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Inhibitors of adenosine consuming parasites through polymer-assisted solution phase synthesis of lipophilic 5′-amido-5′-deoxyadenosine derivatives

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ABSTRACT

Given the more or less global spread of multidrug-resistant plasmodia, structurally diverse starting points for the development of chemotherapeutic agents for the treatment of malaria are urgently needed. Thus, a series of 20 adenosine derivatives with a large lipophilic substituent in N^6-position were prepared in order to evaluate their potential to inhibit the chloroquine resistant *Plasmodium falciparum* strain K1 in vitro. The rationale for synthesis of these structures was the high probability of interactions with multiple adenosine associated targets and the assumption that a large hydrophobic N^6-(4-phenoxy)benzyl substitution should allow the molecules to diffuse across parasite membranes. Starting from readily available inosine, the new compounds were prepared as single isomers using a polymer-assisted acylation protocol enabling the straightforward isolation of the target compounds in pure form. Heterocyclic ring systems were synthesized on-bead on Kenner's safety-catch linker prior to acylation of the scaffold in solution. Most of the highly pure compounds displayed anti-plasmodial activity in the low micromolar or even submicromolar concentration range.

1. Introduction

The year 2008 marked the centennial anniversary of the award of the Nobel Prize to Paul Ehrlich. His impact, however, extended far beyond his prize-winning achievements in immunology.[1] During his early research with lipophilic dyes, he had investigated the effects of methylene blue on malaria causing parasites, and so Ehrlich as well pioneered the quest for drugs against plasmodia. Given the more or less global spread of multidrug-resistant malaria these are once again in urgent demand, today. Several new anti-malarial agents are currently undergoing clinical trials, mainly those resurrected from earlier anti-malarial drug discovery programs.[2] In addition truly novel compounds are being advanced through the drug development process. At present there are four such compounds in Phase III resulting from research funded by the Medicines for Malaria Venture.[3] But looking at the notoriously high failure rate typical of drug discovery, there is still a need for novel starting-points for the development of new low-cost effective therapies for drug-resistant malaria. In continuation of our efforts to identify new adenosine derived nucleosides with anti-plasmodial activity, we focused on the synthesis of adenosine derivatives with dual substitution in 5′- and N^6-position[4] because we already were able to identify active compounds with this substitution pattern before[5] as exemplified by our lead structure (Fig. 1) **1**. Herein we report the polymer-assisted parallel synthesis of a series of 20 carboxylic acid amides of 5′-amino-5′-deoxy-N^6-(4-phenoxy)benzyl adenosine (**6**) (see Scheme 1).

2. Chemistry

The 4-phenoxybenzyl-substituent in template **6** is introduced into 6-deamino-6-chloro adenosine[6] (**2**) using an excess of 4-phenoxybenzylamine (**3**). Compound **3** is accessible starting from cheap 4-phenoxybenzoic acid (not shown). The corresponding carboxylic acid chloride is generated by treatment with thionyl chloride, reacted with ammonia and reduced using lithium alanate following established procedures. The resulting 4-phenoxybenzylamine (**3**) is best purified and stored as its hydrochloride salt. The displace-

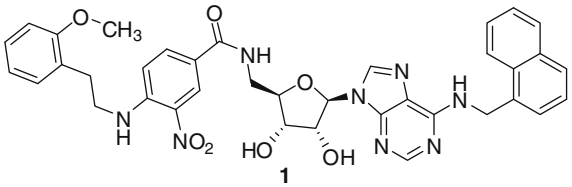

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Figure 1. Lead Structure: 5′,N^6-disubstituted adenosine derivative **1**.

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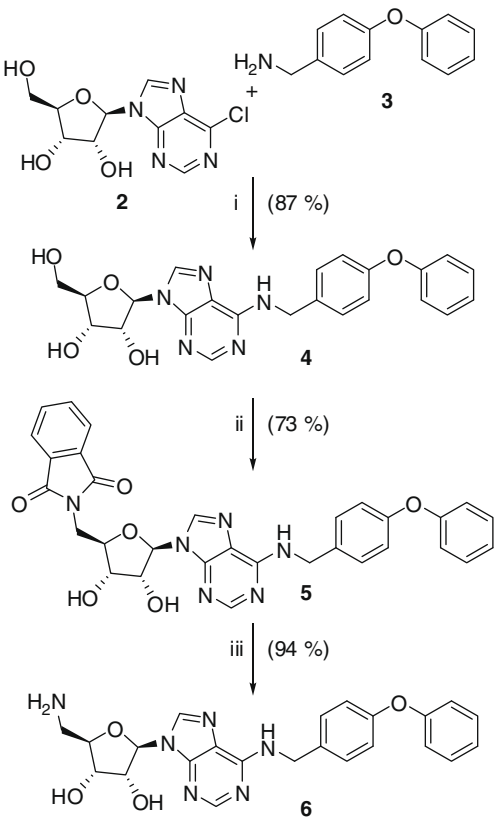
ment of the 5′-hydroxyl group of N^6-substituted adenosine **4** by an amino group is performed using a standard Mitsunobu protocol.[7] In this way, a phthalimide residue is introduced chemoselectively at the most acidic, primary alcohol function and consequently regioselectively in 5′-position. The mandatory removal of the phthalic acid group is usually initiated by the addition of hydrazine. However, in this case this reaction was sluggish and incomplete in our hands, even under forcing conditions. Resort to the alternative methyl hydrazine did not improve the situation, while the use of methylamine lead to the desired removal of the phthaloyl group under mild conditions at room temperature. Necessary purification of **6** was performed using column chromatography over strongly basic ion exchange resin (see Scheme 1).

Meanwhile, polymer-bound acylation reagents were prepared. For the connection of carboxylic acids with primary amines, diverse types of functional anchor groups have been described such as pyrimidinone-linkers,[8] *N*-hydroxysuccinimide-linker,[9] *N*-acylindol-linkers,[10] 2,4,6-trichloro[1,3,5]triazene-linkers,[11] and pyrazolone active esters[12] to name only a few of the most popular. For the first subset of simple carboxylic acids 2,3,5,6-tetrafluoro-4-hydroxy benzoic acid as commercially available couple&release linker was chosen.[13] The labile carboxylic acid-linker bond of acids attached to this linker results from strong electron withdrawing properties of fluoro substituents of the benzene ring. However, the comparably high reactivity of this bond is the reason for the limited applicability in solid-phase synthesis protocols, but renders this construct an attractive choice for the transfer of simple carboxylic acid residues onto nucleophiles. During the attachment of 2,3,5,6-tetrafluoro-4-hydroxy benzoic acid on aminomethylated polystyrene through in situ activation using *N*,*N*′-diisopropyl-carbodiimide (DIC) and benzotriazol-1-ol (*N*-hydroxy benzotriazole, HOBt) the unintended formation of phenolic esters **8** had to be taken into account.

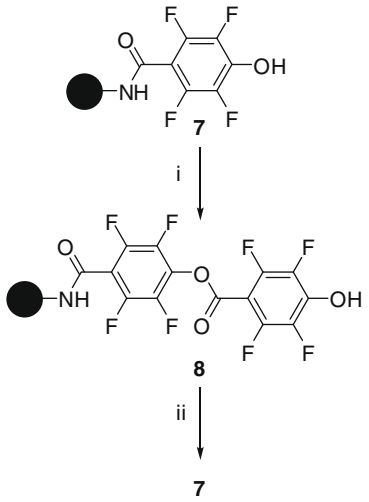
This side reaction can easily be monitored by investigation of the diagnostic infrared absorption at 1765 cm^{-1}. Thus, treatment of **8** with a weak base like piperidine and subsequent washing with hydrochloric acid in *N*,*N*-dimethyl formamide (DMF) is mandatory in order to destroy the side-product quantitatively, remove unbound 2,3,5,6-tetrafluoro-4-hydroxy benzoic acid and thus gain access to linker-construct **7** with free phenolic OH-groups. The appropriate carboxylic acids were coupled to this linker using in situ activation by means of DIC via the corresponding *O*-acylisoureas in the presence of catalytic amounts of 4-dimethylamino-pyridine (DMAP) (see Scheme 2).

