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Solid phase synthesis and antiprotozoal evaluation of di- and trisubstituted 5′-carboxamidoadenosine analogues

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Abstract—The rapid increase of resistance to drugs commonly used in the treatment of tropical diseases such as malaria and African sleeping sickness calls for the prompt development of new safe and efficacious drugs. The pathogenic protozoan parasites lack the capability of synthesising purines de novo and they take up preformed purines from their host through various transmembrane transporters. Adenosine derivatives constitute a class of potential therapeutics due to their selective internalisation by these transporters. Automated solid-phase synthesis can speed up the process of lead finding and we pursued the solid-phase synthesis of di- and trisubstituted 5′-carboxamidoadenosine derivatives by using a safety-catch approach. While efforts with Kenner's sulfonamide linker remained fruitless, successful application of the hydrazide safety-catch linker allowed the construction of two representative combinatorial libraries. Their antiprotozoal evaluation identified two compounds with promising activity: N^6-benzyl-5′-*N*-phenylcarboxamidoadenosine with an IC_{50} value of 0.91 μM against *Trypanosoma brucei rhodesiense* and N^6-diphenylethyl-5′-phenylcarboxamidoadenosine with an IC_{50} value of 1.8 μM against chloroquine resistant *Plasmodium falciparum.*

1. Introduction

WHO estimates that tropical diseases such as malaria and Human African Trypanosomiasis (HAT) are a daily threat to more than 2 billion people.[1] HAT or sleeping sickness, which kills more than 50,000 people each year, is caused by *Trypanosoma brucei* species.[2] *T. b. gambiense* is responsible for the chronic form of the disease, taking months or even years to progress from the early stage into the meningoencephalitic stage. *T. b. rhodesiense* causes the acute form of the disease, requiring just a few weeks to reach this second stage. If left untreated, late stage trypanosomiasis is fatal. Increasing resistance to the common drugs[3] and their cumbersome parenteral administration combined with severe side effects highly demand the development of new safer and more effective drugs.

Plasmodium falciparum, the causative agent of the most severe form of malaria in humans, is responsible for 1.5 million deaths per year, of which more than one million occur in children under 5 years of age.[4] Although chemotherapy and prophylaxis are available, the rapidly growing resistance against classical (and inexpensive) drugs such as chloroquine and sulfadoxine–pyrimethamine articulates the acute need for new efficacious drugs.[5]

Protozoan parasites lack the capability of synthesising purines de novo and therefore are solely dependent on their host for purine uptake.[6] Each genus of protozoan parasite has a distinct and unique complement of purine transporters and salvage enzymes that enable the parasite to scavenge preformed purines from the host.[7] Adenosine derivatives constitute a class of potential therapeutics in the treatment of African trypanosomiasis[8,9] and malaria [10] due to their selective internalisation.

Recently, we reported on a library of adenosine analogues for the first time entirely prepared on a solid phase.[11] The solid-phase sequence leading to 2,N^6-disubstituted

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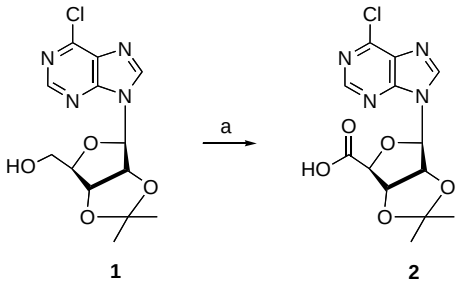
adenosine analogues involved anchoring of the nucleoside to the solid support by its riboside 5′-hydroxyl functionality, while subsequently diversity elements were introduced on the purine skeleton. Antiprotozoal screening of this library revealed adenosine analogues with promising antitrypanosomal and antiplasmodial activities.[12] In our ongoing efforts to design solid-phase mononucleoside syntheses allowing for the automated preparation of these molecules, it was our desire to expand our methodology to the modification of the ribosyl moiety. In the field of antiprotozoal research, 5′-modified adenosine analogues are known as growth inhibitors of multidrug resistant *P. falciparum*,[13] inhibitors of trypanosomal glycolytic enzymes[14] and inhibitors of enzymes involved in trypanosomal polyamine synthesis.[15]

2. Results and discussion

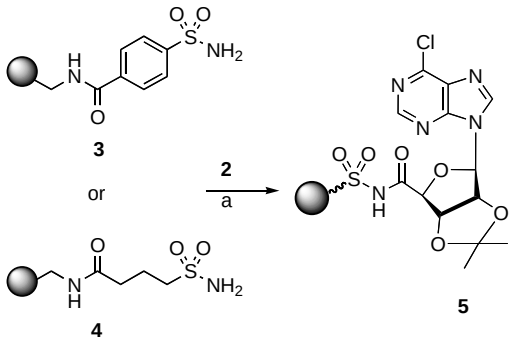
2.1. Chemistry

Our objective consisted of generating 5′-carboxamidoadenosine analogues in a divergent way, thus allowing for the introduction of pharmacophores not only on the purine 2 and N^6 positions, as described previously,[11] but also on the ribosyl 5′-position. Consequently, a procedure had to be devised that granted both the attachment of the nucleoside scaffold to a solid support and the introduction of diversity elements on the three different positions. The proposed strategy involving the safety catch principle[16] is outlined in Scheme 1. Suitably protected 6-chloropurine riboside 5′-carboxylic acid is coupled to the solid phase via a dormant linker. Modifications can be realised on the purine skeleton, while the linker remains intact. When the ribosyl-protective groups (PGs) are removed and the nucleoside is ready for cleavage, the linker is 'switched on.' This sets the stage for combined cleavage and introduction of the final diversity element, leading to the aimed nucleoside carboxamide analogues. In this way, the 5′-position serves both as the anchor to the solid support and the reactive functionality in the final diversification/cleavage step.

To obtain the 5′-carboxylic acid nucleoside precursor, we applied the mild TEMPO–iodobenzene diacetate oxidising system, reported for the 5′-oxidation of common 2′,3′-protected nucleosides,[17] to 2′,3′-isopropylidene-protected 6-chloropurine riboside **1**,[18] which afforded 5′-carboxylic acid **2** in excellent yield (Scheme 2).

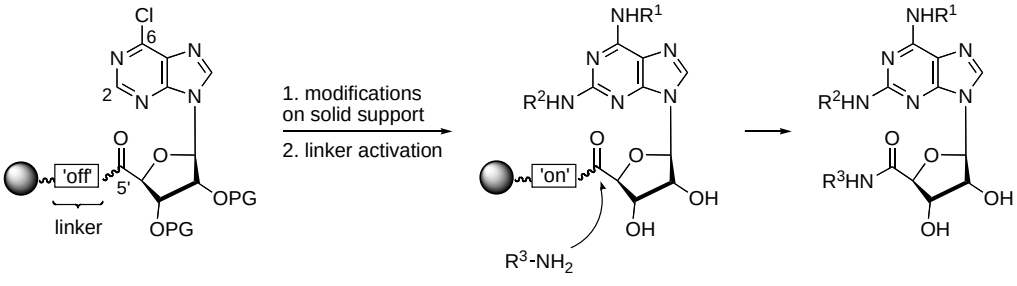


Scheme 2. Reagents: (a) TEMPO, iodobenzene diacetate, CH_3CN, H_2O, 92%.



Scheme 3. Coupling attempts to Kenner's linker. (a) For coupling methods see Table 1.

2.1.1. Solid phase syntheses with Kenner's sulfonamide linker. Initial synthetic efforts towards substituted 5′-carboxamidoadenosine derivatives addressed the coupling of 6-chloropurine riboside-5′-carboxylic acid **2** to Kenner's sulfonamide linker,[16] which has been successfully applied in peptide chemistry, solid-phase organic synthesis and polymer-assisted solution phase synthesis.[19] Kenner's benzenesulfonamide linker **3** (Scheme 3) was selected for its complete stability towards strongly basic/nucleophilic[20] and strongly acidic conditions.[16] At any desired point in the sequence the linker can be activated towards nucleophilic release by alkylation of the acylsulfonamide NH with diazomethane[16] or iodoacetonitrile.[21] Although it was noted that loading efficiencies with Kenner's original benzenesulfonamide linker **3** were poor, especially with sterically demanding carboxylic acids,[21] this linker was at first preferred over Ellman's alkanesulfonamide linker **4**. The reactivity of the NH_2 in sulfonamide linkers has been compared to



Scheme 1. Proposed strategy involving the safety-catch principle.

Table 1. Coupling methods used for loading Kenner's linker[a]

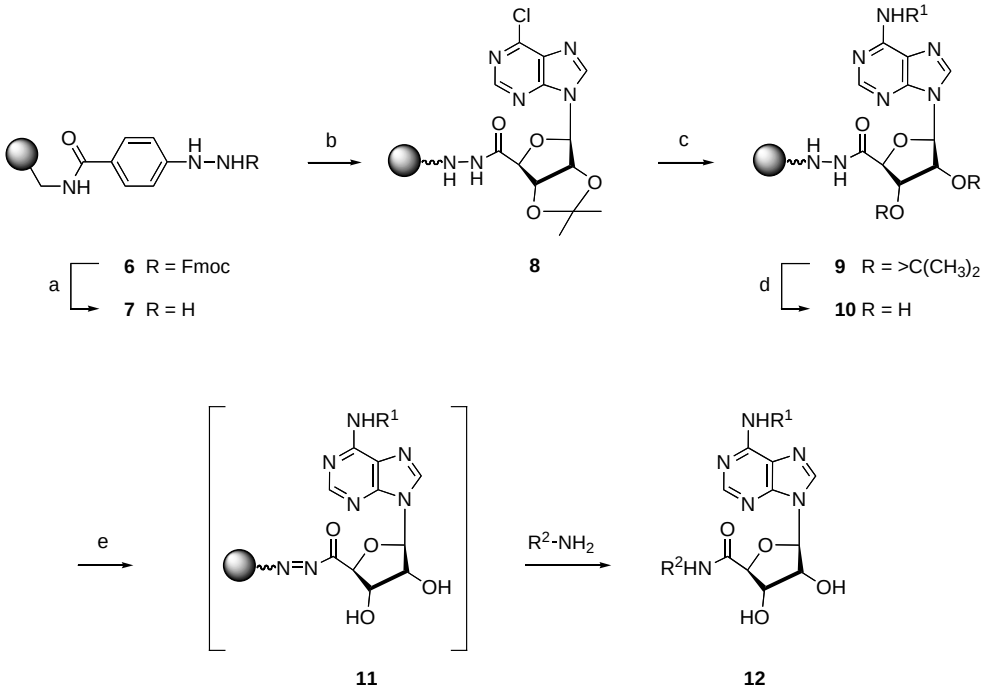
Entry	Method	Base	Solvent	Result
1	Acid **2** (5 equiv), DIC (5 equiv), 1-MeIm[b] (5 equiv)		CH_2Cl_2	—
2	Acid **2** (3 equiv), DIC (3 equiv), DMAP (0.4 equiv)		CH_2Cl_2	—
3	Acid **2** (3 equiv), CIP (3 equiv)	DIPEA (6 equiv)	CH_2Cl_2	2–5%
4	Acid **2** (3 equiv), PyBOP (3 equiv)	DIPEA (6 equiv)	DMF	—
5	Acid **2** (3 equiv), DBC[c] (3 equiv)	Pyridine (4 equiv)	DMF	—
6	Symm. anhydride of **2** (5 equiv), DMAP (1 equiv)	DIPEA (5 equiv)	CH_2Cl_2	2–5%

