphthol, NaH, THF, reflux; (ii) phthalimide potassium, DMF, 90 °C; (iii) hydrazine hydrate, EtOH, reflux; (iv) succinic anhydride, Et_3N, Na_2CO_3, CH_2Cl_2.



Scheme 2. Synthesis of 4-phenyl-benzyl amine (**10**) from 4-phenyl-benzyl alcohol (**7**).

gave satisfactory analytical results unambiguously (Scheme 1).

The commercially available inexpensive amines **15a** and **15c**,**d**,**f** were purchased from various suppliers. The expensive 4-phenyl-benzyl amine **10** as well as the known bifunctional spacer **13** was prepared from readily available starting material. The synthesis of 4-phenyl-benzyl amine (**10**) was thus performed via Mitsunobu reaction starting from 4-phenyl-benzyl alcohol (**7**) yielding *N*-(4-phenyl)benzylphthalimide (**9**). A related approach to access intermediate **9** from 4-phenyl-benzyl chloride and phthalimide potassium was reported by Cho et al. in a preliminary paper, recently, but no analytical data for the obtained compound **9** was made available.[3] The hydrazinolysis of the intermediate **9** to compound **10** proceeded smoothly under standard conditions (Scheme 2).

In order to access the bifunctional spacer **13**, 1,8-dichloro-3,6-dioxa-octane (**11**) was converted to the corresponding azide under phase-transfer catalysis as described by Reeves and Bahr.[4] Subsequent hydrogenolysis in the presence of Pd on charcoal yielded the desired compound **13** (Scheme 3).[5]

This procedure furnished better results than the use of tosyl leaving groups as described for the synthesis of intermediate **3**.

The synthesis of the desired N^6-substituted adenosine derivatives **16a**–**g** was performed by aminolysis of chloro-substituted adenosine derivative **14** with amines **5**, **10**, **13**, and **15a**,**c**,**d** and **f** at slightly elevated temperature (Scheme 4).

The N^6-substituted adenosine derivatives **16a**–**g** served as test compounds for biological evaluation purposes. In addition, **16a** and **b** were used as scaffolds for a polymer-assisted derivatisation protocol, as well.

For the introduction of different acid residues in parallel, a fast and simple workup procedure and avoidance of protecting group operations for the hydroxyl functions of the ribose moiety was regarded as crucial.

Unintentional acylation of the 5′-OH of the ribose ring is a common side reaction in the preparation of adenosine-derived amides. The resulting formed 5′-esters can easily be cleaved but would necessitate a purification step to remove the hydrolysed acid. The use of OH-protecting groups easily circumvents this problem, but would require that the protecting group would have to be removed at the end of the sequence. Therefore one individual purification operation on every single test candidate would be necessary nevertheless. Only a quantitative and chemoselective reaction of the primary amino groups of unprotected **16a** and **b** would enable a rapid parallel derivatisation of theses scaffolds.

It is known that acylated alkylsulfonamides represent chemoselective acylating species.[6] At the same time, the use of polymer-supported reagents in excess and the subsequent removal by filtration are well recognized, too.[7] Thus, the use of carboxylic acid equivalents attached to the Kenner linker (as modified by Ellman and his group) as tool for quantitative and chemoselective acylation of **16a** and **b** to the final products **18a**–**l** and **19a**–**d**, **g**–**i**, and **m** is a quite straightforward approach.[8,9] The isolated yields obtained for

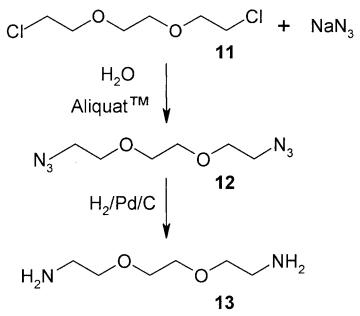
Table 1. Anti-malarial activity of compounds **16a–g**, **18a–l** and **19a–d**, **g–i**, and **m** and purity and yield of products from polymer-assisted synthesis **18a–l** and **19a–d**, **g–i**, and **m**

Compound	IC_{50}[a] (μM)	Yield[b] (%)	Purity[c] (%)
16a	115		
16b	34		
16c	38		
16d	31		
16e	19		
16f	20		
16g	16		
18a	37	93	96
18b	55	98	96
18c	30	97	96
18d	130	98	95
18e	11	87	91
18f	30	92	95
18g	75	98	97
18h	>100	93	96
18i	>100	85	87
18k	>100	98	98
18l	16	82	85
19a	8	93	95
19b	40	98	96
19c	38	97	96
19d	95	95	96
19g	70	95	97
19h	>100	95	96
19i	130	88	92
19m	22	98	96

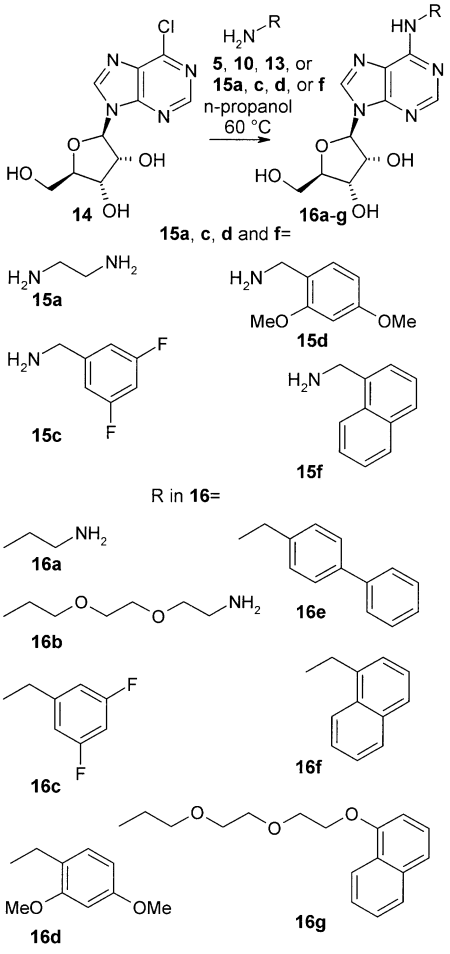
[a]The *P. falciparum* strain Dd2 (Indochina) used in this study is resistant to most commonly used anti-malarial drugs. When the resistance pattern was checked in our laboratory, the Dd2 strain was found to be highly resistant against chloroquine (IC_{50} = 170 nM), pyrimethamine (IC_{50} = 2500 nM), and cycloguanile (IC_{50} = 2200 nM), and 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).
[b]Isolated material.
[c]LC-100% method, UV detection at 254 nm.

compounds **18** and **19** ranged from 82 to 98%, purity was at least 85% and up to 97%. Typically, the yields obtained are higher than 90%, details are given in Table 1.