Because Caddick et al. reported the possibility to transform acrylic acid derivatives bound to this linker (**9**) into branched aliphatic carboxylic acids like **10**{*6*} via radicalic addition of alkyliodides in the presence of tributyl tin hydride and azobisisobutyronitrile (AIBN), we tried to adapt this reaction using 10 different alkyl iodides.[14] Due to the fact that this reaction requires harsh conditions (100 °C, 90 min), that possibly lead to the disintegration of the polymer backbone, in most of the cases no suitable polymer-bound reagents could be obtained. Only in the case of *tert*-butyliodide and 2-iodopropane lead the reaction to the formation of appropriate polymer-bound carboxylic acid equivalents in sufficient purity that could be used in the derivatization of template **6**. In order to avoid ambiguous results, test samples for biological evaluation were not prepared following this route. Identical specimen of 5′-deoxy-5′-[(4-methyl)pentanamido]-N^6-(4-phenoxybenzyl)adenosine (**21**) were synthesized via coupling of 4-methylpentanoic acid to linker construct **7**, and used for testing instead (see Scheme 3).

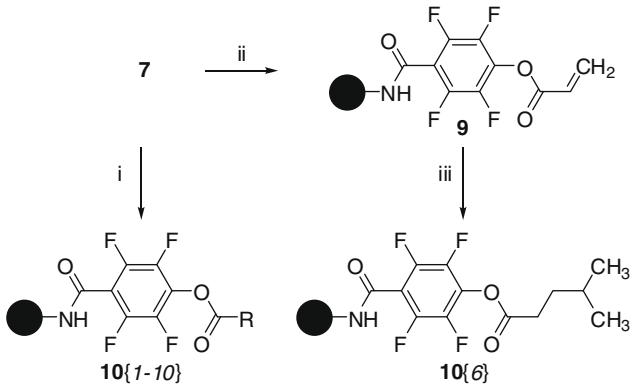
For a second subset of more demanding carboxylic acids we envisioned to prepare benzimidazoles and benzimidazolinones via nuclophilic aromatic substitution. Thus, Kenner's safety-catch linker was attached to aminomethylated polystyrene and loaded with 4-fluoro-3-nitrobenzoic acid to give **11**.[15] This aromatic carboxylic acid has been shown by us[16] and others[17] to be well suited for the quantitative transformation into anilines by treatment with various amines and subsequent reduction of the nitro group using tin-II-chloride-solution in DMF. The resulting substituted *ortho*-



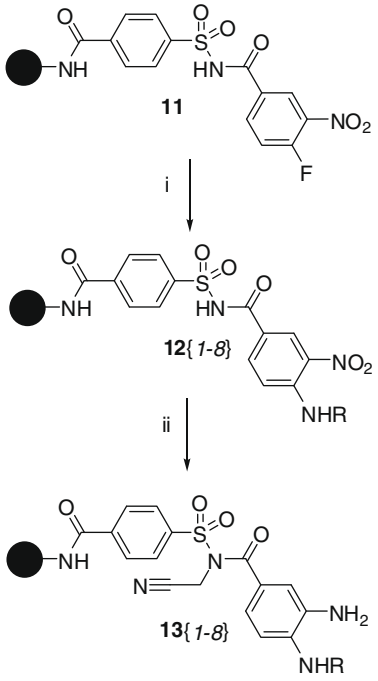
Scheme 1. Synthesis of 5′-amino-5′-deoxy-N^6-(4-phenoxybenzyl)adenosine (**6**). Reagents and conditions: (i) 1-Propanol, Hünig's base, 60 °C, 24 h; 5 °C, 24 h; (ii) dry THF, PPh_3, phthalimide, di-*tert*-butyl-azodicarboxylate 0.5 h, −20 °C; (iii) EtOH, CH_3NH_2, 20 °C, 2 h.



Scheme 2. Aminolysis of active ester **8** resulting from overacylation of linker construct **7**. Reagents and conditions: (i) Unintended overacylation during coupling (conditions as described[13]): 2,3,5,6,-tetrafluoro-4-hydroxybenzoic acid (1.7 equiv), DIC (1.5 equiv), DMF, HOBt (1.5 equiv), 25 °C, 16 h; (ii) piperidine in DMF, HCl in DMF.



Scheme 3. Loading of and C-bond formation on couple&release linker **7** yielding Chemset **10**{*1–10*}. Reagents and conditions: (i) DMF, carboxylic acid RCOOH (for R see Table 1, entries **16–25**) (2 equiv), DMAP (0.2 equiv) DIC (2 equiv), 16 h (ii) as (i), (conditions as described[14]): DMF, acrylic acid (5 equiv) DMAP (0.2 equiv) DIC (5 equiv), 16 h iii) (conditions as described[14]): 2-iodopropane (5 equiv), Bu_3SnH (5 equiv), AIBN (1 equiv), toluene, 100 °C, 1.5 h.

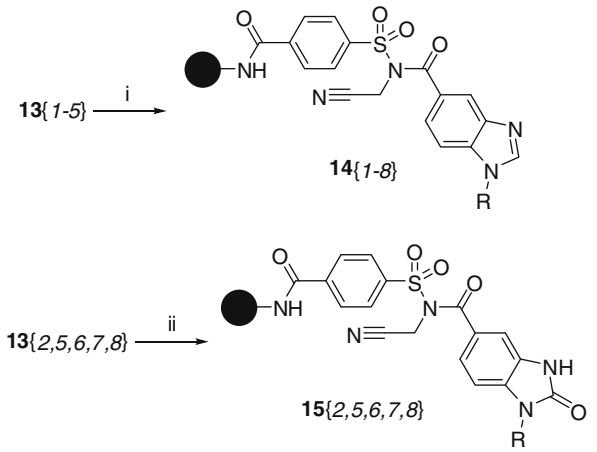


Scheme 4. Nucleophilic aromatic substitution and subsequent reduction yielding *ortho*-dianiline Chemset **13**{*1–8*}. Reagents and conditions: (i) Allylamine, naphthalen-1-ylmethylamine, pentylamine, pyridin-2-methylamine, 3-methoxy-propylamine, 2-cyclohex-1-enyl-ethylamine, 4-methoxy-benzylamine, or butylamine, separately; R groups in Chemsets **12–15**{*1–8*} can be deduced from the residues of these amines; (ii) $SnCl_2$ (excess) in DMF, 25 °C, 10 h, twice.

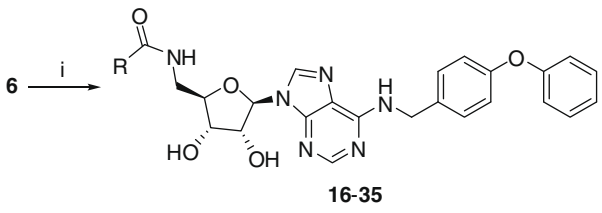
dianilines **13**{*1–8*} enabled the formation of heterocyclic rings typical for drug-like small molecules (see Scheme 4).[18]

By treatment of the first five members of chemset **13**{*1–8*} with carbonic acid *ortho*-esters and subsequent activation of the safety-catch, the benzimidazole chemset **14**{*1–5*} was obtained. Reaction of **13**{*2,5,6,7,8*} with carbonyl diimidazole (CDI) yielded substituted benzimidazolinones that could be activated to chemset **15**{*2,5,6,7,8*}. The polymer bound heterocyclic carboxylic acid equivalents could be used as polymer-bound reagents to generate target compounds **26–35** (see Scheme 5).

The quantitative acylation of template **6** with an excess of the individual polymer-bound reagents was performed in parallel. After completion of the reactions, the resulting amides formed



Scheme 5. Formation of heterocyclic carboxylic acid equivalents **14**{*1–5*} and **15**{*2,5,6,7,8*} as polymer-supported acylation reagents. Reagents and conditions: (i) Triethyl orthoformate (2.5 equiv) in CH_2Cl_2; activation with bromo acetonitril in 1-methyl-pyrrolidin-2-one (NMP), Hünig's base (ii) CDI (4 equiv) in DMF, THF or CH_2Cl_2, repeat; activation with bromo acetonitril in NMP, Hünig's base.



Scheme 6. Polymer-assisted synthesis of target compounds **16–35**. Reagents and conditions: (i) **10**{*1–10*}, **14**{*1–5*}, **15**{*2,5,6,7,8*}, separately.

were filtered over glass filter funnels and the solvent was removed under reduced pressure. In order to remove notorious invisible impurities such as inorganic salts or tiny polymeric fragments of polystyrene beads all compounds were purified over flash-chromatography columns using a medium pressure LC system (see Scheme 6).[19]

3. Results

After an operationally simple to perform parallel chromatographic purification protocol, 20 adenosine derivatives were obtained in high yield and purity and subjected to spectroscopic characterization and biological evaluation. The results of these investigations are listed in Table 1.