[a] Typical coupling times were 20–24 h.
[b] 1-MeIm = 1-methylimidazole, see Ref. 23.
[c] DBC = 2,6-dichlorobenzoylchloride.

that of an alcohol.[21] Therefore, typical esterification reagents are to be used in the coupling procedure. However, attachment of nucleoside 5′-carboxylic acid **2** to Kenner's linker **3** offered significant problems (Scheme 3). The success of attachment to the resin can be assessed by the appearance of a strong carbonyl vibration at approximately 1735 cm^{-1} in the infrared spectrum of the immobilised nucleoside 5′-carboxylic acid derivative. Many coupling procedures were employed, most of them known from the attachment of amino acid residues to the Kenner linker (Table 1). However, loading of the resin, though quite insufficient, was only inferred from experiments with the symmetrical anhydride method or with 2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate (CIP), a coupling reagent known to be particularly effective for sterically demanding couplings.[22] Model experiments in solution (DIC–DMAP, EDC–DMAP and pentafluorophenylester) with carboxylic acid **2** and linker analogue *N*-benzoyl-4-sulfamoylbenzamide, also failed to produce the corresponding acylsulfonamide.

The poor results on solid phase and even in solution were partly ascribed to the moderate nucleophilicity of the benzenesulfonamide linker. Therefore, attachment of carboxylic acid **2** to Ellman's modified alkanesulfonamide linker **4** was attempted, a linker especially designed for enhanced nucleophilicity.[21] Concisely, all efforts using the coupling methods mentioned before gave a comparably poor outcome. From these results, we concluded that steric hindrance combined with the moderate nucleophilicity of the Kenner–Ellman linkers frustrated immobilisation of the nucleoside 5′-carboxylic acid and the sulfonamide strategy was suspended.

Remarkably, several months after we abandoned this approach, a study appeared in the literature concerning the coupling in solution of N^6-benzoyl-2′,3′-isopropylidene adenosine 5′-carboxylic acid to various sulfonamides.[24] Among the range of methods explored the best results were reported with 1.1 equiv of DCC/DMAP and 2 equiv of sulfonamide. Nevertheless, coupling required stirring in dichloromethane for four days,



Scheme 4. Reagents and conditions: (a) 20% piperidine in DMF; (b) **2**, DIC, DMF; (c) R^1-NH_2, NMP, 50 °C; (d) TFA–$HO(CH_2)_2OH$–CH_2Cl_2; (e) 0.5 equiv $Cu(OAc)_2$, R^2-NH_2, THF.

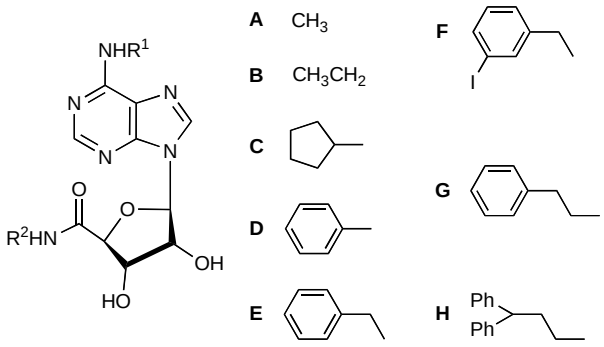
indicating the sluggishness of the reaction, which makes it unsuitable for solid-phase applications.

2.1.2. Safety-catch approach with the arylhydrazide linker. In the arylhydrazide safety catch linker,[25] we found a good alternative. Compared with the sulfonamide NH_2 in Kenner's linker, the hydrazine moiety is sterically much less demanding and has superior nucleophilic properties. The arylhydrazide linker was originally introduced in 1970 by Wieland et al. for the solid-phase synthesis of peptides.[26] The safety-catch concept relies on the fact that the linker is acid and base stable and can be activated under oxidative conditions to generate the reactive acyldiazene. Subsequent attack by a nucleophile present releases nitrogen gas and produces carboxylic acids, esters or amides, when water, alcohols or amines are used as nucleophiles. Recent applications of this linker involve the synthesis of (cyclic)[27] peptides.[28,29]

The solid-phase synthesis of $N5',N^6$-disubstituted 5′-carboxamidoadenosine analogues using the arylhydrazide safety catch linker is depicted in Scheme 4. Following removal of the Fmoc group from commercially available 4-Fmoc-hydrazinobenzoyl AM resin **6** with 20% piperidine in DMF, 5′-carboxylic acid **2** was coupled to hydrazine resin **7** by using DIC as a coupling reagent to render hydrazide **8**. Literature methods for the acylation of resin **7** involve a diimide in combination with an additive such as 1-hydroxybenzotriazole, HOBt.[27–29] In our system, we observed that HOBt displaces the chloroatom in the purine ring.[30] Although omission of this additive required a longer coupling period, effective loading of the resin was achieved as indicated by a bromophenol blue colour test.[31] Introduction of an amino substituent on the purine 6-position was effected in NMP at 50 °C affording purine **9**. Removal of the 2′,3′-isopropylidene group via transketalisation with a cocktail of TFA, ethylene glycol and dichloromethane (5:1:5) yielded resin-bound **10**, which was now ready for cleavage from the resin. The hydrazide linkage was oxidised to acyldiazene **11** by the method of Lowe and co-workers using 0.5 equiv of copper(II) acetate in the presence of a nitrogen nucleophile.[32] Under air atmosphere, only catalytic quantities of copper(II) are required due to the rapid aerial oxidation of copper(I) ions. Although 0.1 equiv of copper(II) suffices to effect oxidation, we used 0.5 equiv to reduce reaction times. The amine present in solution serves a triple goal; first, deprotonation of the hydrazide, second, complexation of the copper ions, thereby preventing them to precipitate from solution, and finally, nucleophilic release under formation of carboxamide **12**. The copper salts were easily removed by passing the solution of the crude product over a silica gel cartridge.

The construction of a 20-membered library validated the developed solid-phase sequence. Purities after solid-phase extraction using a silica gel cartridge ranged from 64% to 99%. Nevertheless, all compounds were subsequently purified by semi-preparative HPLC and isolated by lyophilisation to allow for reliable antiprotozoal evaluation. Products **12a**–**t** were obtained in reasonable yields (19–54% over four solid-phase steps) and high purities (see Table 2). These final yields were comparable to those obtained via an alternative procedure reported during completion of our synthetic work.[33]

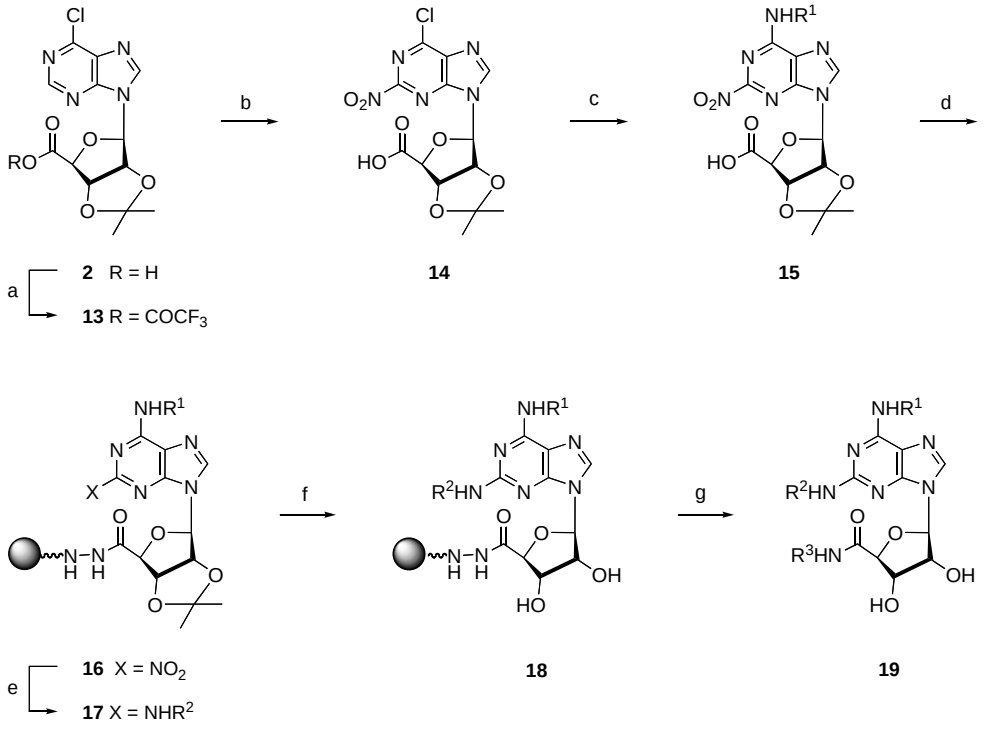
Table 2. Yield and purity of disubstituted 5′-carboxamidoadenosine analogues[a]



Compound	R^1	R^2	Yield (%)	Purity (%)
12a	C	A	43	>99
12b	C	B	37	97
12c	C	C	28	>99
12d	C	D	32	99
12e	E	A	50	>99
12f	E	B	46	98
12g	E	C	45	99
12h	E	D	30	94
12i	F	A	54	97
12j	F	B	44	98
12k	F	C	50	>99
12l	F	D	34	92
12m	G	A	54	>99
12n	G	B	50	99
12o	G	C	36	98
12p	G	D	42	94
12q	H	A	31	97
12r	H	B	32	95
12s	H	C	25	99
12t	H	D	19	99

[a] Overall yield and purity after HPLC purification.