A polymer-assisted protocol reported recently for 2′-amino-2′-deoxyadenosine derivatives was therefore selected as method of choice and adapted for this purpose.[10] Resin aliquots **17a–k**, **m** were prepared from commercially available acids by amide bond forming procedures using in situ anhydride formation. Because the Kenner linker tolerates strongly basic or acidic conditions prior to activation, it is ideally suited for the construction of polymer-bound carboxylic acid equivalent libraries. Via on-bead modifications of carboxylic acids attached to the linker prior to activation, the range of accessible acid residues can be extended significantly. Thus, intermediate nucleophilic substitution of a polymer-bound intermediate as a source for diversity was used for the synthesis of resin **17l**. 4-Fluoro-3-nitro-benzoic acid was initially attached to the sulfamoyl linker yielding an intermediate that enabled synthesis of aniline derivative **17l** by treatment with excess *N*-ethyl benzyl amine. Because the number of available amines is exceptionally great, this drug discovery approach might become especially valuable.[11] This concept is followed by our group.



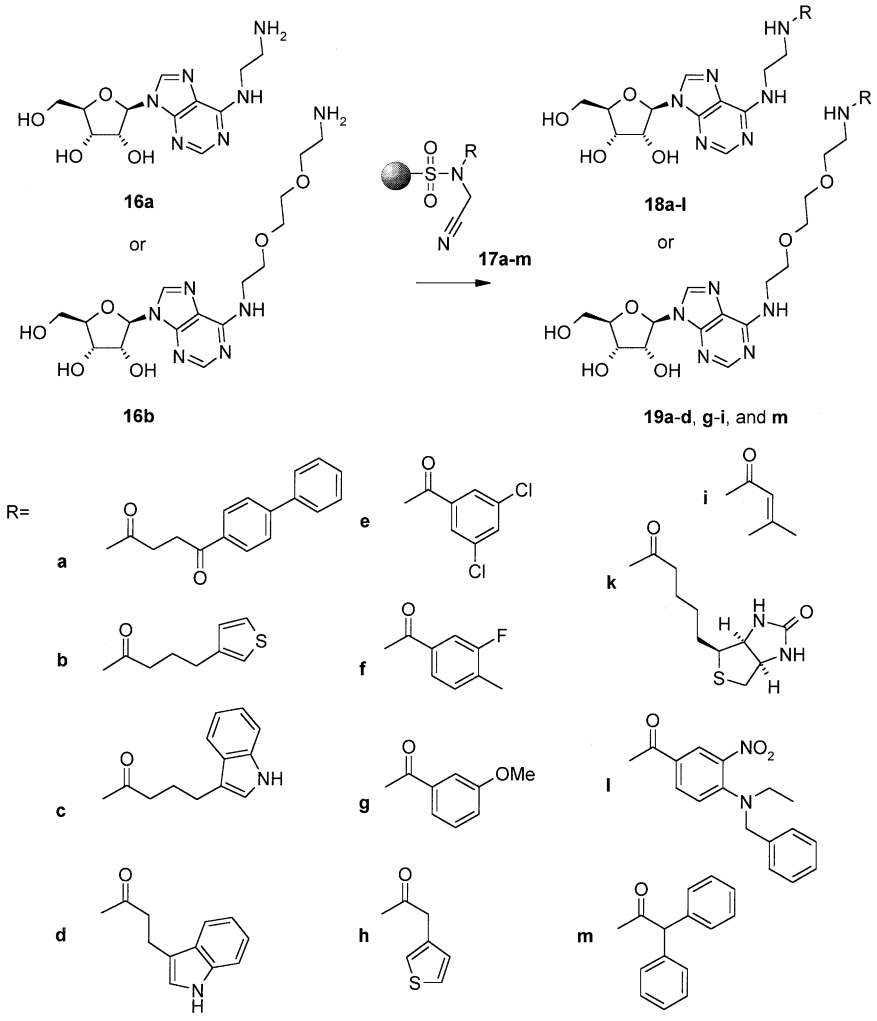
Scheme 3. Synthesis of 8-amino-3,6-dioxa-octylamine (**13**) from 1,8-dichloro-3,6-dioxa-octane (**11**).



Scheme 4. Synthesis of N^6-substituted adenosine derivatives **16a–g**.

Alkylation with bromoacetonitrile as activation step for the Kenner linker is reported to give poor results for aromatic residues adjacent to the sulfamoyl attachment site.[12] For that reason we used prolonged reaction times for this activation protocol to ensure optimal results.

The transfer of the polymer-bound carboxylic acid equivalents to the primary amine functions proceeded by agitation of the beads with the amines in solution at slightly elevated temperatures. Filtration of the beads and evaporation of the resulting product solutions



Scheme 5. Polymer-assisted synthesis of N^6-substituted adenosine derivatives **18a–l** and **19a–d**, **g–i**, and **m**.

yielded compounds **18a–l** and **19a–d**, **g–i**, and **m** ready for biological evaluation (Scheme 5).

Biological testing

Compounds **16a–g**, **18a–l** and **19a–d**, **g–i**, and **m** were evaluated for their inhibitory activity against intraerythrocytic forms of *P. falciparum* using a semi-automated microdilution assay as described.[13–15] The growth of the parasites was monitored through the incorporation of tritium-labelled hypoxanthine (Table 1).

Discussion

Despite of considerable structural diversity most of the N^6-substituted adenosine derivatives displayed moderate but significant anti-malarial activity with IC_{50} values in the range between 10 and 100 μM. Within series **16** different substituents (**16b–g**) lead to comparable activity (16–38 μM) while the ethyl amino derivative **16a** showed reduced activity (115 μM). Within the two heterogeneous series **18** and **19** both compounds that lack activity at the highest concentration tested (100 μM) and compounds acting at the low micromolar range were obtained. The decrease in lipophilicity from 3,5-dichloro over 3-fluoro-4-methyl to 3-methoxy substitution in the series of **18e–g** is in association with a declining activity from 11 μM over 30 μM to 75 μM. The relatively high activity of the *N*-benzyl, *N*-ethyl substituted nitro aniline **18l** (16 μM) is consistent with this tendency. The highest activity of 8 μM was obtained for the biphenyl derivative **19a** with a 13-atom spacer distance to the adenine ring.