4. Discussion

The common key step in the on-bead syntheses of the two types of heterocyclic carboxylic acids are the nucleophilic substitution reactions using various nucleophilic amines. This nucleophilic aromatic substitution is especially well-suited for solid-phase transformations because it is generally possible to achieve complete conversion of the starting material. This is a prerequisite for product purity at the end of multi-step syntheses. Because the treatment with nucleophilic amines will cleave the reactive phenol ester bond, this versatile reaction cannot be applied using a simple couple&release linker intended to react with amines. Quite to the contrary, Kenner's safety-catch linker especially the variants invented by Ellman et al. is stable towards the amines used in the nucleophilic substitution step und thus the appropriate choice for the construction of the heterocyclic carboxylic acid equiva-

Table 1
Residues in target compounds **16–35** as depicted in scheme 6, purity and biological activity

Entry	R	Yield[a] (%)	Purity[b] (%)	IC_{50}[c] (μM)
16	2-Methyl-prop-1-en-1-yl	99	97.2	4.3
17	3-Phenoxy-prop-1-yl	98	100.0	2.8
18	3-Phenyl-prop-1-yl	100	100.0	2.6
19	(Indol-3-yl)prop-1-yl	98	100.0	>8.5
20	(Naphthalen-1-yl)methyl	98	100.0	0.3
21	3-Methyl-but-1-yl	97	100.0	4.6
22	(3-Chlorophenyl)methyl	95	100.0	3.1
23	(3-Methoxyphenyl)methyl	97	100.0	3.4
24	3,5-Dichlorophenyl	83	100.0	3.5
25	(4-Phenoxy)phenyl	98	92.3	3.3
26	1-Allyl-1*H*-benzimidazol-5-yl	100	100.0	2.7
27	1-(Naphthalen-1-yl)methyl-1*H*-benzimidazol-5-yl	100	97.4	2.2
28	1-(Pent-1-yl)-1*H*-benzimidazol-5-yl	99	100.0	1.5
29	1-(Pyridin-2-yl)methyl-1*H*-benzimidazol-5-yl	96	67.4	4.0
30	1-(Methoxyprop-1-yl)-1*H*-benzimidazol-5-yl	98	100.0	2.6
31	1-[2-(Cyclohex-1-en-1-yl)ethyl]2-oxo-2,3-dihydro-1*H*-benzimidazol-5-yl	84	77.1	2.9
32	1-(4-Phenoxymethyl)-2-oxo-2,3-dihydro-1*H*-benzimidazol-5-yl	98	85.4	3.3
33	1-[(Pyrid-2-yl)-methyl]-2-oxo-2,3-dihydro-1*H*-benzimidazol-5-yl	68	100.0	2.1
34	1-(But-1-yl)-2-oxo-2,3-dihydro-1*H*-benzimidazol-5-yl	98	89.4	3.1
35	1-(3-Methoxyprop-1-yl)-2-oxo-2,3-dihydro-1*H*-benzimidazol-5-yl	80	96.5	0.9

[a] Yields as conversion rates (LC ratio of product/starting material prior to work-up).
[b] HPLC, 100% method, detection at 254 nm.
[c] *P. falciparum* chloroquine resistant K1 strain. IC_{50} for standard drug (chloroquine): 0.17 μM.

lents.[20] A disadvantage of this linker is the fact, that an additional activation step at the end of the on-bead transformation is necessary. Therefore, for simple acid residues, that are transferred without chemical manipulation of their structure or subjected to reactions with neutral reagents, phenol based couple&release linkers are advantageous. The second special advantage of the Kenner linker lies in its remarkable selectivity for nitrogen nucleophiles. It has been demonstrated by us[21] and others,[22] that weakly basic amino groups can be acylated with carboxylic acids attached to the activated form of Kenner's linker in the presence of reactive primary alcoholic functions chemoselectively. However, due to the fact that the selected amines in this study contain only reactive primary amino groups attached to primary carbon atoms and less reactive secondary alcoholic functions, this chemoselectivity is easy to achieve with less N-selective linkers, as well.

From a biological viewpoint, the lipophilic character of the compounds prepared is necessary in order to allow the molecules to diffuse across parasite membranes and subsequently interact with a variety of unknown targets, randomly. The molecular target of the compounds synthesized is not known. Our assumption is that the compounds bind to a higher number of different enzymes, some of which comprise adenosine binding motifs with varying affinity. Lately, 5′-amido-5′-deoxyadenosine derivatives have been reported to interact with novel and highly relevant drug targets such as poly(ADP-ribose) polymerase-1[23] and MbtA,[24] an adenylation enzyme required for siderophore biosynthesis of the mycobactins. Ribose-modified N^6-substituted nucleosides are under investigation as ribonucleotide reductase inhibitors.[25] Very recently, the endogenous occurrence of various N^6-benzyladenosine derivatives and their cytokinin activity has been unraveled by Dolezal et al.[26]

In this respect, promiscuity in ligand-target interaction with many different enzymes of the adenosine salvage pathway or enzymes utilizing adenosine containing substrates such as ATP or NAD^+ might be regarded as an advantage in terms of the parasites ability to acquire resistance. From a medicinal chemistry viewpoint however, the high lipophilicity is associated with potentially low bioavailability and problematic solubility but as well might offer the chance for high plasma albumin binding and therefore a cheap galenic depot form causing elevated plasma half-life.

The compounds show the desired activity in the selected model. Therefore it seems rewarding to perform modifications of the adenine ring or seek to reduce the high molecular mass of the compounds and introduce functional groups that improve aqueous solubility. In order to do so, it will be necessary to synthesize new adenosine derived amino-functionalized templates in multistep syntheses with the associated laborious chromatographic purification or preferably following novel glycosylation approaches.[27] The parallel derivatization, however, can be achieved fast and efficiently using the polymer-bound acylating species reported here.

5. Conclusion

Polymer-bound acylating species prepared by simple coupling to a suitable linker or by multi-step solid-phase synthesis are known to be well-suited for the parallel synthesis of carboxylic acid derivatives such as amides. They enable clean and high yielding transformation of unprotected enantiomerically pure amino alcohols like amino deoxynucleosides in solution. The complex scaffolds do not have to be attached to a linker or polymer but nevertheless the resulting mixture can easily be separated by filtration. After consumption of the amine added in limiting amounts, the suspensions obtained contain only the target molecules in solution along with polymer-bound reagents. The already highly pure test compounds can thus be purified rapidly and efficiently for biological evaluation by flash or medium pressure chromatography. As could be demonstrated here, the degree of diversity of a set of carboxylic acids can be broadened by this approach. Especially the convergent connection of heterocycles formed on polymer-support with delicate multifunctional scaffolds enables the rapid generation of complex molecules that are not contained in present portfolios.

6. Experimental

^{1}H NMR spectra were recorded on a Bruker AMX 400 spectrometer, using tetramethylsilane as internal standard. The purity of the target compounds was deduced from ^{1}H NMR data as well as evaluated by HPLC, using a Dionex Summit HPLC-system with a diode

array detector and CC 125/4 Nucleodur 100-5 C18 ec columns, supplied by Macherey-Nagel and water/methanol gradients. Purity was calculated using the UV data at 254 nm using Chromeleon 6.50 software. A second, lower frequency (220 nm) was monitored in order to be able to identify impurities with low absorption coefficients at the standard wavelength 254 nm, that are notoriously present in small molecule libraries. Due to the fact, that all samples were purified over reversed-phase columns prior to analysis, these impurities—if present—were effectively removed prior to analysis and thus absent in detectable amounts. TLC reaction control was performed on Macherey-Nagel Polygram Sil G/UV_{254} precoated microplates, spots were visualized under UV-illumination at 254 nm. LC reaction control was performed on the HPLC system described above. IR-spectra for the detection of erroneously formed 2,3,5,6-tetrafluoro4-hydroxy-benzoic acid esters on the solid support were recorded as KBr tablets on a Nicolet 510P FT-IR spectrometer. High resolution MS data were obtained on a Micromass Autospec instrument (ESI, methanol (1/1, v/v) infusion at 10 μL/min with polyethylene glycol as reference). Microanalyses were obtained using a Hewlett–Packard CHN-analyzer type 185.