While disubstituted adenosine analogues **12a**–**t** were readily synthesised by application of the hydrazide resin, our second goal was the preparation of trisubstituted 5′-carboxamidoadenosine analogues, which required nitration of the purine 2-position.[34] Not surprisingly, TBAN–TFAA nitration of hydrazide resin-bound 6-chloropurine resulted in premature release of the nucleoside from the solid support by N-nitration or oxidation of the hydrazide linkage and subsequent cleavage by nucleophiles present. An alternative approach involving the attachment of 2-nitro-6-chloropurine riboside 5′-carboxylic acid to the hydrazine resin was not an option because of the high reactivity of the purine 6-position in that system. Therefore, a different strategy was pursued entailing a combined solution and solid-phase diversification of the nucleoside. At first, 6-chloropurine **2** was nitrated in solution as shown in Scheme 5. The carboxyl group was protected in situ with TFAA under formation of mixed anhydride **13**, while subsequent addition of TBAN to the reaction mixture resulted in efficient nitration of the purine ring at C2. Aqueous work-up in order to liberate the carboxyl moiety gave 2-nitro-6-chloropurine



Scheme 5. Reagents and conditions: (a) TFAA (3 equiv), CH_2Cl_2, 0 °C; (b) add TBAN (2 equiv), then aqueous work-up, 94%; (c) R^1-NH_2, DIPEA, CH_2Cl_2, rt; (d) **7**, DIC, HOBt, DMF; (e) R^2-NH_2, DIPEA, NMP, 80 °C; (f) TFA/$HO(CH_2)_2OH$/CH_2Cl_2, 5:1:5; (g) 0.5 equiv $Cu(OAc)_2$, THF.

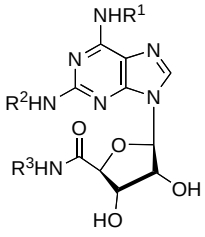
14 in high yield. At this point, the first amino diversity element was introduced in solution by 6-chloro displacement furnishing substituted 6-aminopurines **15**. Ensuing attachment to hydrazine resin **7** was brought about under standard acylation conditions, that is, DIC in combination with HOBt. The use of additive HOBt was allowed because in purine **15** no highly reactive electrophilic positions were present. A bromophenol blue test[31] confirmed quantitative formation of resin **16**. Substitution of the 2-nitro group by nitrogen nucleophiles required gentle heating in NMP to obtain substituted 2,6-diaminopurines **17**. Removal of the 2′,3′-isopropylidene group under acidic conditions gave **18**, which was now fit for cleavage from the solid support. Copper(II) mediated oxidation of the hydrazide linkage in the presence of the final amino diversity element released the desired 2,*N*5′,N^6-trisubstituted 5′-carboxamidoadenosine analogues **19**.

Again, a characteristic library was prepared, demonstrating the efficiency of the developed solid-phase route. After oxidative cleavage from the resin, the copper salts were removed by filtration over a silica gel cartridge, and products were obtained in 67–87% purity (Table 3). Subsequent semi-preparative HPLC and lyophilisation afforded trisubstituted carboxamidoadenosine analogues **19a**–**h** in high purity and 20–57% yield over four solid-phase steps, ready for antiprotozoal screening.

2.2. Biological activity

The results of the screening assays of the di- and trisubstituted carboxamidoadenosine analogues against *T. b. rhodesiense* (STIB 900 strain) and the chloroquine and pyrimethamine resistant *P. falciparum* K1 strain are presented in Table 4. Whereas in our preliminary screening of 2,N^6-disubstituted adenosine analogues the cyclopentyl substituted adenosine analogues belonged to the most active and promising trypanocidal compounds,[12] in the current series neither the introduction of a cyclopentyl group on N^2 nor on N^6 leads to encouraging trypanocidal activities. Nonetheless, for antiplasmodial action the combination with a 5′-cyclopentyl group appears to be optimal for the N^6-benzyl and N^6-*m*-iodobenzyl and N^6-phenethyl substituted adenosine derivatives.

Table 3. Yield and purity of trisubstituted 5′-carboxamidoadenosine analogues[a]



Compound	R^1	R^2	R^3	Yield (%)	Purity (%)
19a	C	C	B	27	97
19b	C	C	C	26	96
19c	C	G	B	35	98
19d	C	G	C	35	99
19e	F	C	B	30	92
19f	F	C	C	57	91
19g	F	G	B	21	99
19h	F	G	C	38	91

[a] Overall yield and purity after HPLC purification.

Table 4. Antiprotozoal activity of di- and trisubstituted 5′-carboxamidoadenosine analogues

Compound	*T.b. rhodesiense* STIB 900 strain IC_{50} (μM)	*P. falciparum* K1 strain IC_{50} (μM)
12a	>75	>10
12b	>75	>10
12c	30.3	7.1
12d	5.4	7.2
12e	37.2	>10
12f	9.7	9.7
12g	4.1	3.0
12h	0.91	4.6
12i	5.1	6.4
12j	4.0	3.4
12k	4.9	2.7
12l	5.4	3.6
12m	>75	>10
12n	38.3	9.7
12o	9.4	5.9
12p	3.3	6.0
12q	27.4	>10
12r	28.3	>10
12s	11.4	5.8
12t	8.9	1.8
19a	16.5	9.8
19b	12.1	7.8
19c	10.2	5.7
19d	6.2	4.9
19e	11.4	5.8
19f	6.5	3.4
19g	6.8	5.5
19h	3.9	4.1
Melarsoprol	0.0069	
Artemisinin		0.0051

On the other hand, we observed that, except for the N^6-*m*-iodobenzyl analogues, the combination with a 5′-phenyl group is most advantageous for trypanocidal activity; N^6-benzyl-5′-*N*-phenylcarboxamidoadenosine **12h** even has submicromolar antitrypanosomal activity with an IC_{50} value of 0.91 μM. Generally, a small 5′-substituent, such as methyl or ethyl, is not favourable for antiprotozoal activity. As also emerged from the previous screenings,[12] the N^6-diphenylethyl derivatives display mainly antimalarial activity. Especially, the combination with an aromatic residue on the 5′ position (**12t**) leads to promising activity with an IC_{50} value of 1.8 μM. Judging from the modest activities of the trisubstituted analogues **19a**–**h**, introduction of an additional substituent on C2 does not improve antiprotozoal capacity.

3. Conclusions

By using the beneficial sterical and electronic properties of the arylhydrazide linker we showed that the safety-catch approach can be a practical synthetic tool leading to di- and trisubstituted 5′-carboxamidoadenosine derivatives. As the arylhydrazide linker seemed incompatible with our TBAN–TFAA nitration, the solid-phase synthesis of trisubstituted 5′-carboxamidoadenosine analogues required a combined solution/solid-phase diversification procedure. The biological evaluation of two typical combinatorial libraries revealed two interesting structural leads for further antiprotozoal optimisation: N^6-benzyl-5′-*N*-phenylcarboxamidoadenosine **12h** with an IC_{50} value of 0.91 μM against *T.b. rhodesiense* and N^6-diphenylethyl-5′-phenylcarboxamidoadenosine **12t** with an IC_{50} value of 1.8 μM against multidrug resistant *P. falciparum*.

4. Experimental

4.1. General synthetic methods

All reagents and solvents were used as commercially available, unless indicated otherwise. Peptide grade solvents were used for solid-phase chemistry. 4-Fmoc-hydrazinobenzoyl AM resin, 100–200 mesh, 0.98 mmol/g, was purchased from Novabiochem, *N*-(4-sulfamoylbenzoyl)aminomethyl polystyrene **3**, 200–400 mesh, 0.9 mmol/g, was purchased from Fluka, *N*-(4-sulfamoylbutyryl)aminomethyl polystyrene **4**, 200–400 mesh and 1.09 mmol/g, was a gift from Solvay Pharmaceuticals, Weesp, NL. Flash chromatography refers to purification using the indicated eluents and Acros silica gel 60 (0.030–0.075 mm). NMR spectra were determined in the indicated solvent at 300 K using a Bruker ARX 400 (400 MHz) spectrometer. NH and OH signals were identified after mixing the sample with a drop of D_2O. For the end-products **12** and **19** coupling constants J = of H-2′, H-3′ and H-4′ were determined after mixing the sample with a drop of D_2O. Infrared spectra of resins were measured in KBr using a DRIFT module (Bruker), vibrations ν reported in cm^{-1}. Mass spectra and accurate mass measurements were performed on a JEOL JMS–SX/SX 102 A Tandem Mass Spectrometer using Fast Atom Bombardment (FAB). A resolving power of 10,000 (10% valley definition) for high resolution FAB mass spectrometry was used. Analytical HPLC was performed on a C_{18} column (Inertsil ODS-3, particle size 3 μm; 4.6 mm × 50 mm) using the following elution gradient: linear gradient of 5–95% aqueous CH_3CN containing 0.04% HCO_2H over 5 min, then 95% aqueous CH_3CN containing 0.04% HCO_2H for 2 min at 2.0 mL min^{-1}. Semi-preparative HPLC was performed on a C_{18} column (Polygosil 60 C-18, particle size 10 μm; 20 mm × 250 mm) using the following elution gradient: linear gradient of 5–95% aqueous CH_3CN containing 0.04% HCO_2H over 15 min, then 95% aqueous CH_3CN containing 0.04% HCO_2H for 6 min at 7.0 mL min^{-1}. Products were detected at λ = 254 nm.