Conclusion

With respect to the structural diversity of the compounds, it seems likely that not a single molecular target is recognised. Potential targets include a variety of nucleotide dependent enzymes, the parasite's nucleoside uptake machinery as well as unrelated cell functions. To further explore their potential as anti-malarial agents, additional adenosine derivatives, also comprising compounds modified at the ribose moiety, will be synthesised. Preliminary results suggest, that novel derivatives obtained by our group posess improved anti-malarial activity and will be reported as Part II of this series, soon.

Experimental

The structures of all compounds were assigned by NMR spectroscopy. NMR spectra were recorded on a Bruker AMX 400 spectrometer, using tetramethylsilane as internal standard. Identity and purity of compounds prepared on larger (g) scale was ascertained by combustion analysis, test samples prepared in mg 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. Yields are reported as isolated material. MS data (FAB) were obtained on a Finnigan MAT 311A instrument with m-nitrobenzylic alcohol as matrix. Elemental compositions were calculated on the basis of microanalysis results obtained on a Heraeus CHN-O rapid instrument. Preparative column chromatography was performed using glass columns (4.5×15 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, spots were visualized under UV-illumination.

Toluene-4-sulfonic acid 2-[2-(2-naphth-1-yloxy-ethoxy)-ethoxy] - ethyl ester (3). To a solution of 14.42 g (0.1 mol) 1-naphthol in 135 mL THF was added 3 g NaH (0.13 mol) and the resulting mixture was refluxed under nitrogen until the hydrogen formation had ceased. The hot solution was poured into another flask containing a solution of 45.8 g (0.1 mol) commercially available triethyleneglycol ditosylate (**1**) in 500 mL THF and refluxed for 2 h. After cooling to room temperature, the precipitate formed was removed by filtration and the solvent was evaporated in vacuo. The resulting red oil was dissolved in dichloromethane and washed with water, dried over sodium sulfate and concentrated to yield 43 g of a mixture of **3**, reactant **1** and the known side-product 2-[2-(2-naphth-1-yloxy-ethoxy)-ethoxy]-ethyl-naphth-1-yl ether (**2**) in a percentage 52:25:23 as calculated from the ^{1}H NMR signal ratio. The compound **3** was obtained in 48% yield (21 g) as yellow oil after chromatographic separation on silica gel using dichloromethane as eluent. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.16 (d, 1H, 8.1), 7.87 (d, 1H, 7.6 Hz), 7.77 (d, 2H, 8.2 Hz), 7.55–7.38 (m, 6H), 6.97 (d, 1H, 7.1 Hz), 4.26 (t, 2H, 4.6 Hz), 4.10 (t, 2H, 4.6 Hz), 3.87 (t, 2H, 4.6 Hz), 3.63–3.58 (m, 4H), 3.53–3.49 (m, 2H), 2.39 (s, 3H, CH_3); calcd ($C_{23}H_{26}O_6S$) C, H, S. C = 64.17, H = 6.09, S = 7.45, found: C = 63.64, H = 6.10, S = 7.28.

N-2-[2-(2-Naphth-1-yloxy-ethoxy)-ethoxy]-ethyl phthalimide (4). A mixture of 860 mg (2.0 mmol) **3** and 410 mg (2.2 mmol) phthalimide potassium salt was stirred in DMF at 90 °C for 17 h and successively at room temperature for 72 h. After adding 50 mL each of dichloromethane and water, the aqeous phase was extracted twice with 25 mL dichloromethane. The organic phases were combined and dried over magnesium sulfate. Filtration over a plug of silica gel and evaporation of the solvent yielded 367 mg (45%) of a yellow oil. An analytical sample was obtained by purification on silica gel using dichloromethane as eluent. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.11 (d, 1H, 8.1), 7.88–7.79 (m, 5H), 7.77 (d, 2H, 8.2 Hz), 7.55–7.38 (m, 4H), 6.90 (d, 1H, 7.1 Hz), 4.18 (t, 2H, 4.6 Hz), 3.75 (t, 2H, 4.6 Hz), 3.69–3.52 (m, 4H); calcd ($C_{24}H_{23}NO_5$) C 71.10, H 5.72, N 3.45, found: C 71.49, H 5.87, N 3.41.

2-[2-(2-Naphth-1-yloxy-ethoxy)-ethoxy]-ethylamine (5). A solution of 12 g crude **4** (30 mmol) and 4 g hydrazine hydrate (66 mmol) in 50 mL ethanol was stirred for 30 min at 50 °C and successively refluxed for 2 h. After cooling to room temperature, 15 mL of concentrated hydrochloric acid was added. After refluxing for 2 h the mixture was cooled to room temperature, again. The pH was adjusted to 1 by addition of hydrochloric acid and the precipitate formed was removed by filtration. The solvent was evaporated and the residue was treated with 1 L of water and alkalized by addition of sodium hydroxide and extracted with dichloromethane. The organic phase was extracted three times with 500 mL dilute hydrochloric acid (1%). The combined acidic phases were alkalized by addition of 6 M NaOH and again extracted with dichloromethane. Evaporation of the combined organic phases yielded 2.79 g (34%) of a brownish oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.20–8.15 (m, 1H), 7.89–7.84 (m, 1H), 7.55–7.46 (m, 3H), 7.41 (t, 1H, 8.2 Hz), 6.90 (d, 1H, 7.1 Hz), 4.28 (t, 2H, 5.1 Hz), 3.90 (t, 2H, 4.6 Hz), 3.70–3.65 (m, 2H), 3.60–3.53 (m, 2H), 3.37 (t, 2H, 6.1 Hz), 2.64 (br s, 4H, 2H exchangeable by D_2O, NH_2); ($C_{16}H_{21}NO_3$) No microanalysis obtained within reasonable range. Therefore, for analytical purposes, derivative **6** was prepared and gave satisfactory results.