6.1. N^6-(4-Phenoxybenzyl)adenosine (4)

To a solution of 5.7 mmol) 1-(6-Chloro-purin-9-yl)-β-d-1-deoxyribofuranose (**2**) in 1-propanol were added 1.1 equiv of 4-phenoxybenzyl amine (**3**) and 1 equiv of Hünig's base. The solution was stirred for 24 h at 60 °C. The reaction was monitored by TLC. After completion of the reaction the solution was stored at 5 °C for 24 h. The product precipitated as a white amorphous powder. After filtration the resulting solid was crystallized from methanol. Yield 87% (2.223 g). ^{1}H NMR: (400 MHz, DMSO-d_6) = δ (ppm) 8.43 (br s, 1H, N^6H), 8.37 (s, 1H, C8–H), 8.22 (s, 1H, C2–H), 7.36 (m, 4H, 4-phenoxybenzyl), 7.10 (t, 1H, 4-phenoxybenzyl, J = 7.4 Hz), 6.95 (m, 4H, 4-phenoxybenzyl), 5.90 (d, 1H, 1′H, J = 6.72 Hz), 5.44 (d, 1H, 3′OH, J = 7.3 Hz), 5.37 (m, 1H, 5′OH), 5.18 (d, 1H, 2′OH, J = 5.5 Hz), 4.70 (br s, 2H, 4-phenoxybenzyl), 4.61 (q, 1H, 2′H, J = 5.5 Hz), 4.01 (m, 1H, 3′H), 3.96 (m, 1H, 4′H), 3.63–3.72 (m, 1H, 5′CH_2), 3.52–3.58 (m, 1H, 5′CH_2). ^{13}C NMR: (126 MHz, DMSO-d_6) = δ (ppm) 156.9, 155.2, 154.4, 152.3, 148.5, 139.8, 135.2, 129.9, 128.9, 123.1, 120.8, 118.6, 118.2, 87.9, 85.9, 73.5, 70.6, 61.6, 42.5. Combustion analysis: %C, 61.44 (calcd 61.46), %H, 5.18 (calcd 5.16), %N, 15.23 (calcd 15.58), mp 141 °C.

6.2. 5′-Deoxy-N^6-(4-phenoxybenzyl)-5′-phthalimido-1-yl-adenosine (5)

To a solution of 4.45 mmol of N^6-(4-phenoxybenzyl)adenosine (**4**) in 31 mL of freshly dried THF (sodium/benzophenone) were added 2.92 g (11.13 mmol) triphenylphosphine and 1.64 g (11.13 mmol) phthalimide. The suspension was cooled down to −20 °C. After the addition of 1.94 g (11.13 mmol) di-*tert*-butyl-azodicarboxylate the suspension was stirred for 30 min at −20 °C and then slowly allowed to warm to room temperature. The reaction was monitored by TLC. After 90 min quantitative conversion could be observed and the solvent was removed under vacuo. Subsequent addition of 10 mL of methanol and storage at 5 °C for 24 h yielded a white solid that was isolated by filtration. The resulting solid was crystallized in methanol. Yield 73% (1.880 g). ^{1}H NMR (500 MHz, DMSO-d_6) = δ (ppm) 8.38 (s, 1H, C8–H), 8.35 (br s, 1H, N^6H), 8.01 (s, 1H, C2–H), 7.84 (m, 5H, phthalimido), 7.36 (m, 4H, 4-phenoxybenzyl), 7.11 (t, 1H, 4-phenoxybenzyl, J = 7.4 Hz), 6.96 (m, 4H, 4-phenoxybenzyl), 5.86 (d, 1H, 1′H, J = 5.5 Hz), 5.49 (d, 1H, 3′OH, J = 6.3 Hz), 5.30 (d, 1H, 2′OH, J = 6.3 Hz), 4.77 (q, 1H, 2′H, J = 5.9 Hz), 4,68 (br s, 2H, 4-phenoxybenzyl), 4.27 (m, 1H, 3′H), 4.14 (m, 1H, 4′H), 3.94–4.01 (m, 1H, 5′CH_2), 3.83–3.90 (m, 1H, 5′CH_2). ^{13}C NMR (126 MHz, DMSO-d_6) = δ (ppm) 167.7, 156.9, 155.1, 152.3, 134.3, 131.4, 129.8, 128.8, 123.1, 123.0, 123.8, 118.6, 118.1, 87.7, 81.2, 72.5, 71.4. HR-ESI-MS $[M+H]^+$ calcd 579.1992, found 579.2004, mp 202 °C.

6.3. 5′-Amino-5′-deoxy-N^6-(4-phenoxybenzyl)adenosine (6)

To a solution of 1.9 mmol of 5′-deoxy-N^6-(4-phenoxybenzyl)-5′-phthalimido-1-yl-adenosine (**5**) in 130 mL ethanol were added 6 mL of a solution of 33% methylamine in ethanol. After 2 h TLC indicated completion of the reaction and the residue was concentrated in vacuo. After purification with a column packed with strongly basic ion exchange resin, the desired amine could be obtained applying a methanol water gradient starting with 5% methanol. The product containing fractions were collected and the solvent was removed in vacuo. Yield 94% (801 mg). ^{1}H NMR (400 MHz, DMSO-d_6) + one drop D_2O = δ (ppm) 8.40 (s, 1H, C8–H), 8.36 (br s, 1H, N^6H), 8.22 (s, 1H, C2–H), 7.36 (m, 4H, 4-phenoxybenzyl), 7.10 (t, 1H, J = 7.4 Hz, 4-phenoxybenzyl), 6.95 (m, 4H, 4-phenoxybenzyl), 5.87 (d, 1H, J = 6.0 Hz, 1′H), 4.72–4.66 (m, 3H, 2′H overlapping 4-phenoxybenzyl-CH_2), 4.16 (m, 1H, 3′H), 3.88 (m, 1H, 4′H), 2.86–2.72 (m, 2H, 5′CH_2). ^{13}C NMR (126 MHz, DMSO-d_6) = δ (ppm) 156.9, 155.2, 154.3, 152.4, 140.2, 140.0, 135.2, 129.9, 128.8, 123.1, 118.6, 118.2, 87.4, 86.0, 73.0, 70.7, 43.7. HR-ESI-MS $[M+H]^+$ calcd 449.1937, found 449.1956, mp 147 °C.

6.4. General procedure for the preparation of simple polymer supported acid, using the 2,3,5,6-tetrafluorobenzoic-4-hydroxy-acid linker

To a flask containing 1 g of 2,3,5,6-tetrafluoro-4-hydroxy-benzoic acid loaded aminomethylated polystyrene (**7**) (prepared from very high load aminomethylated polystyrene, purchased from Novabiochem, Switzerland, batch number A20540) with an initial loading level of 1.1 mmol/g were added 20 mL DMF and the resin was allowed to swell for 10 min. [13] Subsequently, 2 equiv (2.2 mmol) of the appropriate carboxylic acid and 0.22 mmol (27 mg) of DMAP were added to the suspended resin. After the addition of 2.2 mmol (195 μL) of DIC, the mixture was agitated at room temperature for 16 h. The resin beads were filtered off and washed exhaustively with DMF (three times 15 mL), dichloromethane (three times 15 mL) and THF (three times 15 mL) and afterwards dried under vacuo. After careful drying the increase in weight was monitored.

6.5. General procedure for the preparation of compounds 16–25 using the 2,3,5,6-tetrafluoro-4-hydroxy benzoic acid linker construct 7

Resin (200 mg) loaded with the appropriate carboxylic acid (loading level approximately 1 mmol carboxylic acid per gram) were swollen in 2 mL dichloromethane (or alternatively THF). A solution of 9 mg (0.02 mmol) 5′-amino-5′-deoxy-N^6-(4-phenoxybenzyl)adenosine (**6**) in a few drops THF (as little solvent as possible) were added to the suspension. After 12 h in most cases complete conversion of the amine **6** to the target carboxylic acid amide **16–25** could be observed via TLC. Subsequently the resin was washed with dichloromethane and THF and the collected fractions were evaporated under reduced pressure. To ensure product purity, all samples were further purified via MPLC.