4.1.1. General solid-phase procedures. Large-scale solid-phase reactions (>200 mg of resin) were performed in dried glass scintillation vessels, bubbling nitrogen gas through the resin suspension. Small-scale solid-phase reactions (100–200 mg of resin) were run under a nitrogen atmosphere in Radleys Carousel Reaction Station™ using dried modified glass reaction tubes. The tubes were fitted with a glass frit and luer tip to facilitate work-up on the IST VacMaster-20 Sample Processing Station™. Small-scale reactions were gently stirred with a magnetic stirring bar. The modified tubes were heated in a sand bath fitted in the Carousel Reaction Station™. Resins were suspended in 1 mL solvent/

100 mg resin. The resins were washed according to the indicated sequence.

4.2. Synthesis

4.2.1. 6-Chloro-(2,3-*O*-isopropylidene-5-carboxy-*b*-D-ribofuranosyl)-9*H*-purine (2). This compound was synthesised according to a modified literature procedure.[17] A mixture of iodobenzene diacetate (6.72 g; 20.8 mmol), TEMPO (296 mg; 1.90 mmol) and 2′,3′-isopropylidene-protected 6-chloropurine riboside **1**[18] (3.10 g; 9.49 mmol) in water/acetonitrile 1:1 (20 mL) was stirred for 4 h. The reaction mixture was carefully poured into 0.5 M aqueous $NaHCO_3$ (125 mL). After stirring for 10 min, the mixture was washed with CH_2Cl_2 (3× 40 mL). The combined organic layers were back-extracted with water (20 mL). The aqueous layers were combined, acidified with 1 M aqueous HCl and extracted with CH_2Cl_2/EtOH 95:5 (4× 40 mL). Drying with Na_2SO_4 and coevaporation with toluene gave 5′-carboxylic acid **2** as a white solid (2.98 g; 8.74 mmol; 92%). ^{1}H NMR (DMSO-d_6) δ 12.92 (br s, 1H, COOH), 8.84 and 8.78 (2× s, 2× 1H, H-2 and H-8), 6.52 (s, 1H, H-1′), 5.64 (d, J = 5.9, 1H, H-2′), 5.58 (dd, J = 5.9 and 1.3, 1H, H-3′), 4.80 (d, J = 1.3, 1H, H-4′), 1.55 (s, 3H, CH_3), 1.39 (s, 3H, CH_3). IR (KBr) ν 3200, 1728.

4.2.2. Attempted coupling of carboxylic acid 2 to sulfonamide resins 3 or 4. In a typical experiment to a suspension of the sulfonamide resin (100 mg; 0.09 mmol) in 1 mL DMF were added carboxylic acid **2** (153 mg; 0.45 mmol), DIC (70 μL; 0.45 mmol) and 1-methylimidazole (36 μL; 0.45 mmol). After 20–24 h, the resulting resin was washed with the solvent of the reaction (3×), CH_2Cl_2 (3×), MeOH, CH_2Cl_2, MeOH, Et_2O and CH_2Cl_2, Et_2O, CH_2Cl_2 and dried in vacuo at 50 °C. No coupling was observed judging from the absence of a sulfonamide carbonyl vibration at ≈1735 cm^{-1}. For other coupling conditions, see Table 1.

4.2.3. *N*-Benzyl-4-sulfamoyl-benzamide. A mixture of 4-sulfamoyl-benzoic acid (5.0 g; 25 mmol), benzylamine (5.57 mL; 50.0 mmol), EDC (5.75 g; 30.0 mmol) and HOBt (4.05 g; 30.0 mmol) in DMA/CH_2Cl_2 1:1 (2 mL) was stirred for 2 h. Et_2O/EtOAc 1:1 (1 mL) and 5% aqueous $KHSO_4$ (1.5 mL) were added and after stirring for 5 min the mixture was washed with water (3× 2 mL). Drying with Na_2SO_4 and evaporation of the solvent yielded *N*-benzyl-4-sulfamoylbenzamide as a white crystalline solid (4.86 g; 19.0 mmol; 76%). ^{1}H NMR (DMSO-d_6) δ 9.27 (t, J = 6.0, 1H, NH), 8.07 (d, J = 8.4, 2H, HCOAr), 7.92 (d, J = 8.4, 2H, HCOAr), 7.50 (br s, 2H, NH_2), 7.37–7.32 (m, 4H, HBn), 7.29–7.27 (m, 1H, HBn), 4.52 (d, J = 6.0, 2H, CH_2).

4.2.4. Attempted coupling of carboxylic acid 2 to *N*-benzyl-4-sulfamoylbenzamide. In a typical experiment, a mixture of carboxylic acid **2** (80 mg; 0.23 mmol), *N*-benzyl-4-sulfamoylbenzamide (50 mg; 0.20 mmol), EDC (54 mg; 0.28 mmol) and DMAP (2.5 mg; 0.02 mmol) in DMA/CH_2Cl_2 1:1 (2 mL) was stirred at rt. After 18 h, still no reaction had taken place as indicated by TLC analysis. After work-up of the reaction mixture, only starting material was recovered.

4.2.5. Fmoc removal from 2-Fmoc-hydrazinobenzoyl AM resin 6 (7). A suspension of 2-Fmoc-hydrazinobenzoyl AM resin **6** (1.0 g; 0.98 mmol) in DMF/piperidine 4:1 (10 mL) was mixed by nitrogen bubbling for 30 min. Resin **7** was washed with DMF (3×), CH_2Cl_2 (3×), MeOH, CH_2Cl_2, MeOH, Et_2O, CH_2Cl_2, Et_2O and CH_2Cl_2 and dried in vacuo at 50 °C.

4.2.6. Coupling of carboxylic acid 2 to hydrazinobenzoyl AM resin 7 (8). To a suspension of hydrazinobenzoyl AM resin **7** (0.78 g; 0.98 mmol) in DMF (10 mL) were added carboxylic acid **2** (0.84 g; 2.45 mmol) and DIC (384 μL; 2.45 mmol). The reaction was monitored with a bromophenol blue test.[31] After 16 h, the reaction was complete and resin **8** was washed with DMF (3×), CH_2Cl_2 (3×), MeOH, CH_2Cl_2, MeOH, Et_2O, CH_2Cl_2, Et_2O and CH_2Cl_2, and dried in vacuo at 50 °C.

4.2.7. General procedure for the amination by chloro substitution of resin-bound 6-chloropurines 8 (9). A suspension of resin-bound 6-chloropurine **8** (200 mg; 0.18 mmol) and the amine (0.71 mmol) in NMP (2 mL) was gently stirred at 50 °C. After 18 h, resin **9** was washed with NMP (3×), CH_2Cl_2 (3×), MeOH, CH_2Cl_2, MeOH, Et_2O, CH_2Cl_2, Et_2O and CH_2Cl_2.

4.2.8. General procedure for removal of the 2′,3′-isopropylidene group (10). In a typical experiment, resin-bound isopropylidene-protected riboside **9** (0.18 mmol) was washed with a solution of TFA/HO$(CH_2)_2$OH/CH_2Cl_2 5:1:5 (2 mL). After subjecting to this solution (2 mL) for 18 h, resin **10** was washed with CH_2Cl_2 (3×), CH_2Cl_2/DIPEA 9:1 (3×), CH_2Cl_2 (3×), MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, Et_2O, CH_2Cl_2, Et_2O and CH_2Cl_2.

4.2.9. General procedure for oxidative cleavage of the nucleosides (12). In a typical experiment, a suspension of resin **10** (0.18 mmol), amine (0.89 mmol) and $Cu(OAc)_2$ (16 mg; 0.09 mmol) in THF (2 mL) was gently stirred for 22 h under an air atmosphere. The resin was washed with THF (3×), MeOH, THF, MeOH, THF, MeOH and THF (2×). The combined washings were passed over a silica gel cartridge (Supelco, 1 g of silica) and the solvents were evaporated. The end products were purified by semi-preparative HPLC and isolated by lyophilisation.

4.2.10. N^6-Cyclopentyl-5′-*N*-methylcarboxamidoadenosine (12a). Yield: 28 mg; 0.077 mmol; 43%. ^{1}H NMR (DMSO-d_6) δ 8.98 (q, J = 4.5, 1H, CONH), 8.41 and 8.31 (2× s, 2× 1H, H-2 and H-8), 7.88 and 7.79 (2× d, J = 5.0, 1H, N^6-H rotamers), 5.98 (d, J = 7.5, 1H, H-1′), 5.77 (br s, 1H, OH), 5.57 (d, J = 5.8, 1H, OH), 5.12 and 4.53 (2× m, 1H, CH rotamers), 4.61 (dd, J = 7.5 and 4.7, 1H, H-2′), 4.34 (s, 1H, H-4′), 4.16 (d, J = 4.7, 1H, H-3′), 2.74 (d, J = 4.5, 3H, CH_3), 2.01–1.93 (m, 2H, cyclopentyl), 1.77–1.72 (m, 2H, cyclopentyl), 1.72–1.54 (m, 4H, cyclopentyl). *m/z* 363.1789 (M^++H, $C_{16}H_{23}N_6O_4$ requires 363.1781).

4.2.11. N^6-Cyclopentyl-5′-*N*-ethylcarboxamidoadenosine (12b). Yield: 25 mg; 0.067 mmol; 37%. ^{1}H NMR (DMSO-d_6) δ 8.94 (t, J = 5.3, 1H, CONH), 8.40 and 8.28 (2× s, 2× 1H, H-2 and H-8), 7.88 and 7.76 (2× d,

J = 6.3, 1H, N^6-H rotamers), 5.98 (d, J = 7.5, 1H, H-1′), 5.76 (d, J = 3.9, 1H, OH), 5.56 (d, J = 6.3, 1H, OH), 5.12 and 4.55 (2× m, 1H, CH rotamers), 4.63 (dd, J = 7.5 and 4.7, 1H, H-2′), 4.32 (d, J = 1.3, 1H, H-4′), 4.16 (dd, J = 4.7 and 1.3, 1H, H-3′), 3.24 (dq, J = 7.0 and 5.3, 2H, CH_2), 2.00-1.94 (m, 2H, cyclopentyl), 1.76–1.73 (m, 2H, cyclopentyl), 1.70–1.56 (m, 4H, cyclopentyl), 1.10 (t, J = 7.0, 3H, CH_3). *m/z* 377.1927 (M^++H, $C_{17}H_{25}N_6O_4$ requires 377.1937).