2-[2-(2-Naphth-1-yloxy-ethoxy)-ethoxy]-ethyl succinamic acid (6). A solution of 1.92 g (7 mmol) **5** in 10 mL dichloromethane was treated with 3 mL triethylamine and combined with a suspension of 2.00 g (20 mmol) succinic anhydride and 5 g (48 mmol) sodium carbonate in 100 mL dichloromethane. After 72 h TLC analysis indicated consumption of reactant **5**. The reaction mixture was extracted with 600 mL 0.5 M NaOH solution in three portions, acidified by means of dilute hydrochloric acid (3.7%) and extracted with dichloromethane. After drying over magnesium sulfate and evaporation of the solvent 1.31 g (50%) of a pure yellow oil was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.05 (br s, 1H, OH, D_2O-exchangable), 8.20–8.15 (m, 1H), 7.91 (t, 1H, 5.6 Hz, NH, D_2O-exchangable), 7.89–7.84 (m, 1H), 7.55–7.48 (m, 2H), 7.41 (t, 1H, 7.6 Hz), 6.98 (d, 2H, 7.1 Hz), 4.28 (t, 2H, 4.6 Hz), 3.90 (t, 2H, 4.6 Hz), 3.70–3.66 (m, 2H), 3.59–3.53 (m, 2H), 3.42 (t, 2H, 6.1 Hz, C<u>H</u>$_2$–CH$_2$–N), 3.19 ('q', 2H, 5.6/6.1 Hz, CH$_2$–N, simplifies upon treatment with D_2O to: t, 6.1 Hz), 2.40 (t, 2H, 6.1 Hz, CH$_2$–CH$_2$ succinamic acid), 2.31 (t, 2H, 6.1 Hz, CH$_2$–CH$_2$ succinamic acid); calcd ($C_{20}H_{25}NO_6$) C 63.99, H 6.71, N 3.73, found: C 63.74, H 6.82, N 3.68.

***N*-(4-Phenyl)benzylphthalimid (9).** ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.93–7.85 (m, 4H), 7.63 (d, 4H, J = 8.14 Hz), 7.47–7.33 (m, 5H), 4.82 (s, 2H). ^{13}C NMR

(100 MHz, DMSO-d_6) δ (ppm) = 168.10, 140.10, 139.75, 136.23, 134.96, 131.93, 129.28, 128.40, 127.83, 127.29, 127.00, 123.61, 40.93. calcd ($C_{21}H_{15}NO_2$) C = 80.49, H = 4.82, N = 4.47, found: C = 80.11, H = 4.76, N = 4.20.

General procedure for the synthesis of compounds 16a–g

A solution of 1-(6-chloro-purin-9-yl)-β-D-1-deoxy-ribofuranose (**14**) in *n*-propanol was treated with 1.1 equivalents of the appropriate amine and 1 equivalent of Hünig's base at 60 °C. The reaction was monitored by TLC and terminated when the starting material had disappeared (12–24 h). The volatile components were removed by evaporation. The residue of the primary amines **16a** and **b** was purified over Dowex® OH^- (1×2–200) with MeOH as eluent. Compounds **16c–g** were crystallized from MeOH without resort to chromatographic purification.

N^6-(3,6-Dioxa-8-aminooctyl)adenosine (16b)

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.37 (s, 1H), 8.23 (s, 1H), 7.79 (bs, 1H), 5.90 (d, 1H, J = 6.11 Hz), 5.45 (bs, 1H), 5.41 (bs, 1H), 5.20 (bs, 1H), 4.65–4.56 (m, 1H), 4.20–4.12 (m, 1H), 4.00–3.94 (m, 1H), 3.66–3.55 (m, 12 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 154.52, 152.22, 148.26, 139.73, 87.82, 85.77, 73.40, 70.53, 69.44, 69.39, 69.33, 66.54, 66.46, 61.54, 48.48; calcd ($C_{16}H_{27}ClN_6O_6$ as hydrochloride) C 44.19, H 6.26, Cl 8.15, N 19.32, found: C 44.55, H 6.38, Cl 8.32, N 19.22. HRFAB-MS $[M+H]^+$ calcd 399.1992, found 399.2015.

N^6 - (3,5 - Difluorobenzyl)adenosine (16c). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.54 (bs, 1H), 8.42 (s, 1H), 8.23 (s, 1H), 7.10–7.03 (m, 3H), 5.92 (d, 1H, J = 6.10 Hz), 5.46 (d, 1H, J = 6.11 Hz), 5.37–5.34 (m, 1H), 5.20 (d, 1H, J = 4.58 Hz), 4.72 (bs, 2H), 4.63 (dd, 1H, J = 6.10, 5.60 Hz), 4.16 (dd, 1H, J = 4.58, 3.05 Hz), 3.98 (dd, 1H, J = 3.56, 3.06 Hz), 3.71–3.66 (m, 1H), 3.59–3.53 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 162.22 (dd, 2C, J_{CF} = 246, 12 Hz), 154.24, 152.22, 144.92, 140.08, 110.03, 109.78, 101.97, 87.82, 85.77, 73.42, 70.50, 61.51, 42.31; calcd ($C_{17}H_{17}F_2N_5O_4$) C 51.91, H 4.36, N 17.80, found: C 51.59, H 4.50, N 17.48.

N^6 - (2,4 - Dimethoxybenzyl)adenosine (16d). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.37 (bs, 1H), 8.11 (s, 1H), 8.08 (bs, 1H), 7.63 (d, 1H, J = 7.63 Hz), 6.55 (d, 1H, J = 2.55 Hz), 6.43 (dd, 1H, J = 6.10, 2.55 Hz), 5.90 (d, 1H, J = 6.11 Hz), 5.45 (d, 1H, J = 6.11 Hz), 5.42–5.39 (m, 1H), 5.19 (d, 1H, J = 4.58 Hz), 4.67–4.54 (m, 3H, benzyl CH_2 and 2′H are overlapping), 4.16–413 (m, 1H), 3.99–3.93 (m, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 3.69–3.65 (m, 1H), 3.58–3.52 (m, 1H), ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 159.36, 157.43, 152.23, 139.75, 127.57, 104.07, 98.08, 87.85, 85.80, 73.34, 70.55, 61.57, 55.28, 55.04; calcd ($C_{19}H_{23}N_5O_6$) C 54.67, H 5.55, N 16.78, found: C 54.45, H 5.65, N 16.50.

N^6 - [(4 - Phenyl)benzyl]adenosine (16e). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.54 (bs, 1H), 8.40 (s, 1H), 8.22 (bs, 1H), 7.63–7.58 (m, 4H), 7.46–7.41 (m, 4H), 7.34 (t, 1H, J = 7.63 Hz), 5.91 (d, 1H, J = 6.10 Hz), 5.47 (d, 1H, J = 6.10 Hz), 5.42–5.37 (m, 1H), 5.20 (d, 1H, 4.58 Hz), 4.75 (bs, 2H), 4.63 (dd, 1H, J = 6.10, 5.09 Hz), 4.19–4.14 (m, 1H), 4.00–3.95 (m, 1H), 3.70–3.65 (m, 1H), 3.58–3.53 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 154.85, 152.73, 140.38, 140.34, 138.94, 129.24, 128.06, 127.61, 126.92, 88.29, 86.25, 73.82, 71.00, 62.10, 42.95. HRFAB-MS $[M+H]^+$ calcd 434.1829, found 434.1848.

