A new entry to adenosine analogues via purine nitration - Combinatorial synthesis of antiprotozoal agents and adenosine receptor ligands
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Solid phase synthesis of di- and trisubstituted 5’-carboxamidoadenosine analogues

ABSTRACT
Application of the hydrazide safety-catch linker allowed the solid phase synthesis of two small combinatorial libraries of di- and trisubstituted 5’-carboxamidoadenosine derivatives, respectively. A 5’-carboxylate nucleoside scaffold is attached to the solid support via an aryl hydrazide linkage. Following diversification reactions at the purine system and removal of the 2’,3’-protective groups, the hydrazide linkage in I is oxidised. The resulting acyl diazene species II reacts with amines in situ releasing 5’-carboxamidoadenosine analogues III.
3.1 INTRODUCTION

In the previous chapter a robust solid phase synthesis of 2,N_6-disubstituted adenosine analogues was described, in which the nucleoside was anchored to the solid support by the 5'-hydroxyl functionality and diversity elements were introduced on the purine skeleton. The target adenosine derivatives make up for potential therapeutics in the treatment of African trypanosomiasis^{1,2} and malaria^{3} (see chapter 5). Moreover they constitute a promising class of drugs acting at the adenosine receptors, which play a modulatory role in a myriad of cellular functions.\(^4\) In our 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.

Adenosine 5'-carboxamide analogues are known as highly active agonists for the adenosine receptor.\(^5\) Probably the most conspicuous example, depicted in Figure 3.1, remains 5'-N-ethylcarboxamido adenosine 1, NECA,\(^6\) which is a high affinity, non-selective adenosine receptor agonist (see also chapter 4). Usually, the affinity for the adenosine receptors increases when the 5'-hydroxyl moiety is replaced with a 5'-N-(m)ethylcarboxamido group.\(^7\) In the field of antiprotozoal research 5'-modified adenosine analogues are known as growth inhibitors of multidrug resistant *Plasmodium falciparum* (cf. structure 2 in Figure 3.1),\(^8\) inhibitors of trypanosomal glycolytic enzymes\(^10\) and inhibitors of enzymes involved in trypanosomal polyamine synthesis.\(^11\)

![Figure 3.1](image)

**Figure 3.1.** Biologically active 5'-modified adenosine analogues;\(^8\) values taken from reference 8;\(^b\) values taken from reference 9.
Literature methods for the solution phase synthesis of 5'-substituted carboxamidoadenosine analogues are summarised in Scheme 3.1. They entail 5'-oxidation of 2',3'-isopropylidene (2-chloro)adenosine with potassium permanganate under strongly basic or acidic conditions, or oxidation of 2',3'-isopropylidene inosine with chromium trioxide in glacial acetic acid, leading to a 5'-carboxylic acid residue in moderate to good yields (50-84%). Immediate amidation is followed, mediated by thionyl chloride or a peptide coupling reagent. Any substitutions on the purine base are brought about subsequently.

Scheme 3.1. Literature methods for the synthesis of 5'-carboxamidoadenosine analogues.

Our objective consisted of generating 5'-carboxamidoadenosine analogues in a divergent way, thus allowing for the introduction of pharmacophores both on the purine 2 and N6 positions as described in the previous chapter, and on the sugar 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 three different positions. The proposed strategy involving the safety catch principle is outlined in Scheme 3.2. 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 are removed and the nucleoside is ready for cleavage, the

Scheme 3.2. Proposed strategy involving the safety catch principle.
linker is 'switched on', thereby setting 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.

**SAFETY CATCH APPROACH**

The safety catch principle has first been described by Kenner in 1971 in the field of solid phase peptide chemistry. The concept relies on complete stability of the safety catch linker over a wide range of reaction conditions, while at the end of the solid phase sequence a two step cleavage process is applied. The first step involves activation of the linker, the second step involves the actual cleavage. The main advantage of these linkers is that if there is a need to use conditions similar to the cleavage conditions during the synthesis, this can be accommodated as the linker is stable until activated. The safety catch principle is perhaps best illustrated by the rediscovery and improvement of Kenner’s method by Backes and Ellman, as is depicted in Scheme 3.3. A carboxylic acid is coupled to a sulfonamide linker affording acylsulfonamide 5. Under strongly basic or nucleophilic conditions the acylsulfonamide NH is deprotonated (pKₐ ~ 2.5), thereby deactivating the carbonyl moiety and preventing nucleophilic attack. When the solid supported synthesis is completed, N-alkylation activates the linker towards nucleophilic displacement. Kenner’s original procedure involved treatment with diazomethane to afford the N-methyl acylsulfonamide 6a. Backes and Ellman however improved this activation method by using iodoacetonitrile as alkylating agent to generate N-cyanomethyl acylsulfonamide 6b. The enhanced reactivity of 6b enables cleavage with aromatic amines. An