4.2.12. N^6-Cyclopentyl-5′-*N*-cyclopentylcarboxamidoadenosine (12c). Yield: 21 mg; 0.050 mmol; 28%. ^{1}H NMR (DMSO-d_6) δ 8.55 (d, J = 7.0, 1H, CONH), 8.42 and 8.22 (2× s, 2× 1H, H-2 and H-8), 7.89 (br s, 1H, N^6-H), 5.97 (d, J = 7.5, 1H, H-1′), 5.74 (d, J = 4.3, 1H, OH), 5.56 (d, J = 6.4, 1H, OH), 5.09 and 4.62 (2× m, 1H, CH rotamers), 4.72–4.68 (m, 1H, H-2′), 4.32 (d, J = 1.6, 1H, H-4′), 4.15–4.08 (m, 2H, H-3′ and CH), 2.00–1.81 (m, 4H, cyclopentyl), 1.77–1.32 (m, 12H, cyclopentyl). *m/z* 417.2247 (M^++H, $C_{20}H_{29}N_6O_4$ requires 417.2250).

4.2.13. N^6-Cyclopentyl-5′-*N*-phenylcarboxamidoadenosine (12d). Yield: 24 mg; 0.057 mmol; 32%. ^{1}H NMR (DMSO-d_6) δ 10.52 (s, 1H, CONH), 8.47 and 8.23 (2× s, 2× 1H, H-2 and H-8), 7.91 (br s, 1H, N^6-H), 7.65 (d, J = 7.7, 2H, H_{Ar}), 7.40 (t, J = 7.7, 2H, H_{Ar}), 7.16 (t, J = 7.7, 1H, H_{Ar}), 6.07 (d, J = 7.1, 1H, H-1′), 5.87 (d, J = 4.3, 1H, OH), 5.67 (d, J = 6.3, 1H, OH), 5.09 and 4.59 (2× m, 1H, CH rotamers), 4.63 (dd, J = 7.1 and 4.5, 1H, H-2′), 4.54 (d, J = 1.9, H-4′), 4.34 (dd, J = 4.5 and 1.9, 1H, H-3′), 1.99–1.96 (m, 2H, cyclopentyl), 1.75–1.70 (m, 2H, cyclopentyl), 1.67–1.59 (m, 4H, cyclopentyl). *m/z* 425.1908 (M^++H, $C_{21}H_{25}N_6O_4$ requires 425.1937).

4.2.14. N^6-Benzyl-5′-*N*-methylcarboxamidoadenosine (12e). Yield: 35 mg; 0.090 mmol; 50%. ^{1}H NMR (DMSO-d_6) δ 8.92 (q, J = 4.6, 1H, CONH), 8.56 (br s, 1H, N^6-H), 8.44 and 8.31 (2× s, 2× 1H, H-2 and H-8), 7.37–7.29 (m, 4H, H_{Ar}), 7.23 (t, J = 7.4, 1H, H_{Ar}), 6.00 (d, J = 7.6, 1H, H-1′), 5.77 (d, J = 4.0, 1H, OH), 5.59 (d, J = 6.3, 1H, OH), 5.19 and 4.74 (2× br s, 2H, CH_2 rotamers), 4.62 (dd, J = 7.6 and 4.6, 1H, H-2′), 4.34 (d, J = 1.1, 1H, H-4′), 4.17 (dd, J = 4.6 and 1.1, 1H, H-3′), 2.73 (d, J = 4.6, 3H, CH_3). *m/z* 385.1633 (M^++H, $C_{18}H_{21}N_6O_4$ requires 385.1624).

4.2.15. N^6-Benzyl-5′-*N*-ethylcarboxamidoadenosine (12f). Yield: 33 mg; 0.083 mmol; 46%. ^{1}H NMR (DMSO-d_6) δ 8.90 (t, J = 5.6, 1H, CONH), 8.56 (br s, 1H, N^6-H), 8.44 and 8.28 (2× s, 2× 1H, H-2 and H-8), 7.37–7.29 (m, 4H, H_{Ar}), 7.23 (t, J = 7.2, 1H, H_{Ar}), 5.99 (d, J = 7.6, 1H, H-1′), 5.79 (d, J = 3.9, 1H, OH), 5.60 (d, J = 6.1, 1H, OH), 5.20 and 4.70 (2× m, 1H, CH_2 rotamers), 4.63 (dd, J = 7.6 and 4.7, 1H, H-2′), 4.32 (d, J = 1.2, 1H, H-4′), 4.16 (dd, J = 4.7 and 1.2, 1H, H-3′), 3.24 (dq, J = 7.2 and 5.6, 2H, CH_2), 1.09 (t, J = 7.2, 3H, CH_3). *m/z* 399.1758 (M^++H, $C_{19}H_{23}N_6O_4$ requires 399.1781).

4.2.16. N^6-Benzyl-5′-*N*-cyclopentylcarboxamidoadenosine (12g). Yield: 35 mg; 0.081 mmol; 45%. ^{1}H NMR (DMSO-d_6) δ 8.57–8.52 (m, 2H, CONH and N^6-H), 8.47 and 8.22 (2× s, 2× 1H, H-2 and H-8), 7.37–7.29 (m, 4H, H_{Ar}), 7.23 (t, J = 7.1, 1H, H_{Ar}), 5.99 (d, J = 7.4, 1H, H-1′), 5.75 (d, J = 4.2, 1H, OH), 5.58 (d, J = 6.3, 1H, OH), 5.18 and 4.74 (2× m, 1H, CH_2 rotamers), 4.65–4.62 (m, 1H, H-2′), 4.33 (d, J = 1.4, 1H, H-4′), 4.17–4.08 (m, 2H, H-3′ and CH), 1.92–1.84 (m, 2H, cyclopentyl), 1.73–1.67 (m, 2H, cyclopentyl) 1.62–1.39 (m, 4H, cyclopentyl). *m/z* 439.2116 (M^++H, $C_{22}H_{27}N_6O_4$ requires 439.2094).

4.2.17. N^6-Benzyl-5′-*N*-phenylcarboxamidoadenosine (12h). Yield: 24 mg; 0.054 mmol; 30%. ^{1}H NMR (DMSO-d_6) δ 10.49 (s, 1H, CONH), 8.58 (br s, 1H, N^6-H), 8.52 and 8.23 (2× s, 2× 1H, H-2 and H-8), 7.65 (d, J = 8.1, 2H, H_{Ar}), 7.41–7.29 (m, 6H, H_{Ar}), 7.24–7.22 (m, 1H, H_{Ar}), 7.15 (t, J = 7.3, 1H, H_{Ar}), 6.08 (d, J = 7.0, 1H, H-1′), 5.90 (br s, 1H, OH), 5.70 (br s, 1H, OH), 5.17 and 4.76 (2× m, 1H, CH_2 rotamers), 4.66–4.61 (m, 1H, H-2′), 4.55 (d, J = 1.7, H-4′), 4.35 (dd, J = 4.5 and 1.7, 1H, H-3′). *m/z* 447.1808 (M^++H, $C_{23}H_{23}N_6O_4$ requires 447.1781).

4.2.18. N^6-(3-Iodobenzyl)-5′-*N*-methylcarboxamidoadenosine (12i). Yield: 37 mg; 0.073 mmol; 54%. ^{1}H NMR (DMSO-d_6) δ 8.89 (q, J = 4.7, 1H, CONH), 8.60 (br s, 1H, N^6-H), 8.47 and 8.32 (2× s, 2× 1H, H-2 and H-8), 7.75 (s, 1H, H_{Ar}), 7.61 (d, J = 7.8, 1H, H_{Ar}), 7.39 (d, J = 7.8, 1H, H_{Ar}), 7.13 (t, J = 7.8, 1H, H_{Ar}), 6.00 (d, J = 7.5, 1H, H-1′), 5.76 (d, J = 4.1, 1H, OH), 5.58 (d, J = 6.2, 1H, OH), 5.15 and 4.70 (2× br s, 2H, CH_2 rotamers), 4.62 (dd, J = 7.5 and 4.7, 1H, H-2′), 4.34 (d, J = 1.3, 1H, H-4′), 4.17 (dd, J = 4.6 and 1.3, 1H, H-3′), 2.73 (d, J = 4.7, 3H, CH_3). *m/z* 511.0599 (M^++H, $C_{18}H_{20}IN_6O_4$ requires 511.0591).

4.2.19. N^6-(3-Iodobenzyl)-5′-*N*-ethylcarboxamidoadenosine (12j). Yield: 31 mg; 0.059 mmol; 46%. ^{1}H NMR (DMSO-d_6) δ 8.86 (t, J = 5.5, 1H, CONH), 8.61 (br s, 1H, N^6-H), 8.46 and 8.29 (2× s, 2× 1H, H-2 and H-8), 7.75 (s, 1H, H_{Ar}), 7.61 (d, J = 7.8, 1H, H_{Ar}), 7.39 (d, J = 7.8, 1H, H_{Ar}), 7.13 (t, J = 7.8, 1H, H_{Ar}), 6.00 (d, J = 7.5, 1H, H-1′), 5.77 (d, J = 4.1, 1H, OH), 5.59 (d, J = 6.3, 1H, OH), 5.15 and 4.70 (2× m, 1H, CH_2 rotamers), 4.63 (dd, J = 7.5 and 4.6, 1H, H-2′), 4.33 (s, 1H, H-4′), 4.17 (d, J = 4.6, 1H, H-3′), 3.23 (dq, J = 7.2 and 5.5, 2H, CH_2), 1.09 (t, J = 7.2, 3H, CH_3). *m/z* 525.0752 (M^++H, $C_{19}H_{22}IN_6O_4$ requires 525.0747).