6.6. 5′-Deoxy-5′-[(3,3-dimethyl)acrylamido]-N^6-(4-phenoxybenzyl)adenosine (16)

Conversion rate 99%. Purity HPLC after MPLC = 97.2% (254 nm). ^{1}H NMR (400 MHz, hexadeutero [D_6] dimethylsulfoxide DMSO) = δ

(ppm) 8.43 (br s, 1H, N^6H), 8.36 (s, 1H, C8–H), 8.25 (s, 1H, C2–H), 8.09 (t, 1H, amido, J = 5.8 Hz), 7.36 (m, 4H, 4-phenoxybenzyl), 7.10 (t, 1H, 4-phenoxybenzyl, J = 7.4 Hz), 6.96 (m, 4H, 4-phenoxybenzyl), 5.85 (d, 1H, 1′H, J = 6.6 Hz), 5.70 (br s, 1H, acryl-CH), 5.32 (br s, 2H, 3′OH and 2′OH), 4.69 (m, 3H, 2′H overlapping 4-phenoxybenzyl), 4.05 (m, 1H, 3′H), 3.97 (m, 1H, 4′H), 3.35–3.46(m, 2H, 5′CH_2 overlapping H_2O), 2.08 (s, 3H, methyl), 1.78 (s, 3H, methyl). HR-ESI-MS $[M+H]^+$ calcd 530.2278, found 530.2281.

6.7. 5′-Deoxy-5′-[(4-phenoxy)butanamido]-N^6-(4-phenoxybenzyl)adenosine (17)

Conversion rate 98%. Puritiy HPLC after MPLC = 100.0% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 8.44 (br s, 1H, N^6H), 8.36 (s, 1H, C8–H), 8.28 (m, 2H, C2–H overlapping amido), 7.36 (m, 4H, 4-phenoxybenzyl), 7.24 (m, 2H, phenoxy), 7.10 (t, 1H, 4-phenoxybenzyl, J = 7.4 Hz), 6.96 (m, 4H, 4-phenoxybenzyl), 6.89 (m, 3H, phenoxy), 5.85 (d, 1H, 1′H, J = 6.4 Hz), 5.43 (d, 1H, 3′OH, J = 5.6 Hz), 5.25 (d, 1H, 2′OH, J = 4.3 Hz), 4.70 (m, 3H, 2′H overlapping 4-phenoxybenzyl), 4.05 (m, 1H, 3′H), 3.95 (m, 3H, 4′H overlapping CH_2), 3.39–3.59 (m, 2H, 5′CH_2 overlapping H_2O), 2.31 (t, 2H, CH_2, J = 7.3 Hz), 1.94 (m, 2H, CH_2). HR-ESI-MS $[M+H]^+$ calcd 610.2540, found 610.2544.

6.8. 5′-Deoxy-5′-[(4-phenyl)butanamido]-N^6-(4-phenoxybenzyl)adenosine (18)

Conversion rate 100%. Purity HPLC after MPLC = 100.0% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 8.43 (br s, 1H, N^6H), 8.36 (s, 1H, C8–H), 8.19 (m, 2H, C2–H C2–H overlapping amido), 7.36 (m, 4H, 4-phenoxybenzyl), 7.24 (m, 2H, phenyl), 7.08–7.16 (m, 4H, phenyl overlapping 4-phenoxybenzyl), 6.95 (m, 4H, 4-phenoxybenzyl), 6.89 (m, 3H, phenoxy), 5.85 (d, 1H, 1′H, J = 6.4 Hz), 5.42 (d, 1H, 3′OH, J = 6.1 Hz), 5.26 (d, 1H, 2′OH, J = 4.6 Hz), 4.69 (m, 3H, 2′H overlapping 4-phenoxybenzyl), 4.05 (m, 1H, 3′H), 3.97 (m, 1H, 4′H), 3.39–3.59 (m, 2H, 5′CH_2 overlapping H_2O), 2.54 (t, 2H, CH_2, J = 7.7 Hz), 2.14 (t, 2H, CH_2, J = 7.4 Hz), 1.79 (m, 2H, CH_2). HR-ESI-MS $[M+H]^+$ calcd 595.2669, found 595.2363.

6.9. 5′-Deoxy-5′-[(3-indolyl)butanamido]-N^6-(4-phenoxybenzyl)adenosine (19)

Conversion rate 98%. Purity HPLC after MPLC = 100.0% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 10.71 (s, 1H, indol-NH), 8.42 (br s, 1H, N^6H), 8.36 (s, 1H, C8–H), 8.21 (s, 1H, C2–H), 8.18 (t, 1H, amido, J = 5.6 Hz), 7.47 (d, 1H, J = 7.9 Hz, indol), 7.36 (m, 5H, 4-phenoxybenzyl and indol), 7.08 (m, 1H, indol), 7.02 (t, 1H, 4-phenoxybenzyl, J = 6.9 Hz), 6.96 (m, 5H, 4-phenoxybenzyl and indol), 5.86 (d, 1H, 1′H, J = 6.4 Hz), 5.44 (br s, 1H, 3′OH), 5.26 (br s, 1H, 2′OH), 4.70 (m, 3H, 2′H overlapping benzyl-CH_2), 4.06 (m, 1H, 3′H), 3.98 (m, 1H, 4′H), 3.34–3.48(m, 2H, 5′CH_2 overlapping H_2O), 2.66 (t, 2H, 5″CH_2, J = 7.4 Hz), 2.20 (t, 2H, 5″CH_2, J = 7.4 Hz), 1.87 (m, 2H, 5″CH_2). HR-ESI-MS $[M+H]^+$ calcd 634.2814, found 634.2778.

6.10. 5′-Deoxy-5′-[(1-naphthyl)acetamido]-N^6-(4-phenoxybenzyl)adenosine (20)

Conversion rate 98%. Purity HPLC after MPLC = 100.0% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 8.47 (t, 1H, amido, J = 5.9 Hz), 8.42 (br s, 1H, N^6H), 8.38 (s, 1H, C8–H), 8.25 (s, 1H, C2–H), 8.03 (m, 1H, naphthyl), 7.90 (m, 1H, naphthyl), 7.80 (m, 1H, naphthyl), 7.49 (m, 2H, naphthyl), 7.32–7.43 (m, 6H, 4-phenoxybenzyl overlapping naphthyl), 7.10 (m, 1H, 4-phenoxybenzyl), 6.95 (m, 4H, 4-phenoxybenzyl), 5.88 (d, 1H, 1′H, J = 6.1 Hz), 5.44 (d, 1H, 3′OH, J = 5.9), 5.24 (d, 1H, 2′OH, J = 4.6 Hz), 4.72 (m, 3H, 2′H overlapping benzyl), 4.08 (m, 1H, 3′H), 3.98 (m, 1H, 4′H), 3.94 (s, 2H, CH_2) 3.40–3.50 (m, 2H, 5′CH_2). HR-ESI-MS $[M+H]^+$ calcd 617.2512, found 617.2495.

6.11. 5′-Deoxy-5′-[(4-methyl)pentanamido]-N^6-(4-phenoxybenzyl)adenosine (21)

The biological test sample was not synthesized via **9** but as the other amides **16–25** by coupling of the appropriate carboxylic acid (in this case 4-methylpentanoic acid) to the linker construct **7**. Conversion rate 97%. Purity HPLC after MPLC = 100.0% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 8.44 (br s, 1H, N^6H), 8.36 (s, 1H, C8–H), 8.25 (s, 1H, C2–H), 8.13 (t, 1H, amido, J = 5.6 Hz), 7.36 (m, 4H, 4-phenoxybenzyl), 7.10 (t, 1H, 4-phenoxybenzyl, J = 7.4 Hz), 6.96 (m, 4H, 4-phenoxybenzyl), 5.85 (d, 1H, 1′H, J = 6.4 Hz), 4.68 (m, 3H, 2′H overlapping benzyl), 4.04 (m, 1H, 3′H), 3.95 (m, 1H, 4′H), 3.38–3.45 (m, 2H, 5′H overlapping H_2O), 2.10 (t, 2H, CH_2, J = 8.0 Hz), 1.48 (m, 1H, CH), 1.37 (m, 2H, CH_2), 0.83 (d, 6H, CH_3, J = 6.6 Hz). HR-ESI-MS $[M+H]^+$ calcd 547.2669, found 547.2692.