N^6-[3,6-Dioxa-8-(1-naphthoxy)octyl]adenosine (16g). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.37 (s, 1H), 8.23 (bs, 1H), 8.18 (d, 1H, J = 7.57 Hz), 7.77 (bs, 1H), 7.52–7.46 (m, 3H), 7.40 (t, 1H, J = 7.89 Hz), 6.96 (d, 1H, J = 7.57 Hz), 5.92 (d, 1H, J = 5.99 Hz), 5.45 (d, 1H, J = 6.30 Hz), 5.41 (dd, 1H, J = 4.73, 2.52 Hz), 5.19 (d, 1H, J = 4.73 Hz), 4.63 (dd, 1H, J = 5.99, 5.04 Hz), 4.26 (t, 2H, J = 4.41, 4.73 Hz), 4.18–4.16 (m, 1H), 3.99 (dd, 1H, J = 3.47, 3.15 Hz), 3.89 (t, 2H, J = 4.41, 4.73 Hz), 3.71–3.55 (m, 10 H), HRFAB-MS $[M+H]^+$ calcd 526.2302, found 526.2346.

Synthesis of polymer-bound acids 17

To a flask containing 2.0 g of dry 4-sulfamylbenzoylaminomethyl polystyrene 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) 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 dry THF and preactivated via in situ anhydride formation by adding 780 μL (5 mmol) *N*,*N*-diisopropylcarbodiimide. After addition of 580 μL Hünig's base (3.4 mmol) and 15 mg (0.12 mmol) 4-(dimethylamino)-pyridine 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 THF (two times 5 mL), methanol (two times 5 mL), and THF (two 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. Activation: the sulfonamide linker of 400 mg (approximately 0.4 mmol) of the resins obtained was activated for cleavage by alkylation with 640 μL (9 mmol) bromoacetonitrile, and 340 μL (2 mmol) Hünig's base in 4 mL 1-methylpyrrolidone overnight and washed with dry dimethylsulfoxide (five times 3 mL) and THF (five times 5 mL). Resin **17l** was obtained by aminolysis of 4-fluoro-3-nitro-benzoic acid attached to the linker with excess *N*-ethyl benzyl amine.

General procedure for the synthesis of compounds 18a–l and 19a–d, g–i, and m

The activated polymer-supported acids **17** resulting from the alkylation of 400 mg (approximately 0.4 mmol) described above were transferred to the amino group of

10 μmol the appropriate amine dissolved in 0.5 mL NMP, by shaking at 55 °C in 5 mL THF. The reaction was monitored by TLC and terminated when the starting material was quenched (6–96 h). Polymer beads and particulates were removed by filtration, the beads where extracted exhaustively with dry THF and the combined THF fractions were evaporated to furnish the target compounds.

N^6-(2-{4-Oxo-4-[(4-phenyl)-phenyl]butanamido}ethyl)-adenosine (18a). From resin **17a** and amine **16a**. Yield: 93%, purity: 96%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.37 (s, 1H), 8.23 (bs, 1H), 8.06 (d, 2H, J = 8.14 Hz), 7.89 (bs, 1H), 7.84 (d, 2H, J = 8.14 Hz), 7.77 (d, 2H, J = 7.63 Hz), 7.66 (d, 1H, J = 7.63 Hz), 7.54–7.43 (m, 3H), 5.90 (d, 1H, J = 6.10 Hz), 5.45 (d, 1H, J = 6.10 Hz), 5.41 (dd, 1H, J = 4.58, 2.54 Hz), 5.20 (d, 1H, J = 4.58 Hz), 4.62 (dd, 1H, J = 4.60 Hz), 4.17–4.12 (m, 1H), 3.99–3.95 (m, 1H), 3.70–3.65 (m, 1H), 3.58–3.52 (m, 3H, 5′H and CH_2 overlapped), 3.29–3.25 (m, 2H), 2.50–2.45 (m, 2H, overlapped by DMSO signal). HRFAB-MS $[M+H]^+$ calcd 547.2306, found 547.2326.

N^6-{2-[4-(3-Thienyl)butanamido]ethyl}adenosine (18b). From resin **17b** and amine **16a**. Yield: 98%, purity: 96%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.36 (s, 1H), 8.21 (bs, 1H), 7.95 (t, 1H, J = 5.59 Hz), 7.87 (bs, 1H), 7.30 (dd, 1H, J = 4.07, 1.01 Hz), 6.92 (dd, J = 3.57, 1.52 Hz), 6.82 (d, 1H, J = 3.57 Hz), 5.89 (d, 1H, J = 6.10 Hz), 5.45 (d, 1H, J = 6.10 Hz), 5.41 (dd, 1H, J = 4.58, 3.05, 4.07 Hz), 5.20 (d, 1H, J = 5.20 Hz), 4.61 (dd, 1H, J = 6.11, 5.08 Hz), 4.15 (dd, 1H, J = 5.08, 4.57, 3.06 Hz), 3.97 (dd, 1H, J = 3.57, 3.05 Hz), 3.70–3.65 (m, 1H), 3.58–3.52 (m, 3H, 5′H and CH_2 overlapped), 3.30–3.28 (m, 2H), 2.75 (t, 1H, J = 7.63 Hz), 2.12 (t, 2H, J = 7.12, 7.63 Hz), 2.10 (t, 2H, J = 7.63 Hz), 1.85–1.77 (m, 2H). HRFAB-MS $[M+H]^+$ calcd 463.1764, found 463.1736.

N^6-{2-[(3-Indolyl)butanamido]ethyl}adenosine (18c). From resin **17c** and amine **16a**. Yield: 97%, purity: 96%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 10.74 (s, 1H), 8.36 (s, 1H), 8.21 (bs, 1H), 7.94 (t, 1H, J = 5.60 Hz), 7.88 (bs, 1H), 7.49 (d, 1H, J = 7.62 Hz), 7.33 (d, 1H, J = 7.63 Hz), 7.09 (s, 1H), 7.05 (t, 1H, J = 7.63, 7.12 Hz), 6.95 (t, 1H, J = 7.63, 7.12 Hz), 5.89 (d, 1H, J = 6.10 Hz), 5.45 (d, 1H, J = 6.62 Hz), 5.41 (dd, 1H, J = 4.58, 2.54 Hz), 5.19 (d, 1H, J = 4.57 Hz), 4.61 (dd, 1H, J = 6.11, 5.08 Hz), 4.15 (dd, 1H, J = 4.58, 3.56 Hz), 3.97 (dd, 1H, J = 3.56, 3.05 Hz), 3.70–3.65 (m, 1H), 3.58–3.52 (m, 3H, 5′H and CH_2 overlapped), 3.30–3.28 (m, 2H), 2.65 (t, 2H, J = 7.63, 7.12 Hz), 2.13 (t, 2H, J = 7.63, 7.12 Hz), 1.85 (t, 2H, J = 7.63, 7.12 Hz). HRFAB-MS $[M+H]^+$ calcd 496.2309, found 496.2270.