![Scheme 3.3. Kenner's safety catch approach.](image-url)
alternative linker, alkanesulfonamide 4, was developed to facilitate activation of acylsulfonamide 5, when carboxylic acid residues with $\alpha$-electron-withdrawing groups, like amino acids, are attached.\textsuperscript{17} Both sulfonamide linkers have successfully been applied in peptide chemistry,\textsuperscript{18,22} solid phase organic synthesis\textsuperscript{16,23} and polymer assisted solution phase synthesis.\textsuperscript{9,24} Over the past decade many other safety catch linkers have been developed, that are activated by for example oxidation reactions\textsuperscript{25} or removal of protective groups.\textsuperscript{26}

In this chapter the development is described of a solid phase sequence towards di- and trisubstituted 5’carboxamidoadenosine derivatives by application of the safety catch principle.

### 3.2 SOLID PHASE SYNTHESSES WITH KENNER’S SULFONAMIDE LINKER

Initial synthetic efforts towards substituted 5’carboxamidoadenosine derivatives addressed the coupling of 6-chloropurine riboside-5’carboxylic acid to Kenner’s sulfonamide linker. The mild TEMPO-iodobenzene diacetate oxidising system reported for the 5’-oxidation of common 2’,3’-protected nucleosides was applied to 2’,3’-isopropylidene protected 6-chloropurine riboside 8 affording 5’-carboxylic acid 9 in excellent yield (Scheme 3.4).\textsuperscript{27} Kenner’s benzenesulfonamide linker 3 was selected for its complete stability towards strongly basic/nucleophilic and strongly acidic conditions. Although it was noted that loading efficiencies with Kenner’s original benzenesulfonamide linker 3 were poor, especially with sterically demanding carboxylic acids,\textsuperscript{18} this linker was at first preferred over Ellman’s alkanesulfonamide linker 4. The solid phase synthesis of trisubstituted 5’carboxamidoadenosine derivatives requires the on-resin nitration of the purine 2-position. The risk of concomittant N-nitration of benzenesulfonamide linker 3 is reduced because the nucleophilicity of the acylsulfonamide NH is attenuated by the electron-withdrawing benzene ring.

The reactivity of the sulfonamide linker has been compared to that of an alcohol.\textsuperscript{18} Therefore typical esterification reagents are to be used in the coupling procedure. However, attachment of nucleoside 5’-carboxylic acid 9 to Kenner’s linker 3 offered significant problems.
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 aminoacid residues to the Kenner linker. But 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 (see Table 3.1).\(^{28}\)

**Table 3.1. Coupling methods used for loading Kenner’s linker.**

<table>
<thead>
<tr>
<th>entry</th>
<th>coupling method(^a)</th>
<th>base</th>
<th>solvent</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>acid 9 (5 equiv), DIC (5 equiv), 1-Melm(^b) (5 equiv)</td>
<td></td>
<td>DCM</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>acid 9 (3 equiv), DIC (3 equiv), DMAP (0.4 equiv)</td>
<td></td>
<td>DCM</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>acid 9 (3 equiv), CIP (3 equiv)</td>
<td>DIPEA (6 equiv)</td>
<td>DCM</td>
<td>+/-</td>
</tr>
<tr>
<td>4</td>
<td>acid 9 (3 equiv), PyBOP (3 equiv)</td>
<td>DIPEA (6 equiv)</td>
<td>DMF</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>acid 9 (3 equiv), DBC(^c) (3 equiv)</td>
<td>pyridine (4 equiv)</td>
<td>DMF</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>symm. anhydride of 9 (5 equiv), DMAP (1 equiv)</td>
<td>DIPEA (5 equiv)</td>
<td>DCM</td>
<td>+/-</td>
</tr>
</tbody>
</table>

\(^a\) Couplings endured 20-24 h;\(^b\) 1-Melm=1-methylimidazole, see reference 29;\(^c\) DBC=2,6-dichlorobenzoylchloride.

Model experiments in solution (DIC-DMAP, EDC-DMAP, pentafluorophenylester) with carboxylic acid 9 and linker analogue 12, obtained by amidation of benzoic acid 11 with benzylamine, failed to produce acylsulfonamide 13 (Scheme 3.5).

Scheme 3.5. (a) Benzylamine, EDC, HO\(_{\text{Bt}}\), THF, 76%. (b) see text for coupling attempts.

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 9 to Ellman’s modified alkanesulfonamide linker 4 was attempted, a linker especially designed for enhanced nucleophilicity.\(^{17}\) 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, months after this approach was abandoned a study appeared in literature concerning the coupling in solution of N°-benzoyl-2',3'-isopropylidene adenosine 5'-carboxylic acid to various sulfonamides. Among the various methods explored the best results were reported with 1.1 equivalents of DCC/DMAP and two equivalents of sulfonamide. Nevertheless, coupling required stirring in dichloromethane for four days, indicating the sluggishness of the reaction, which makes it unsuitable for solid phase applications.