6.12. 5′-Deoxy-5′-[(3-chlorophenyl)acetamido]-N^6-(4-phenoxybenzyl)adenosine (22)

Conversion rate 95%. Purity HPLC after MPLC = 100.0% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 8.42 (br s, 1H, N^6H), 8.38 (m, 2H, C8–H overlapping amido), 8.25 (s, 1H, C2–H), 7.36 (m, 4H, 4-phenoxybenzyl), 7.20 (m, 3H, benzyl), 7.18 (m, 1H, benzyl), 7.10 (t, 1H, 4-phenoxybenzyl, J = 7.4 Hz), 6.96 (m, 4H, 4-phenoxybenzyl), 5.87 (d, 1H, 1′H, J = 5.9 Hz), 4.68 (m, 3H, 2′H overlapping benzyl), 4.07 (m, 1H, 3′H), 3.94 (m, 1H, 4′H), 3.48 (s, 2H, CH_2), 3.36–3.46 (m, 2H, 5′H overlapping water). HR-ESI-MS $[M+H]^+$ calcd 601.1966, found 601.1957.

6.13. 5′-Deoxy-5′-[(3-methoxyphenyl)acetamido]-N^6-(4-phenoxybenzyl)adenosine (23)

Conversion rate 97%. Purity HPLC after MPLC = 100.0% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 8.42 (br s, 1H, N^6H), 8.34 (m, 2H, C8–H overlapping amido), 8.24 (s, 1H, C2–H), 7.36 (m, 4H, 4-phenoxybenzyl), 7.17 (t, 1H, methoxyphenyl, J = 7.9 Hz), 7.10 (t, 1H, 4-phenoxybenzyl, J = 7.4 Hz), 6.96 (m, 4H, 4-phenoxybenzyl), 6.89 (m, 3H, phenoxy), 6.80 (m, 3H, methoxyphenyl), 5.86 (d, 1H, 1′H, J = 6.1 Hz), 5.43 (br s, 2H, 3′OH overlapping 2′OH), 4.70 (m, 3H, 2′H overlapping 4-phenoxybenzyl), 4.07 (m, 1H, 3′H), 3.95 (m, 1H, 4′H), 3.69 (s, 3H, methoxy), 3.42 (s, 2H, CH_2), 3.31 (m, 2H, 5′H overlapping water). HR-ESI-MS $[M+H]^+$ calcd 597.2462, found 597.2439.

6.14. 5′-Deoxy-5′-(3,5-dichlorobenzamido)-N^6-(4-phenoxybenzyl)adenosine (24)

Conversion rate 83%. Purity HPLC after MPLC = 100.0% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 8.88 (m, 1H, amido), 8.39 (br s, 1H, N^6H), 8.37 (s, 1H, C8–H), 8.15 (s, 1H, C2–H), 7.86 (s, 1H, phenyl), 7.85 (s, 1H, phenyl), 7.80 (t, 1H, phenyl, J = 1.9 Hz), 7.35 (m, 4H, 4-phenoxybenzyl), 7.10 (m, 1H, 4-phenoxybenzyl), 6.96 (m, 4H, 4-phenoxybenzyl), 5.87 (d, 1H, 1′H, J = 5.9 Hz), 5.46 (br s, 1H, 3′OH), 5.28 (br s, 1H, 2′OH), 4.76 (m, 1H, 2′H), 4.69 (br s, 2H, CH_2), 4.20 (m, 1H, 3′H), 4.07 (m, 1H, 4′H), 3.55–3.65 (m, 2H, 5′CH_2). HR-ESI-MS $[M+H]^+$ calcd 621.1447, found 621.1420.

6.15. 5′-Deoxy-5′-(4-phenoxybenzamido)-N^6-(4-phenoxybenzyl)adenosine (25)

Conversion rate 98%. Purity HPLC after MPLC = 92.3% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 8.62 (m, 1H, amido), 8.39

(br s, 1H, N^6H), 8.38 (s, 1H, C8–H), 8.15 (s, 1H, C2–H), 7.87 (d, 2H, 4-phenoxyphenyl, J = 8.9 Hz), 7.43 (m, 2H, 4-phenoxyphenyl), 7.35 (m, 4H, 4-phenoxybenzyl), 7.20 (t, 1H, phenoxyphenyl, J = 7.4 Hz), 7.09 (m, 3H, 4-phenoxybenzyl overlapping 4-phenoxyphenyl), 7.01 (d, 2H, 4-phenoxyphenyl, J = 8.7 Hz), 6.96 (m, 4H, 4-phenoxybenzyl), 5.87 (d, 1H, 1′H, J = 6.4 Hz), 5.44 (br s, 2H, 3′OH overlapping 2′OH), 4.76 (t, 1H, 2′H, J = 5.6 Hz), 4.69 (br s, 2H, CH_2), 4.19 (m, 1H, 3′H), 4.09 (m, 1H, 4′H), 3.60 (m, 2H, 5′CH_2). HR-ESI-MS $[M+H]^+$ calcd 645.2462, found 645.2467.

6.16. General procedure for the solid phase synthesis of benzimidazole carboxylic acids

(A) Nucleophilc substitution. To a suspension of 400 mg (approx. 0.4 mmol) resin **11** in 6 mL DMF a tenfold excess of the appropriate amine (4 mmol) in neat form or a solution thereof in DMF is added. The suspension is agitated for 10 h and a color change of the yellowish slurry to bright orange is visible The resin is washed with DMF (five times) and THF (five times) and dried under reduced pressure. (B) Reduction of the nitro group. 400 mg (approx. 0.4 mmol) of the nitrobenzene-containing resin **12** are suspended in a freshly prepared solution of $SnCl_2$ in DMF (c = 2 mol/l) and agitated for 10 h. The suspension is filtered, resuspended in another aliquot of freshly prepared $SnCl_2$-solution (c = 2 mol/l) in DMF and agitated for 10 h once again. The orange color of the resin changes to pale yellow. The resin is washed with DMF (five times) and immediately used for following transformations or washed THF (five times) as well and dried under reduced pressure for storage. (C) Ring closing reaction. An amount of 1 g (approx. 1 mmol) of the appropriate resin **13**{*1–5*} is suspended in 20 mL freshly distilled CH_2Cl_2 (distillation over $CaCl_2$). To this suspension 420 μL (2.5 mmol) triethyl orthoformate are added and the mixture is shaken for 48 h. The resin is filtered over a glass filter funnel, washed with CH_2Cl_2 (five times) and THF (three times) and dried under reduced pressure. (D) Activation of the Kenner linker. The sulfonamide linker of 400 mg (approx. 0.4 mmol) resin was activated for cleavage by alkylation with 520 μL (6.4 mmol) bromoacetonitrile, and 580 μL (3.4 mmol) Hünig's base in 6 mL NMP overnight and washed with dry DMSO (five times 6 mL) and THF (five times 10 mL).

6.17. Acylation of adenosine template 6

Resin (300 mg) loaded with the appropriate carboxylic acid (loading level approximately 1 mmol carboxylic acid per gram) were swollen in 3 mL THF. A solution of 13 mg (0.029 mmol) 5′-Amino-5′-deoxy-N^6-(4-phenoxybenzyl)adenosine (**6**) in a few drops THF (as little solvent as possible) were added to the suspension. After 12 h in most cases complete conversion of the amine (**6**) to the target carboxylic acid amides **26–30** could be observed via TLC. Subsequently the resin was washed with dichloromethane and THF and the collected fractions were evaporated under reduced pressure. To ensure product purity, all samples were further purified via MPLC.

6.18. 5′-Deoxy-5′-[5-(1-prop-2-enyl)-1*H*-benzimidazolyl]carboxamido-N^6-(4-phenoxybenzyl)adenosine (26)

Conversion rate 100%. Purity HPLC after MPLC = 100% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 8.66 (t, 1H, J = 6.1 Hz, amido-NH), 8.38 (m, 2H, C8–H overlapping amino), 8.32 (s, 1H, amidino-CH), 8.26 (s, 1H, C2–H), 8.20 (s, 1H, benzene), 7.81 (dd, 1H, J = 1.5/8.7 Hz, benzene), 7.60 (d, 1H, J = 8.7 Hz, benzene), 7.36 (m, 4H, 4-phenoxybenzyl), 7.10 (t, 1H, J = 7.4 Hz, 4-phenoxybenzyl), 6.96 (m, 4H, 4-phenoxybenzyl), 6.11–5.99 (m, 1H, allyl), 5.87 (d, 1H, J = 6.4 Hz, 1′H), 5.21 (dd, 1H, J = 1.4/10.2 Hz, allyl), 5.10 (dd, 1H, J = 1.4/17.4 Hz, allyl), 4.95 (d, 2H, J = 5.6 Hz, allyl), 4.79 (m, 1H, 2′H), 4.69 (br s, 2H, benzyl-CH_2), 4.20 (m, 1H, 3′H), 4.11 (m, 1H, 4′H), 3.62 (m, 2H, 5′H). HR-ESI-MS $[M+H]^+$ calcd 633.2574, found 633.2575.