4.2.20. N^6-(3-Iodobenzyl)-5′-*N*-cyclopentylcarboxamidoadenosine (12k). Yield: 38 mg; 0.068 mmol; 50%. ^{1}H NMR (DMSO-d_6) δ 8.61 (br s, 1H, N^6-H), 8.51 (d, J = 7.1, 1H, CONH), 8.49 and 8.23 (2× s, 2× 1H, H-2 and H-8), 7.75 (s, 1H, H_{Ar}), 7.61 (d, J = 7.8, 1H, H_{Ar}), 7.39 (d, J = 7.8, 1H, H_{Ar}), 7.13 (t, J = 7.8, 1H, H_{Ar}), 6.00 (d, J = 7.4, 1H, H-1′), 5.75 (d, J = 3.5, 1H, OH), 5.59 (d, J = 5.6, 1H, OH), 5.16 and 4.69 (2× m, 1H, CH_2 rotamers), 4.65–4.62 (m, 1H, H-2′), 4.33 (d, J = 1.4, 1H, H-4′), 4.17–4.08 (m, 2H, H-3′ and CH), 1.98–1.80 (m, 2H, cyclopentyl), 1.74–1.69 (m, 2H, cyclopentyl) 1.58–1.39 (m, 4H, cyclopentyl). *m/z* 565.1039 (M^++H, $C_{22}H_{26}IN_6O_4$ requires 565.1060).

4.2.21. N^6-(3-Iodobenzyl)-5′-*N*-phenylcarboxamidoadenosine (12l). Yield: 26 mg; 0.046 mmol; 34%. ^{1}H NMR (DMSO-d_6) δ 10.47 (s, 1H, CONH), 8.61 (br s, 1H, N^6-H), 8.54 and 8.24 (2× s, 2× 1H, H-2 and H-8), 7.75 (s, 1H, H_{Ar}), 7.65 (d, J = 8.1, 2H, H_{NHAr}), 7.61 (d, J = 7.8, 1H, H_{Ar}), 7.41–7.31 (m, 3H, H_{Ar} and H_{NHAr}), 7.17–7.11

(m, 2H, H_{Ar} and H_{NHAr}), 6.09 (d, J = 7.0, 1H, H-1′), 5.91 (br s, 1H, OH), 5.71 (br s, 1H, OH), 5.19 and 4.69–4.61 (2× m, 2H, CH_2 rotamers and H-2′), 4.56 (d, J = 2.0, H-4′), 4.35 (dd, J = 4.5 and 2.0, 1H, H-3′). *m/z* 573.0770 (M^++H, $C_{23}H_{22}IN_6O_4$ requires 573.0747).

4.2.22. N^6-(2-Phenethyl)-5′-*N*-methylcarboxamidoadenosine (12m). Yield: 29 mg; 0.073 mmol; 54%. ^{1}H NMR (DMSO-d_6) δ 8.95 (q, J = 4.5, 1H, CONH), 8.42 and 8.36 (2× s, 2× 1H, H-2 and H-8), 8.05 (br s, 1H, N^6-H), 7.35–7.29 (m, 4H, H_{Ar}), 7.23–7.20 (m, 1H, H_{Ar}), 5.99 (d, J = 7.5, 1H, H-1′), 5.76 (d, J = 4.2, 1H, OH), 5.57 (d, J = 6.4, 1H, OH), 4.61 (dd, J = 7.5 and 4.5, 1H, H-2′), 4.33 (s, 1H, H-4′), 4.17 (d, J = 4.5, 1H, H-3′), 4.10 and 3.75–3.72 (2× m, 2H, CH_2 rotamers), 2.95 (t, J = 7.5, 2H, $PhCH_2$), 2.74 (d, J = 4.5, 3H, CH_3). *m/z* 399.1774 (M^++H, $C_{19}H_{23}N_6O_4$ requires 399.1781).

4.2.23. N^6-(2-Phenethyl)-5′-*N*-ethylcarboxamidoadenosine (12n). Yield: 28 mg; 0.068 mmol; 50%. ^{1}H NMR (DMSO-d_6) δ 8.92 (t, J = 5.5, 1H, CONH), 8.42 and 8.32 (2× s, 2× 1H, H-2 and H-8), 8.56 and 7.94 (2× br s, 1H, N^6-H rotamers), 7.33–7.28 (m, 4H, H_{Ar}), 7.23–7.20 (m, 1H, H_{Ar}), 5.99 (d, J = 7.6, 1H, H-1′), 5.77 (d, J = 4.1, 1H, OH), 5.58 (d, J = 6.4, 1H, OH), 4.63 (dd, J = 7.6 and 4.6, 1H, H-2′), 4.33 (d, J = 1.1, 1H, H-4′), 4.17 (dd, J = 4.6 and 1.1, 1H, H-3′), 4.10 and 3.77–3.73 (2× m, 2H, CH_2 rotamers), 3.24 (dq, J = 7.2 and 5.5, 2H, CH_2), 2.95 (t, J = 7.5, 2H, $PhCH_2$), 1.11 (t, J = 7.2, 3H, CH_3). *m/z* 413.1943 (M^++H, $C_{20}H_{25}N_6O_4$ requires 413.1937).

4.2.24. N^6-(2-Phenethyl)-5′-*N*-cyclopentylcarboxamidoadenosine (12o). Yield: 22 mg; 0.049 mmol; 36%. ^{1}H NMR (DMSO-d_6) δ 8.55 (d, J = 7.0, 1H, CONH), 8.43 and 8.26 (2× s, 2× 1H, H-2 and H-8), 8.05 and 7.97 (2× br s, 1H, N^6-H rotamers), 7.31–7.27 (m, 4H, H_{Ar}), 7.24–7.20 (m, 1H, H_{Ar}), 5.98 (d, J = 7.4, 1H, H-1′), 5.77 (br s, 1H, OH), 5.59 (br s, 1H, OH), 5.18 and 4.74 (2× m, 1H, CH_2 rotamers), 4.65–4.61 (m, 1H, H-2′), 4.33 (s, 1H, H-4′), 4.15 (d, J = 4.5, 1H, H-3′), 4.17–4.09 (m, 1H, CH), 4.06 and 3.76–3.72 (2× m, 2H, CH_2 rotamers), 2.95 (t, J = 7.4, 2H, $PhCH_2$), 1.98–1.82 (m, 2H, cyclopentyl), 1.74–1.62 (m, 2H, cyclopentyl) 1.59–1.36 (m, 4H, cyclopentyl). *m/z* 453.2255 (M^++H, $C_{23}H_{29}N_6O_4$ requires 453.2250).

4.2.25. N^6-(2-Phenethyl)-5′-*N*-phenylcarboxamidoadenosine (12p). Yield: 26 mg; 0.057 mmol; 42%. ^{1}H NMR (DMSO-d_6) δ 10.46 (s, 1H, CONH), 8.48 and 8.26 (2× s, 2× 1H, H-2 and H-8), 7.98 (br s, 1H, N^6-H), 7.65 (d, J = 7.5, 2H, H_{NHAr}), 7.40 (t, J = 7.5, 2H, H_{NHAr}), 7.34–7.27 (m, 4H, H_{Ar}), 7.23–7.20 (m, 1H, H_{Ar}), 7.16 (t, J = 7.5, 1H, H_{Ar}), 6.08 (d, J = 7.0, 1H, H-1′), 5.81 (d, J = 4.2, 1H, OH), 5.63 (d, J = 6.1, 1H, OH), 4.70 (dd, J = 7.0 and 4.6, 1H, H-2′), 4.55 (d, J = 2.0, 1H, H-4′), 4.35 (dd, J = 4.6 and 2.0, 1H, H-3′), 4.04 and 3.78–3.74 (2× m, 1H, CH_2 rotamers), 2.96 (t, J = 7.5, 2H, $PhCH_2$). *m/z* 461.1953 (M^++H, $C_{24}H_{25}N_6O_4$ requires 461.1937).

4.2.26. N^6-(2,2-Diphenylethyl)-5′-*N*-methylcarboxamidoadenosine (12q). Yield: 26 mg; 0.056 mmol; 31%. ^{1}H NMR (DMSO-d_6) δ 8.93 (q, J = 4.7, 1H, CONH), 8.39 and 8.36 (2× s, 2× 1H, H-2 and H-8), 7.96 (br s, 1H, N^6-H), 7.36 (d, J = 7.3, 4H, H_{Ar}), 7.30 (t, J = 7.3, 4H, H_{Ar}), 7.19 (t, J = 7.3, 2H, H_{Ar}), 7.20 (t, J = 7.2, 2H, H_{Ar}), 5.97 (d, J = 7.4, 1H, H-1′), 5.77 (br s, 1H, OH), 5.58 (br s, 1H, OH), 4.68–4.55 and 4.18–4.14 (2× m, 5H, H-2′, H-3′, CH_2 and CH rotamers), 4.33 (s, 1H, H-4′), 2.74 (d, J = 4.7, 3H, CH_3). *m/z* 475.2067 (M^++H, $C_{25}H_{27}N_6O_4$ requires 475.2094).

4.2.27. N^6-(2,2-Diphenylethyl)-5′-*N*-ethylcarboxamidoadenosine (12r). Yield: 28 mg; 0.058 mmol; 32%. ^{1}H NMR (DMSO-d_6) δ 8.90 (t, J = 5.6, 1H, CONH), 8.36 (s, 2H, H-2 and H-8), 7.96 and 7.76 (2× br s, 1H, N^6-H rotamers), 7.36 (d, J = 7.3, 4H, H_{Ar}), 7.32 (t, J = 7.3, 4H, H_{Ar}), 7.19 (t, J = 7.3, 2H, H_{Ar}), 5.97 (d, J = 7.4, 1H, H-1′), 5.78 (br s, 1H, OH), 5.58 (br s, 1H, OH), 4.64–4.54 and 4.17–4.13 (2× m, 5H, H-2′, H-3′, CH_2 and CH rotamers), 4.32 (s, 1H, H-4′), 3.23 (dq, J = 7.2 and 5.6, 2H, CH_2), 1.11 (t, J = 7.2, 3H, CH_3). *m/z* 489.2241 (M^++H, $C_{26}H_{29}N_6O_4$ requires 489.2250).

4.2.28. N^6-(2,2-Diphenylethyl)-5′-*N*-cyclopentylcarboxamidoadenosine (12s). Yield: 24 mg; 0.045 mmol; 25%. ^{1}H NMR (DMSO-d_6) δ 8.52 (d, J = 7.2, 1H, CONH), 8.38 and 8.29 (2× s, 2× 1H, H-2 and H-8), 7.97 and 7.73 (2× br s, 1H, N^6-H rotamers), 7.35 (d, J = 7.4, 4H, H_{Ar}), 7.29 (t, J = 7.4, 4H, H_{Ar}), 7.19 (t, J = 7.4, 2H, H_{Ar}), 5.96 (d, J = 7.3, 1H, H-1′), 5.73 (d, J = 4.3, 1H, OH), 5.55 (d, J = 6.4, 1H, OH), 4.64–4.54 and 4.19–4.08 (2× m, 6H, H-2′, H-3′, CH and CH_2 and CH rotamers), 4.32 (s, 1H, H-4′), 1.97–1.82 (m, 2H, cyclopentyl), 1.73–1.69 (m, 2H, cyclopentyl) 1.58–1.32 (m, 4H, cyclopentyl). *m/z* 529.2547 (M^++H, $C_{29}H_{33}N_6O_4$ requires 529.2563).