N^6-{2-[(3-Indolyl)propanamido]ethyl}adenosine (18d). From resin **17d** and amine **16a**. Yield: 98%, purity: 95%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.73 (s, 1H), 8.37 (s, 1H), 8.23 (bs, 1H), 8.01 (t, 1H, J = 5.60 Hz), 7.89 (bs, 1H), 7.52 (d, 1H, J = 7.63 Hz), 7.33 (d, 1H, J = 8.14 Hz), 7.09 (s, 1H), 7.05 (t, 1H, J = 7.63, 7.12 Hz), 6.96 (t, 1H, J = 7.63, 7.12 Hz), 5.90 (d, 1H, J = 6.10 Hz), 5.45 (d, 1H, J = 6.10 Hz), 5.43–5.40 (m, 1H), 5.20 (d, 1H, J = 5.09 Hz), 4.62 (dd, 1H, J = 5.60, 6.11 Hz), 4.15 (dd, 1H, J = 4.58, 3.05 Hz), 3.97 (dd, 1H, J = 3.56, 3.06 Hz), 3.70–3.65 (m, 1H), 3.58–3.53 (m, 3H), 3.32–3.28 (m, 2H), 2.91 (t, 2H, J = 8.14, 7.12 Hz), 2.43 (t, 2H, J = 8.14, 7.63 Hz). HRFAB-MS $[M+H]^+$ calcd 482.2153, found 482.2134.

N^6-[2-(3,5-Dichlorobenzamido)ethyl]adenosine (18e). From resin **17e** and amine **16a**. Yield: 87%, purity: 91%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.80 (t, 1H, J = 5.09, 5.59 Hz), 8.37 (s, 1H), 8.22 (bs, 1H), 8.03 (bs, 1H), 7.84 (d, 2H, J = 7.84 Hz), 7.82–7.79 (m, 1H), 5.90 (d, 1H, J = 6.11 Hz), 5.45 (d, 1H, J = 6.10 Hz), 5.40 (dd, 1H, J = 4.58, 2.55 Hz), 5.20 (d, 1H, J = 4.58 Hz), 4.61 (dd, 1H, J = 5.59, 5.60 Hz), 4.16–4.13 (m, 1H), 3.97 (dd, 1H, J = 3.05, 3.56 Hz), 3.70–3.65 (m, 3H, 5′H and CH_2 overlapped), 3.58–3.50 (m, 3H, 5′H and CH_2 overlapped). HRFAB-MS $[M+H]^+$ calcd 483.0951, found 483.0912.

N^6-[2-(3-Fluoro-4-methylbenzamido)ethyl]adenosine (18f). From resin **17f** and amine **16a**. Yield: 92%, purity: 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.61 (t, 1H, J = 4.58 Hz), 8.37 (s, 1H), 8.23 (s, 1H), 8.02 (bs, 1H), 7.60–7.57 (m, 2H), 7.38 (dd, 1H, J = 8.13, 7.63 Hz), 5.90 (d, 1H, J = 5.60 Hz), 5.46 (d, 1H, J = 6.61 Hz), 5.41 (dd, 1H, J = 4.58, 2.55 Hz), 5.20 (d, 1H, J = 4.58 Hz), 4.62 (dd, 1H, J = 5.60, 6.11 Hz), 4.15 (t, 1H, J = 4.58, 3.56 Hz), 3.97 (dd, 1H, J = 3.56, 3.06 Hz), 3.70–3.66 (m, 3H, 5′H and CH_2 overlapped), 3.58–3.49 (m, 3H, 5′H and CH_2 overlapped), 2.28 (s, 3H). HRFAB-MS $[M+H]^+$ calcd 447.1793, found 447.1802.

N^6-[2-(3-Methoxybenzamido)ethyl]adenosine (18g). From resin **17g** and amine **16a**. Yield: 98%, purity: 97%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.58 (t, 1H, J = 5.09, 4.57 Hz), 8.36 (s, 1H), 8.23 (bs, 1H), 8.01 (bs, 1H), 7.42–7.34 (m, 3H), 7.09 (dd, 1H, J = 5.09, 2.03, 1.52, Hz), 5.90 (d, 1H, J = 6.11 Hz), 5.45 (d, 1H, J = 6.11 Hz), 5.40 (dd, 1H, J = 4.57, 2.55 Hz), 5.20 (d. 1H, J = 4.58 Hz), 4.61 (dd, 1H, J = 6.10, 5.60 Hz), 4.14 (dd, 1H, J = 4.58, 3.05 Hz), 3.97 (dd, 1H, J = 3.56, 3.05 Hz), 3.79 (s, 3H), 3.70–3.65 (m, 3H, 5′H and CH_2 overlapped), 3.58–3.51 (m, 3H, 5′H and CH_2 overlapped), HRFAB-MS $[M+H]^+$ calcd 445.1836, found 445.1812.

N^6-{2-[(3-Thienyl)acetamido]ethyl}adenosine (18h). From resin **17h** and amine **16a**. Yield: 93%, purity: 96%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.36 (s, 1H), 8.21 (bs, 1H), 8.10 (t, 1H, J = 5.60, Hz), 7.41–7.39 (m, 1H), 7.23–7.20 (m, 1H), 6.98 (dd, 1H, J = 3.56, 1.27 Hz), 5.90 (d, 1H, J = 6.11 Hz), 5.46 (bs, 1H), 5.38 (bs, 1H), 5.18 (bs, 1H), 4.62–4.60 (m, 1H), 4.16–4.14 (m, 1H), 3.98–3.96 (m, 1H), 3.70–3.66 (m, 1H), 3.62–3.48 (m, 3H, 5′H and CH_2 overlapped), 3.41 (s, 2H), 3.41 (d, 2H, J = 5.60 Hz), 3.33–3.28 (m, 2H, by H_2O signal overlapped). HRFAB-MS $[M+H]^+$ calcd 435.1451, found 435.1400.