6.19. 5′-Deoxy-5′-{5-[1-(1-naphthalen-1-yl)methyl]-1*H*-benzimidazolyl}carboxamido-N^6-(4-phenoxybenzyl)adenosine (27)

Conversion rate 100%. Purity HPLC after MPLC = 97.4% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 8.65 (t, 1H, J = 5.6 Hz, amido-NH), 8.47 (s, 1H, amidino-CH), 8.38 (m, 2H, C8–H overlapping amino), 8.28 (s, 1H, C2–H), 8.19 (m, 2H, naphthyl overlapping benzene), 7.98 (m, 1H, naphthyl), 7.88 (m, 1H, benzene), 7.76 (dd, 1H, J = 1.5/8.4 Hz, benzene), 7.60 (m, 3H, naphthyl), 7.44 (m, 1H, naphthyl), 7.35 (m, 4H, 4-phenoxybenzyl), 7.10 (t, 1H, J = 6.4 Hz, 4-phenoxybenzyl), 7.05 (d, 1H, J = 6.6 Hz, naphthyl), 6.96 (m, 4H, 4-phenoxybenzyl), 6.06 (s, 2H, naphthylmethyl), 5.87 (d, 1H, J = 6.4 Hz, 1′H), 5.62 (m, 1H, 3′OH), 5.25 (d, 1H, J = 4.6 Hz, 2′OH), 4.79 (m, 1H, 2′H), 4.69 (br s, 2H, benzyl-CH_2), 4.19 (m, 1H, 3′H), 4.10 (m, 1H, 4′H), 3.61 (m, 2H, 5′H). HR-ESI-MS $[M+H]^+$ calcd 733.2887, found 733.2859.

6.20. 5′-Deoxy-5′-{5-[1-(1-pentyl)-1*H*-benzimidazolyl]-carboxamido}-N^6-(4-phenoxybenzyl)adenosine (28)

Conversion rate 99%. Purity HPLC after MPLC = 100% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 8.65 (t, 1H, J = 5.6 Hz, amido-NH), 8.39 (m, 2H, C8–H overlapping amino), 8.31 (s, 1H, C2–H), 8.25 (m, 1H, amidino-CH), 8.19 (br s, 1H, benzene), 7.82 (m, 1H, benzene), 7.69 (d, 1H, J = 8.4 Hz, benzene), 7.35 (m, 4H, 4-phenoxybenzyl), 7.10 (t, 1H, J = 8.4 Hz, 4-phenoxybenzyl), 6.95 (m, 4H, 4-phenoxybenzyl), 5.87 (d, 1H, J = 6.4 Hz, 1′H), 5.62 (m, 2H, 3′OH overlapping 2′OH), 4.80 (m, 1H, 2′H), 4.69 (br s, 2H, benzyl-CH_2), 4.20 (m, 1H, 3′H), 4.10 (m, 3H, 4′H overlapping pentyl), 3.62 (m, 2H, 5′H), 0.90–0.82 (m, 7H, pentyl); one signal of 2H is missing due to overlapping with DMSO signal. HR-ESI-MS $[M+H]^+$ calcd 649.2887, found 649.2848.

6.21. 5′-Deoxy-N^6-(4-phenoxybenzyl)-5′-{5-[1-(1-pyrid-2-ylmethyl)-1*H*-benzimidazolyl]carboxamido}adenosine (29)

Conversion rate 96%. Purity HPLC after MPLC = 67.4% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 8.66 (t, 1H, J = 5.7 Hz, amido-NH), 8.50 (m, 1H, pyridyl), 8.46 (s, 1H, C8–H), 8.37 (m, 2H, C2–H overlapping amino), 8.26 (m, 1H, amidino-CH), 8.19 (br s, 1H, benzene), 7.88–7.74 (m, 2H, benzene overlapping pyridyl), 7.56 (d, 1H, J = 8.7 Hz, benzene), 7.35 (m, 4H, 4-phenoxybenzyl), 7.29 (m, 2H, pyridyl), 7.10 (t, 1H, J = 8.4 Hz, 4-phenoxybenzyl), 6.96 (m, 4H, 4-phenoxybenzyl), 5.88 (d, 1H, J = 6.4 Hz, 1′H), 5.63 (s, 2H, methylene), 5.21 (m, 2H, 3′OH overlapping 2′OH), 4.77–4.65 (m, 2H, 2′H overlapping benzyl-CH_2), 4.18 (m, 1H, 3′H), 4.10 (m, 1H, 4′H), 3.62 (m, 2H, 5′H). HR-ESI-MS $[M+H]^+$ calcd 684.2683, found 684.2706.

6.22. 5′-Deoxy-5′-{5-[1-(3-methoxypropyl)-1*H*-benzimidazolyl]carboxamido}-N^6-(4-phenoxybenzyl)adenosine (30)

Conversion rate 98%. Purity HPLC after MPLC = 100% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 8.66 (t, 1H, J = 5.4 Hz, amido-NH), 8.38 (m, 2H, C8–H overlapping amino), 8.30 (s, 1H, C2–H), 8.25 (m, 1H, amidino-CH), 8.19 (br s, 1H, benzene), 7.82 (m, 1H, benzene), 7.65 (d, 1H, J = 8.7 Hz, benzene), 7.36 (m, 4H, 4-phenoxybenzyl), 7.10 (t, 1H, J = 7.4 Hz, 4-phenoxybenzyl), 6.95 (m, 4H, 4-phenoxybenzyl), 5.87 (d, 1H, J = 6.6 Hz, 1′H), 4.79 (m, 1H, 2′H), 4.69 (br s, 2H, benzyl-CH_2), 4.32 (t, 2H, J = 7.1 Hz, propylene), 4.20 (m, 1H, 3′H), 4.11 (m, 1H, 4′H), 3.61 (m, 2H, 5′H), 3.21 (s,

3H, methoxy), 2.03 (m, 2H, propylene); one signal of 2H is missing due to overlapping with DMSO signal. HR-ESI-MS $[M+H]^+$ calcd 665.2836, found 665.2861.

6.23. General procedure for the solid-phase synthesis of benzimidazolinone carboxylic acids

(A) Nucleophilc substitution (see Section 6.16) (B) reduction of the nitro group (see Section 6.16) (C) ring closing reaction. An amount of 1 g (approx. 1 mmol) of the appropriate resin **13**{*2,5,6,7,8*} is suspended in 20 mL dry DMF (stored over molsieve), THF or CH_2Cl_2. To this suspension 660 mg (4 mmol) CDI are added and the mixture is shaken for 12 h. The color of the resin often changes from pale yellow to red. The resin is filtered over a glass filter funnel and subjected to the same procedure once again. The resin is filtered over a glass filter funnel, washed extensively with DMF (five times), CH_2Cl_2 (five times) and THF (five times) and dried under reduced pressure, (D) activation of the Kenner linker (see Section 6.16).

Acylation of adenosine template **6** to yield the target carboxylic acid amides **31–35** was performed as described above for **26–30**.