4.2.29. N^6-(2,2-Diphenylethyl)-5′-*N*-phenylcarboxamidoadenosine (12t). Yield: 18 mg; 0.034 mmol; 19%. ^{1}H NMR (DMSO-d_6) δ 10.49 (s, 1H, CONH), 8.44 and 8.31 (2× s, 2× 1H, H-2 and H-8), 7.97 and 7.79 (2× br s, 1H, N^6-H rotamers), 7.65 (d, J = 7.8, 2H, HNHAr), 7.42–7.28 (m, 10H, H_{NHAr} and H_{Ar}), 7.21–7.10 (m, 3H, H_{NHAr} and H_{Ar}), 6.06 (d, J = 6.9, 1H, H-1′), 5.88 (br s, 1H, OH), 5.68 (br s, 1H, OH), 4.70–4.60 (m, 2H, H-2′ and CH), 4.54 (s, 1H, H-4′), 4.34 (m, 1H, H-3′), 4.18–4.14 (m, 1H, CH_2). *m/z* 537.2259 (M^++H, $C_{30}H_{29}N_6O_4$ requires 537.2250).

4.2.30. 2-Nitro-6-chloro-(2,3-*O*-isopropylidene-5-carboxy-β-D-ribofuranosyl)-9*H*-purine (14). TFAA (1.27 mL; 9.0 mmol) was added to a suspension of 6-chloropurine carboxylic acid **2** (1.07 g; 3.0 mmol) in dry CH_2Cl_2 (24 mL) at 0 °C and the mixture was stirred until a clear solution of **13** was obtained (30 min). TBAN (1.46 g; 4.8 mmol) was added and the reaction mixture was stirred for an additional 2 h at 0 °C. The reaction mixture was divided between water (20 mL) and Et_2O (75 mL) and the organic layer was washed with water (3× 20 mL). The combined water layers were extracted with EtOAc (20 mL) and the EtOAc layer was washed with water (10 mL). DIPEA (3.6 mL; 20 mmol) was added to the combined organic layers and they were extracted twice with water (60 mL, 30 mL). Extra DIPEA (0.3 mL; 3 mmol) was added to the organic layer, which was again washed with water (30 mL). The combined water layers were

washed with Et_2O and the pH was adjusted to ~2–3 with oxalic acid (0.54 g; 6.0 mmol). After extraction of the carboxylic acid with EtOAc (40 mL, 15 mL and 15 mL) and washing of the combined organic layers with water (20 mL), the organic layer was dried with Na_2SO_4 and the solvent was evaporated. Nitrated product **14** was obtained as a yellow foam (1.09 g; 2.82 mmol; 94%). ^{1}H NMR (DMSO-d_6) δ 12.97 (br s, 1H, OH), 9.20 (s, 1H, H-8), 6.62 (s, 1H, H-1′), 5.67 (d, J = 5.9, 1H, H-2′), 5.63 (d, J = 5.9, 1H, H-3′), 4.77 (s, 1H, H-4′), 1.57 (s, 3H, CH_3), 1.40 (s, 3H, CH_3).

4.2.31. 2′,3′-*O*-Isopropylidene-2-nitro-N^6-cyclopentyladenosine 5′-carboxylic acid (15a). To a solution of 2-nitro-6-chloropurine **14** (1.09 g; 2.82 mmol) in CH_2Cl_2 (15 mL) were added DIPEA (1.97 mL; 11.3 mmol) and cyclopentylamine (0.36 mL; 3.67 mmol) and the solution was stirred for 18 h. The reaction mixture was divided between water (75 mL) and Et_2O (50 mL) and the organic layer was extracted with water (2× 20 mL). The combined water layers were washed with Et_2O (25 mL) and the pH was adjusted to ~2–3 with oxalic acid. The acidic water layer was extracted with EtOAc (3× 30 mL) and the combined organic layers were washed with water (20 mL), dried with Na_2SO_4 and coevaporated with toluene (3×). Trituration with CH_2Cl_2 furnished adenosine carboxylic acid **15a** as a yellow solid (0.70 g; 1.61 mmol; 57%). ^{1}H NMR (DMSO-d_6) δ 12.78 (br s, 1H, OH), 8.80 (d, J = 7.7, 1H, NH), 8.56 (s, 1H, H-8), 6.44 (s, 1H, H-1′), 5.68 (dd, J = 5.8 and 1.5, 1H, H-3′), 5.52 (d, J = 5.8, 1H, H-2′), 4.74 (d, J = 1.5, 1H, H-4′), 5.13 and 4.50 (2× m, 1H, CH rotamers), 2.01–1.96 (m, 2H, cyclopentyl), 1.75–1.55 (m, 6H, cyclopentyl), 1.54 (s, 3H, CH_3), 1.39 (s, 3H, CH_3).

4.2.32. 2′,3′-*O*-Isopropylidene-2-nitro-N^6-(3-iodobenzyl)adenosine 5′-carboxylic acid (15b). This compound was prepared by the method described for **15a**. After trituration with CH_2Cl_2, adenosine carboxylic acid **15b** was obtained as a yellow solid (0.92 g; 1.58 mmol; 53%). ^{1}H NMR (DMSO-d_6) δ 12.81 (br s, 1H, OH), 9.36 and 9.24 (2 × t, J = 6.1, 1H, NH rotamers), 8.60 (s, 1H, H-8), 7.85 and 7.78 (2× s, 1H, H_{Ar} rotamers) 7.64 (d, J = 7.7, 1H, H_{Ar}), 7.45 (d, J = 7.7, 1H, H_{Ar}), 7.16 (t, J = 7.7, 1H, H_{Ar}), 6.46 (s, 1H, H-1′), 5.69 (dd, J = 5.9 and 1.5, 1H, H-3′), 5.52 (d, J = 5.9, 1H, H-2′), 4.75 (d, J = 1.5, 1H, H-4′), 5.21 and 4.66 (2× d, J = 6.1, 2H, CH_2 rotamers), 1.54 (s, 3H, CH_3), 1.38 (s, 3H, CH_3).

4.2.33. General procedure for coupling of carboxylic acid 15 to hydrazinobenzoyl AM resin 7 (16). To a suspension of hydrazinobenzoyl AM resin **7** (0.78 g; 0.98 mmol) in DMF (5 mL) were added carboxylic acid **15** (1.47 mmol), HOBt (198 mg; 1.47 mmol) and DIC (230 μL; 1.47 mmol). After 16 h, resin **16** was washed with DMF (3×), CH_2Cl_2 (3×), MeOH, CH_2Cl_2, MeOH, Et_2O, CH_2Cl_2, Et_2O and CH_2Cl_2 and dried in vacuo at 50 °C.

4.2.34. General procedure for the amination by nitro substitution of resin-bound 2-nitropurines 16 (17). A suspension of resin-bound 2-nitropurine **16** (200 mg; 0.16 mmol) and the amine (0.71 mmol) in NMP (2 mL) was gently stirred at 80 °C. After 24 h, resin **17** was washed with NMP (3×), CH_2Cl_2 (3×), MeOH, CH_2Cl_2, MeOH, Et_2O, CH_2Cl_2, Et_2O and CH_2Cl_2.

4.2.35. General procedure for the removal of the 2′,3′-isopropylidene group (18). See general procedure for **10**.

4.2.36. General procedure for oxidative cleavage of the nucleosides from the resin (19). See general procedure for **12**.

4.2.37. 2-Cyclopentylamino-N^6-cyclopentyl-5′-*N*-ethylcarboxamidoadenosine (19a). Yield: 20 mg; 0.043 mmol; 27%. ^{1}H NMR (DMSO-d_6) δ 8.14 (br s, 1H, CONH), 8.00 (s, 1H, H-8), 7.18 (br s, 1H, N^6-H), 6.16 (br s, 1H, 2-NH), 5.84 (d, J = 6.8, 1H, H-1′), 5.59 (br s, 1H, OH), 5.51 (d, J = 5.7, 1H, OH), 4.74–4.70 (m, 1H, H-2′), 4.50–4.44 (m, 1H, N^6-CH), 4.25 (s, 1H, H-4′), 4.21–4.15 (m, 2H, 2-NHC*H* and H-3′), 3.27–3.23 (m, 1H, *H*CH), 3.22–3.11 (m, 1H, HC*H*), 1.95–1.89 (m, 4H, cyclopentyl), 1.77–1.31 (m, 12H, cyclopentyl), 1.03 (t, J = 7.0, 3H, CH_3). *m/z* 460.2685 (M^++H, $C_{22}H_{34}N_7O_4$ requires 460.2672).

4.2.38. 2-Cyclopentylamino-N^6-cyclopentyl-5′-*N*-cyclopentylcarboxamidoadenosine (19b). Yield: 21 mg; 0.042 mmol; 26%. ^{1}H NMR (DMSO-d_6) δ 8.05 (s, 1H, H-8), 7.88 (d, J = 7.1, 1H, CONH), 7.13 (br s, 1H, N^6-H), 6.21 (br s, 1H, 2-NH), 5.87 (d, J = 6.8, 1H, H-1′), 5.53 (br s, 2H, 2× OH), 4.66–4.62 (m, 1H, H-2′), 4.53–4.45 (m, 1H, N^6-CH), 4.27 (s, 1H, H-4′), 4.22 (m, 1H, H-3′), 4.21–4.15 (m, 1H, 2-NHC*H*), 4.05–4.00 (m, 1H, CONHC*H*), 1.94–1.33 (m, 24H, cyclopentyl). *m/z* 500.2982 (M^++H, $C_{25}H_{38}N_7O_4$ requires 500.2985).