N^6-[2-(3,3-Dimethylacrylamido)ethyl]adenosine (18i). From resin **17i** and amine **16a**. Yield: 85%, purity:

87%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.36 (s, 1H), 8.22 (bs, 1H), 7.88 (bs, 1H N^6-H and t, 1H NH amid J = 5.60 Hz overlapped), 5.89 (d, 1H, J = 6.10 Hz), 5.61 (s, 1H), 5.45 (d, 1H, J = 6.62 Hz), 5.41 (dd, 1H, J = 4.57, 2.55 Hz), 5.20 (d, 1H, J = 4.57 Hz), 4.61 (dd, 1H, J = 6.10, 5.09 Hz), 4.16–4.13 (m, 1H), 3.97 (dd, 1H, J = 3.56, 3.05 Hz), 3.70–3.65 (m, 1H), 3.58–3.52 (m, 3H, 5′H and CH_2 overlapped), 2.06 (s, 3H), 1.77 (s, 3H). HRFAB-MS $[M+H]^+$ calcd 393.1887, found 393.1857.

N^6-[(2-Biotinylamido)ethyl]adenosine (18k). From resin **17k** and amine **16a**. Yield: 98%, purity: 98%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.36 (s, 1H), 8.22 (s, 1H), 7.94 (t, 1H, J = 5.60 Hz), 7.85 (bs, 1H), 6.41(s, 1H), 6.35 (s, 1H), 5.89 (d, 1H, J = 6.10 Hz), 5.45 (d, 1H, J = 6.10 Hz), 5.42 (dd, 1H, J = 4.58, 2.55 Hz), 5.20 (d, 1H), 4.61 (dd, 1H), 4.31–4.28 (m, 1H), 4.16–4.09 (m, 2H), 3.98–3.95 (m, 1H), 3.70–3.65 (m, 1H), 3.58–3.52 (m, 3H, 5′H and CH_2 overlapped), 3.08–3.03 (m, 1H), 2.82(dd, 1H, J = 5.09, 7.63 Hz), 2.58(d, 1H, J = 12.21 Hz), 2.05 (t, 2H, J = 7.12, 7.63 Hz), 1.64–1.20(m, 6H). HRFAB-MS $[M+H]^+$ calcd 537.2245, found 537.2249.

N^6-{2-[4-(N-ethyl-N-benzylamino)-3-nitrobenzamido]ethyl}adenosine (18l). From resin **17l** and amine **16a**. Yield: 82%, purity: 85%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.61 (t, 1H, J = 5.60, 5.08 Hz), 8.36 (s, 1H), 8.22 and 8.21 (2s, 2H overlapped), 8.01 (bs, 1H), 7.90 (dd, 1H, J = 6.61, 2.04 Hz), 7.33–7.21 (m, 6H), 5.89 (d, 1H, J = 6.10 Hz), 5.46 (d, 1H, J = 5.60 Hz), 5.39 (dd, 1H, J = 4.58, 2.54 Hz), 5.20 (d, 1H, J = 4.57 Hz), 4.61 (dd, 1H, J = 5.60, 5.08 Hz), 4.44 (s, 2H), 4.14 (dd, 1H, J = 4.58, 3.05 Hz), 3.96 (dd, 1H, J = 3.56, 3.05 Hz), 3.70–3.63 (m, 3H, 5′H and CH_2 overlapped), 3.58–3.48 (m, 3H, 5′H and CH_2 overlapped), 3.18 (q, 2H, J = 7.12, 7.13 Hz), 1.07 (t, 3H, J = 7.13, 7.12 Hz). HRFAB-MS $[M+H]^+$ calcd 593.2473, found 593.2448.

N^6-(3,6-Dioxa-8-{4-oxo-4-[(4-phenyl)-phenyl]butanamido}octyl)adenosine (19a). From resin **17a** and amine **16b**. Yield: 93%, purity: 95%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.36 (s, 1H), 8.22 (bs, 1H), 8.06 (d, 2H, J = 8.14 Hz), 7.98 (t, 1H, J = 5.60 Hz), 7.83 (d, 2H, J = 8.14 Hz), 7.76 (d, 2H, J = 7.63 Hz), 7.70–7.65 (m, 1H), 7.53–7.41 (m, 3H), 5.89 (d, 1H, J = 6.10 Hz), 5.45 (d, 1H, J = 6.11 Hz), 5.40 (dd, 1H, J = 4.58, 2.54 Hz), 5.20 (d, 1H, J = 4.58 Hz), 4.61 (dd, 1H, J = 6.11, 5.08 Hz), 4.15 (dd, 1H, J = 4.58, 3.05 Hz), 3.97 (dd, 1H, J = 3.56, 3.05 Hz), 3.70–3.51 (m, 10H), 3.42–3.37 (m, 2H), 3.25 (t, 2H, J = 6.61 Hz), 3.22–3.17 (m, 2H), 2.50–2.47 (m, 2H, overlapped by DMSO signal). HRFAB-MS $[M+H]^+$ calcd 635.2830, found 635.2838.

N^6-{3,6-Dioxa-8-[4-(3-thienyl)butyramido)octyl]adenosine (19b). From resin **17b** and amine **16b**. Yield: 98%, purity: 96%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.39 (s, 1H), 8.24 (s, 1H), 7.92 (bs,1H), 7.86 (t, 1H, J = 5.60 Hz), 7.29 (dd, 1H, J = 4.07, 1.02 Hz), 6.92 (dd, 1H, J = 3.56, 1.52 Hz), 6.83 (d, 1H, J = 3.58 Hz), 5.90 (d, 1H, J = 6.10 Hz), 4.59 (t, 1H, J = 5.60, 5.08 Hz), 4.16–4.14 (m, 1H), 3.97 (t, 1H, J = 3.56, 3.06 Hz), 3.69–3.49 (m, 14 H), 2.75 (t, 2H, J = 7.63 Hz), 2.12 (t, 2H, J = 7.63, 7.12 Hz), 1.84–1.77 (m, 2H). HRFAB-MS $[M+H]^+$ calcd 551.2289, found 551.2247.