6.24. 5′-Deoxy-5′-{5-[1-(2-cyclohex-1-enylethyl)-2-oxo-2,3-dihydro-1*H*-benzimidazolyl]carboxamido}-N^6-(4-phenoxybenzyl)adenosine (31)

Conversion rate 84%. Purity HPLC after MPLC = 77.1% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 8.49 (m, 1H, amido-NH), 8.35 (m, 2H, C8–H overlapping amino), 8.18 (s, 1H, C2–H), 7.50 (m, 1H, benzene), 7.44 (s, 1H, benzene), 7.35 (m, 4H, 4-phenoxybenzyl), 7.10 (t, 1H, J = 7.4 Hz, 4-phenoxybenzyl), 7.05 (m, 1H, benzene), 6.96 (m, 4H, 4-phenoxybenzyl), 5.87 (d, 1H, J = 6.4 Hz, 1′H), 5.25 (m, 1H, cyclohexenyl), 4.77 (m, 1H, 2′H), 4.69 (br s, 2H, benzyl-CH_2), 4.18 (m, 1H, 3′H), 4.09 (m, 1H, 4′H), 3.88 (t, 2H, J = 6.9 Hz, ethylene), 3.59 (m, 2H, 5′H), 2.23 (t, 2H, J = 7.7 Hz, ethylene), 1.98 (m, 2H, cyclohexenyl), 1.80 (m, 2H, cyclohexenyl), 1.53 (m, 2H, cyclohexenyl), 1.42 (m, 2H, cyclohexenyl). HR-ESI-MS $[M+H]^+$ calcd 717.3149, found 717.3137.

6.25. 5′-Deoxy-5′-{5-[1-(4-methoxybenzyl)-2-oxo-2,3-dihydro-1*H*-benzimidazolyl]carboxamido}-N^6-(4-phenoxybenzyl)-adenosine (32)

Conversion rate 98%. Purity HPLC after MPLC = 85.4% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 11.47 (br s, 1H, urea-NH), 8.83 (t, 1H, J = 6.0 Hz, amido-NH), 8.66 (m, 2H, C8–H overlapping benzene), 8.48 (s, 1H, C2–H), 7.84 (dd, 1H, J = 1.6/8.2 Hz, benzene), 7.81 (d, 1H, J = 1.6 Hz, benzene), 7.66 (m, 4H, 4-phenoxybenzyl), 7.57 (d, 2H, J = 8.7 Hz, benzyl), 7.41 (m, 2H, benzene überlappt 4-phenoxybenzyl), 7.26 (m, 4H, phenoxybenzyl), 7.17 (d, 2H, J = 8.7 Hz, benzyl), 6.17 (d, 1H, J = 6.3 Hz, 1′H), 5.78 (m, 1H, 3′OH), 5.60 (m, 1H, 2′OH), 5.26 (br s, 2H, benzyl-CH_2), 5.03 (m, 3H, benzyl overlapping 2′H), 4.48 (m, 1H, 3′H), 4.38 (m, 1H, 4′H), 4.00 (s, 3H, methoxy), 3.89 (m, 2H, 5′H). HR-ESI-MS $[M+H]^+$ calcd 751.2605, found 751.2594.

6.26. 5′-Deoxy-5′-{5-[1-(1-pyrid-2yl-methyl)-2-oxo-2,3-dihydro-1*H*-benzimidazolyl]carboxamido}-N^6-(4-phenoxybenzyl)adenosine (33)

Conversion rate 68%. Purity HPLC after MPLC = 100% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 11.2 (br s, 1H, urea-NH), 8.55 (m, 1H, amido-NH), 8.47 (m, 1H, pyridyl), 8.37 (m, 2H, C8–H überlappt amino), 8.17 (s, 1H, C2–H), 7.74 (m, 1H, benzene), 7.52 (m, 1H, benzene), 7.35 (m, 4H, phenoxybenzyl), 7.23 (m, 3H, pyridyl), 7.10 (m, 1H, benzene), 7.01 (m, 1H, 4-phenoxybenzyl), 6.96 (m, 4H, 4-phenoxybenzyl), 5.86 (d, 1H, J = 6.1 Hz, 1′H), 5.41 (d, 1H, J = 6.1 Hz, 3′OH), 5.24 (d, 1H, J = 4.6 Hz, 2′OH), 5.13 (s, 2H, pyridylmethyl), 4.75 (m, 1H, 2′H), 4.70 (br s, 2H, 4-phenoxyphenyl-CH_2), 4.16 (m, 1H, 3′H), 4.08 (m, 1H, 4′H), 3.60 (m, 2H, 5′H). HR-ESI-MS $[M+H]^+$ calcd 700.2632, found 700.2666.

6.27. 5′-Deoxy-5′-{5-[1-(1-butyl)-2-oxo-2,3-dihydro-1*H*-benzimidazolyl]carboxamido}-N^6-(4-phenoxybenzyl)adenosine (34)

Conversion rate 98%. Purity HPLC after MPLC = 89.4% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 8.55 (br s, 1H, urea-NH), 8.38 (m, 2H, amido-NH overlapping C8–H), 8.18 (s, 1H, C2–H), 7.57 (m, 1H, benzene), 7.49 (m, 1H, benzene), 7.35 (m, 4H, phenoxybenzyl), 7.15 (d, 1H, J = 8.1 Hz, benzene), 7.10 (m, 1H, 4-phenoxybenzyl), 6.96 (m, 4H, 4-phenoxybenzyl), 5.87 (d, 1H, J = 6.4 Hz, 1′H), 5.37 (m, 2H, 3′OH overlapping 2′OH), 4.77 (m, 1H, 2′H), 4.69 (br s, 2H, 4-phenoxyphenyl-CH_2), 4.18 (m, 1H, 3′H), 4.09 (m, 1H, 4′H), 3.80 (t, 2H, J = 7.0 Hz, butyl), 3.60 (m, 2H, 5′H), 1.61 (m, 2H, butyl), 1.27 (m, 2H, butyl), 0.88 (t, 2H, J = 7.3 Hz, butyl). HR-ESI-MS $[M+H]^+$ calcd 665.2836, found 665.2802.

6.28. 5′-Deoxy-5′-{5-[1-(3-methoxypropyl)-2-oxo-2,3-dihydro-1*H*-benzimidazolyl]carboxamido}-N^6-(4-phenoxybenzyl)adenosine (35)

Conversion rate 80%. Purity HPLC after MPLC = 96.5% (254 nm). ^{1}H NMR (400 MHz, DMSO-d_6) = δ (ppm) 11.1 (br s, 1H, urea-NH), 8.55 (m, 1H, amido-NH), 8.37 (m, 2H, C8–H overlapping amino), 8.18 (s, 1H, C2–H), 7.57 (m, 1H, benzene), 7.49 (m, 1H, benzene), 7.35 (m, 4H, phenoxyphenyl), 7.10 (m, 2H, benzene overlapping 4-phenoxyphenyl), 6.96 (m, 4H, 4-phenoxyphenyl), 5.88 (d, 1H, J = 6.4 Hz, 1′H), 5.46 (m, 2H, 3′OH overlapping 2′OH), 4.76 (m, 1H, 2′H), 4.69 (br s, 2H, 4-phenoxyphenyl-CH_2), 4.18 (m, 1H, 3′H), 4.09 (m, 1H, 4′H), 3.84 (t, 2H, J = 6.7 Hz, propylene), 3.60 (m, 2H, 5′H), 3.31 (m, 2H, propylene overlapping H_2O), 3.20 (s, 3H, methoxy), 1.85 (m, 2H, propylene). HR-ESI-MS $[M+H]^+$ calcd 681.2785, found 681.2748.

6.29. Growth of *Plasmodium falciparum parasites*

In vitro activity against erythrocytic stages of *P. falciparum* was determined using a [^{3}H]hypoxanthine incorporation assay, using the chloroquine and pyrimethamine resistant K1 strain.[28] Compounds, including chloroquine (Sigma C6628) as standard, were dissolved in DMSO at 10 mg/mL and added to parasite cultures incubated in RPMI 1640 medium without hypoxanthine, supplemented with HEPES (5.94 g/L), $NaHCO_3$ (2.1 g/L), neomycin (100 U/mL), AlbuMAX (5 g/L), and washed human red cells A^+ at 2.5% hematocrit (0.3% parasitemia). Serial doubling dilutions of each drug were prepared in 96-well microtiter plates and incubated in a humidified atmosphere at 37 °C; 4% CO_2, 3% O_2, 93% N_2. After 48 h, 50 μL of [^{3}H]hypoxanthine (=0.5 μCi) in medium was added to each well of the plate. The plates were incubated for a further 24 h under the same conditions. The plates were then harvested with a Betaplate cell harvester (Wallace, Zurich, Switzerland), and the red blood cells were transferred onto a glass fiber filter and then washed with distilled water. The dried filters were inserted into a plastic foil with 10 mL of scintillation fluid and counted in a Betaplate liquid scintillation counter (Wallace, Zürich, Switzerland). IC_{50} values were calculated from sigmoidal inhibition curves using Microsoft Excel.[29]

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