4.2.39. 2-(2-Phenethylamino)-N^6-cyclopentyl-5′-*N*-ethylcarboxamidoadenosine (19c). Yield: 28 mg; 0.056 mmol; 35%. ^{1}H NMR (DMSO-d_6) δ 8.11 (br s, 1H, CONH), 8.03 (s, 1H, H-8), 7.33–7.18 (m, 6H, N^6-H and H_{Ar}), 6.35 (br s, 1H, 2-NH), 5.86 (d, J = 6.8, 1H, H-1′), 5.60 (d, J = 3.6, 1H, OH), 5.51 (d, J = 5.7, 1H, OH), 4.75–4.71 (m, 1H, H-2′), 4.54–4.48 (m, 1H, N^6-CH), 4.27 (s, 1H, H-4′), 4.19 (m, 1H, H-3′), 3.53–3.43 (m, 2H, 2-NHCH_2), 3.22–3.16 (m, 1H, *H*CH), 3.14–3.07 (m, 1H, HC*H*), 2.89–2.86 (m, 2H, PhCH_2), 1.99–1.96 (m, 2H, cyclopentyl), 1.75–1.71 (m, 2H, cyclopentyl), 1.68–1.51 (m, 4H, cyclopentyl), 1.00 (t, J = 7.2, 3H, CH_3). *m/z* 496.2686 (M^++H, $C_{25}H_{34}N_7O_4$ requires 496.2672).

4.2.40. 2-(2-Phenethylamino)-N^6-cyclopentyl-5′-*N*-cyclopentylcarboxamidoadenosine (19d). Yield: 30 mg; 0.056 mmol; 35%. ^{1}H NMR (DMSO-d_6) δ 8.09 (s, 1H, H-8), 7.91 (d, J = 7.0, 1H, CONH), 7.31–7.20 (m, 6H, N^6-H and H_{Ar}), 6.41 (br s, 1H, 2-NH), 5.89 (d, J = 5.7, 1H, H-1′), 5.53 (br s, 2H, 2× OH), 4.67–4.63 (m, 1H, H-2′), 4.53–4.49 (m, 1H, N^6-CH), 4.29 (s, 1H, H-4′), 4.21 (m, 1H, H-3′), 4.04–4.00 (m, 1H, CONHCH), 3.59–3.44 (m, 2H, 2-NHCH_2), 2.88–2.84 (m, 2H, PhCH_2), 1.97–1.94 (m, 2H, cyclopentyl), 1.83–1.24 (m, 14H, cyclopentyl). *m/z* 536.2975 (M^++H, $C_{28}H_{38}N_7O_4$ requires 536.2985).

4.2.41. 2-Cyclopentylamino-N^6-(3-iodobenzyl)-5′-*N*-ethylcarboxamidoadenosine (19e). Yield: 30 mg; 0.045 mmol; 30%. ^{1}H NMR (DMSO-d_6) δ 8.15–7.99 (m, 3H, CONH,

H-8 and N^6-H), 7.77 (s, 1H, H_{Ar}), 7.59 (d, J = 7.7, 1H, H_{Ar}), 7.40 (d, J = 7.7, 1H, H_{Ar}), 7.13 (t, J = 7.7, 1H, H_{Ar}), 6.20 (br s, 1H, 2-NH), 5.86 (d, J = 6.8, 1H, H-1′), 5.45 (br s, 2H, 2× OH), 4.70 (dd, J = 6.8 and 5.5, 1H, H-2′), 4.63-4.59 (m, 2H, N^6-CH_2), 4.26 (d, J = 2.0, 1H, H-4′), 4.20 (dd, J = 5.5 and 2.0, 1H, H-3′), 4.14–4.11 (m, 1H, 2-NHC*H*), 3.24–3.10 (m, 1H, CONHCH_2), 1.91–1.84 (m, 2H, cyclopentyl), 1.68-1.60 (m, 2H, cyclopentyl), 1.52–1.43 (m, 4H, cyclopentyl), 1.03 (t, J = 7.2, 3H, CH_3). *m/z* 608.1456 (M^++H, $C_{24}H_{31}IN_7O_4$ requires 608.1482).

4.2.42. 2-Cyclopentylamino-*N*^{6}-(3-iodobenzyl)-5′-*N*-cyclopentylcarboxamidoadenosine (19f). Yield: 55 mg; 0.086 mmol; 57%. ^{1}H NMR (DMSO-d_6) δ 8.10 (s, 1H, H-8), 7.99 (br s, 1H, N^6-H), 7.87 (d, J = 6.9, 1H, CONH), 7.75 (s, 1H, H_{Ar}), 7.59 (d, J = 7.8, 1H, H_{Ar}), 7.38 (d, J = 7.8, 1H, H_{Ar}), 7.13 (t, J = 7.8, 1H, H_{Ar}), 6.30 (d, J = 7.3, 1H, 2-NH), 5.87 (d, J = 6.5, 1H, H-1′), 5.52–5.49 (m, 2H, 2× OH), 4.65–4.59 (m, 3H, H-2′ and N^6-CH_2), 4.27 (s, 1H, H-4′), 4.22 (m, 1H, H-3′), 4.14–4.10 (m, 1H, 2-NHC*H*), 4.09–4.00 (m, 1H, CONHC*H*), 1.84–1.25 (m, 16H, cyclopentyl). *m/z* 648.1769 (M^++H, $C_{27}H_{35}IN_7O_4$ requires 648.1795).

4.2.43. 2-(2-Phenethylamino)-*N*^{6}-(3-iodobenzyl)-5′-*N*-ethylcarboxamidoadenosine (19g). Yield: 20 mg; 0.032 mmol; 21%. ^{1}H NMR (DMSO-d_6) δ 8.14–8.00 (m, 3H, CONH, H-8 and N^6-H), 7.77 (s, 1H, H_{Ar}), 7.60 (d, J = 7.8, 1H, H_{Ar}), 7.39 (d, J = 7.8, 1H, H_{Ar}), 7.28 (t, J = 7.3, 2H, H_{Ph}), 7.24–7.10 (m, 4H, H_{Ar} and H_{Ph}), 6.49 (br s, 1H, 2-NH), 5.89 (d, J = 6.9, 1H, H-1′), 5.51 (br s, 2H, 2× OH), 4.72–4.62 (m, 3H, H-2′ and N^6-CH_2), 4.29 (d, J = 2.1, 1H, H-4′), 4.21 (m, 1H, H-3′), 3.51–3.33 (m, 2H, 2-NHCH_2), 3.23–3.16 (m, 1H, *H*CHCH$_3$), 3.14–3.08 (m, 1H, HC*H*CH$_3$), 2.81 (t, J = 7.0, 2H, PhCH_2), 1.00 (t, J = 7.2, 3H, CH_3). *m/z* 644.1458 (M^++H, $C_{27}H_{31}IN_7O_4$ requires 644.1482).

4.2.44. 2-(2-Phenethylamino)-*N*^{6}-(3-iodobenzyl)-5′-*N*-cyclopentylcarboxamidoadenosine (19h). Yield: 39 mg; 0.057 mmol; 38%. ^{1}H NMR (DMSO-d_6) δ 8.14 (s, 1H, H-8), 8.06 (br s, 1H, N^6-H), 7.92 (d, J = 7.3, 1H, CONH), 7.75 (s, 1H, H_{Ar}), 7.59 (d, J = 7.7, 1H, H_{Ar}), 7.38 (d, J = 7.7, 1H, H_{Ar}), 7.30 (t, J = 7.1, 2H, H_{Ph}), 7.20–7.09 (m, 4H, H_{Ar} and H_{Ph}), 6.47 (br s, 1H, 2-NH), 5.90 (d, J = 6.7, 1H, H-1′), 5.54 (m, 2H, 2× OH), 4.68–4.62 (m, 3H, H-2′ and N^6-CH_2), 4.29 (d, J = 2.0, 1H, H-4′), 4.22 (m, 1H, H-3′), 4.05–4.01 (m, 1H, CONHC*H*), 3.45-3.33 (m, 2H, 2-NHCH_2), 2.81–2.77 (m, 2H, PhCH_2), 1.81–1.76 (m, 2H, cyclopentyl), 1.60–1.25 (m, 6H, cyclopentyl). *m/z* 684.1805 (M^++H, $C_{30}H_{35}IN_7O_4$ requires 684.1795).

4.3. Antiprotozoal activity

4.3.1. *Trypanosoma brucei rhodesiense*. Minimum essential medium (50 μl) supplemented according to Baltz et al.[35] with 2-mercaptoethanol and 15% heat-inactivated horse serum was added to each well of a 96-well microtitre plate. Serial drug dilutions were prepared covering a range from 90 to 0.123 μg/mL. Then 10^4 bloodstream forms of *T. b. rhodesiense* STIB 900 in 50 μL were added to each well and the plate was incubated at 37 °C under a 5% CO_2 atmosphere for 72 h. Ten microlitres of Alamar Blue (12.5 mg resazurin dissolved in 100 mL distilled water) was then added to each well and incubation was continued for a further 2–4 h. The plate was then read in a Spectramax Gemini XS microplate fluorometer (Molecular Devices Cooperation, Sunnyvale, CA, USA) using an excitation wavelength of 536 nm and an emission wavelength of 588 nm.[36] Fluorescence development was measured and expressed as percentage of the control. Data were transferred into the graphic program Softmax Pro (Molecular Devices) which calculated IC_{50} values.

4.3.2. *Plasmodium falciparum*. Antiplasmodial activity was determined using the K1 strain of *P. falciparum* (resistant to chloroquine and pyrimethamine). A modification of the [^{3}H]hypoxanthine incorporation assay was used.[37] Briefly, infected human red blood cells in RPMI 1640 medium with 5% Albumax II were exposed to serial drug dilutions in microtitre plates. After 48 h of incubation at 37 °C in a reduced oxygen atmosphere, 0.5 μCi [^{3}H]hypoxanthine was added to each well. Cultures were incubated for a further 24 h before they were harvested onto glass-fibre filters and washed with distilled water. The radioactivity was counted using a Betaplate™ liquid scintillation counter (Wallac, Zurich, Switzerland). The results were recorded as counts per minute (cpm) per well at each drug concentration and expressed as percentage of the untreated controls. From the sigmoidal inhibition curves, IC_{50} values were calculated. Assays were run in duplicate and repeated once.

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