N^6-{3,6-Dioxa-8-[4-(3-indolyl)butanamido)octyl]adenosine (19c). From resin **17c** and amine **16b**. Yield: 97%, purity: 96%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.74 (s, 1H), 8.37 (s, 1H), 8.23 (bs, 1H); 7.86 (t, 1H, J = 5.60, 5.09 Hz), 7.78 (bs, 1H), 7.50 (d, 1H, J = 7.63 Hz), 7.33 (d, 1H, J = 8.14 Hz), 7.09 (s, 1H), 7.05 (t, 1H, J = 7.63, 7,13 Hz), 6.95 (t, 1H, J = 7.63, 7.13 Hz), 5.91 (d, 1H, J = 6.10 Hz), 5.52 (bs, 1H), 5.43 (bs, 1H), 5.22 (bs, 1H), 4.62 (t, 1H, J = 5.60 Hz), 4.17–4.15 (m, 1H), 3.99–3.97 (m, 1H), 3.70–3.50 (m, 10H), 3.22–3.17 (m, 2H), 2.65 (t, 2H, J = 7.63, 7.12 Hz), 2.14 (t, 2H, J = 7.63 Hz), 1.93–1.82 (m, 2H). HRFAB-MS $[M+H]^+$ calcd 584.2833, found = 584.2849.

N^6-{3,6-Dioxa-8-[3-(3-indolyl)propanamido)octyl]adenosine (19d). From resin **17d** and amine **16b**. Yield: 95%, purity: 96%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.74 (s, 1H), 8.37 (s, 1H), 8.23 (bs, 1H), 7.92 (t, 1H, J = 5.60 Hz), 7.78 (bs, 1H), 7.52 (d, 1H, J = 7.63 Hz), 7.33 (d, 1H, J = 8.14 Hz), 7.08 (s, 1H), 7.05 (t, 1H, J = 7.63, 7.12 Hz), 6.96 (t, 1H, J = 7.63, 7.12 Hz), 5.91 (d, 1H, J = 6.61 Hz), 5.46 (bs, 1H), 5.42 (bs, 1H), 5.21 (bs, 1H), 4.63–4.61 (m, 1H), 4.17–4.15 (m, 1H), 4.00–3.96 (m, 1H), 3.70–3.47 (m, 10 H), 3.21–3.17 (m, 2H), 2.91 (t, 2H, J = 8.14, 7.12 Hz), 2.44 (t, 2H, J = 8.14, 7.12 Hz). HRFAB-MS $[M+H]^+$ calcd 570.2677, found 570.2692.

N^6-[3,6-Dioxa-8-(3-methoxybenzamido)octyl]adenosine (19g). From resin **17g** and amine **16b**. Yield: 95%, purity: 97%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.51 (t, 1H, J = 5.59, 5.09 Hz), 8.36 (s, 1H), 8.21 (bs, 1H), 7.78 (bs, 1H), 7.42–7.33 (m, 3H), 7.08–7.06 (m, 1H), 5.89 (d, 1H, J = 6.10 Hz), 5.45 (d, 1H, J = 6.10 Hz), 5.40 (dd, 1H, J = 4.58, 2,54 Hz), 5.20 (d, 1H, J = 4.58 Hz), 4.60 (dd, 1H, J = 6.10, 5.09 Hz), 4.16–4.13 (m, 1H), 3.96 (dd, 1H, J = 3.56, 3.05 Hz), 3.79 (s, 3H), 3.70–3.51 (m, 12H), 3.40–3.38 (m, 2H). HRFAB-MS $[M+H]^+$ calcd 533.2361, found = 533.2331.

N^6-[3,6-Dioxa-8-(3-thienyl)acetamido)octyl]adenosine (19h). From resin **17h** and amine **16b**. Yield: 95%, purity: 96%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.37 (s, 1H), 8.23 (bs, 1H), 8.06 (t, 1H, J = 5.60, 5.06 Hz), 7.44–7.42 (m, 1H), 7.23–7.21 (m, 1H), 7.02–6.99 (m, 1H), 5.90 (d, 1H, J = 6.11 Hz), 5.46 (bs, 1H), 5.42 (bs, 1H), 5.21 (bs, 1H), 4.64–4.57 (m, 1H), 4.18–4.13 (m, 1H), 3.70–3.46 (m, 10H), 3.42 (s, 2H), 3.41 (d, 2H, J = 5.60 Hz), 3.22–3.18 (m, 2H). HRFAB-MS $[M+H]^+$ calcd 523.1976, found 523.2018.

N^6-[3,6-Dioxa-8-(3,3-dimethylacrylamido)octyl]adenosine (19i). From resin **17i** and amine **16b**. Yield: 88%, purity: 92%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.36 (s, 1H), 8.22 (bs, 1H), 7.78 (t, 1H, J = 5.09 Hz, and bs 1H overlapped), 5.89 (d, 1H, J = 6.10 Hz), 5.64 (s, 1H), 5.45 (d, 1H, J = 6.10 Hz), 5.41 (dd, 1H, J = 4.58, 2.54 Hz), 5.20 (d, 1H, J = 4.57 Hz), 4.61 (dd, 1H, J = 6.11, 5.08 Hz), 4.15 (dd, 1H, J = 4.58, 3.56 Hz), 3.96

(dd, 1H, $J = 3.56$, 3.05 Hz), 3.70–3.49 (m, 10H), 3.41–3.38 (m, 2H), 3.22–3.18 (m, 2H), 2.06 (s, 3H), 1.75 (s, 3H). HRFAB-MS $[M+H]^+$ calcd 481.2411, found 481.2462.

N^6 - [3,6 - Dioxa - 8 - (diphenylacetamido)octyl]adenosine (19m). From resin **17m** and amine **16b**. Yield: 98%, purity: 96%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.36 (s, 1H), 8.31 (t, 1H, $J = 5.60$, 5.34 Hz), 8.22 (bs, 1H), 7.73 (bs 1H), 7.29 (s, 4H), 7.28 (s, 4H), 7.23–7.18 (m, 2H), 5.90 (d, 1H, $J = 6.11$ Hz), 5.44 (bs, 1H), 5.38 (bs, 1H), 5.19 (bs, 1H), 4.96 (s, 1H), 4.64–4.58 (m, 1H), 4.17–4.14 (m, 1H), 3.98–3.96 (m, 1H), 3.70–3.47 (m, 10H), 3.42 (t, 2H, $J = 5.85$, 5.60 Hz), 3.26–3.21 (m, 2H). HRFAB-MS $[M+H]^+$ calcd 593.2724, found 593.2698.

In vitro measurement of *P. falciparum* growth inhibition

The *P. falciparum* strain Dd2 was cultivated by a modification of the method described by Trager and Jensen.[15] 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 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 measured using a β-counter (Matrix 9600, Packard).

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