### 3.3 SOLID PHASE SYNTHESSES WITH THE HYDRAZIDE LINKER

The experiments with the sulfonamide linker indicated the need for a sterically undemanding linker that would allow the attachment of the sterically encumbered nucleosidic carboxylic acid to the resin. In our opinion the arylhydrazide safety catch linker makes up for a good alternative. The linker was originally introduced in 1970 by Wieland and coworkers for the solid phase synthesis of peptides. 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 acyldiazenes as is outlined in Scheme 3.6. A carboxylic acid residue is attached to hydrazine resin furnishing aryl hydrazide 15. At the end of a solid phase sequence aryl hydrazide 16 is oxidised to afford the highly electrophilic acyldiazene species 17. Subsequent attack by a nucleophile present releases nitrogen gas and carboxylic acids, esters or amides, when water, alcohols or amines are used as nucleophiles. Recent applications of this linker involve the synthesis of (cyclic) peptides, while elegant work of Waldmann’s group was reported using a diametrical approach, represented in Scheme 3.7, in which a functionalised aryl hydrazine was
coupled to a resin bound carboxylic acid, thus allowing for the solid supported synthesis of substituted aromatic species without leaving a trace of the linkage to the solid support. The aryl hydrazide linker was shown to be stable under a wide range of reaction conditions, including palladium catalyzed transformations, as well as Wittig and Grignard reactions.

Scheme 3.7. Traceless linker concept of the aryl hydrazide linkage.

\[ \text{Scheme 3.7. Traceless linker concept of the aryl hydrazide linkage.} \]

\[ \text{N}^{5'},\text{N}^6\text{-DISUBSTITUTED 5'-CARBOXAMIDOADENOSINE ANALOGUES} \]

The choice for the aryl hydrazide linker proved to be rewarding in the sense that the solid phase synthesis of N\textsuperscript{5},N\textsuperscript{6}-disubstituted 5'-carboxamido-adenosine analogues could be accomplished. The sequence using the aryl hydrazide safety catch linker is depicted in Scheme 3.8. After removal of the Fmoc group from commercially available 4-Fmoc-hyrazinobenzoyl AM resin 18 with 20 % piperidine in DMF, 5'-carboxylic acid 9 was coupled to hydrazine resin 19 by using DIC as a coupling reagent to render hydrazide 20. Literature methods for the acylation of resin 19 involve a diimide in combination with an additive like 1-hydroxybenzotriazole, HOBt. In our system we observed that HOBt displaces the chloroatom in the purine ring. Although omission of this additive required a longer coupling period, effective loading of the resin was achieved as indicated by a bromophenol blue test. Introduction of an amino substituent on the purine 6-position was effected in NMP at 50 °C affording purine 21. The 2',3'-isopropylidene group was removed by using a cocktail of TFA, ethyleneglycol and dichloromethane (5:1:5) to yield resin bound 22, which was now ready for cleavage from the resin. The hydrazide linkage was oxidised by the method of Lowe and coworkers using 0.5 equivalent of copper(II)acetate in the presence of a nitrogen nucleophile. Only catalytic quantities of copper(II) are required due to the rapid aerial oxidation of copper(I) ions. Although 0.1 equivalent of copper(II) is essentially enough to effect oxidation, a larger amount was used to reduce reaction times. The amine present in solution serves a triple goal; firstly, deprotonation of the hydrazide, secondly, complexation of the
5'-Carboxamidoadenosine analogues

![Chemical structure](image)

Scheme 3.8. (a) 20% piperidine in DMF; (b) 9, Dic, DMF; (c) R1-NH2, NMP, 50°C; (d) TFA-HO(CH2)2OH-CH2Cl2 (5:1:5); (e) 0.5 equiv Cu(OAc)2, R2-NH2, THF.

copper ions, thereby preventing them to precipitate from solution and finally nucleophilic release under formation of carboxamide 23. The copper salts were easily removed by passing the solution of the crude product over a silica gel cartridge.

In order to validate the developed solid phase sequence a small 20-membered library was synthesised. Again, amines were selected that contained pharmacophores known from adenosine receptor and antiprotozoal research. 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 biological evaluation. Products 23a-t were obtained in reasonable yields (19-54% over four solid phase steps) and high purities (see Table 3.2 on page 54).

2,N5',N6'-TRISUBSTITUTED 5'-CARBOXAMIDOADENOSINE ANALOGUES

While disubstituted adenosine analogues 23a-t were readily synthesised by application of the hydrazide resin, our second goal was the preparation of trisubstituted 5'-carboxamido-adenosine analogues, which required nitration of the purine 2-position. 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 present nucleophiles. Another approach by linking a 2-nitro-6-
Table 3.2. Library of $N^6,N^7$-disubstituted 5′-carboxamidoadenosine analogues.$^a$

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>Purity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23a</td>
<td>43%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>23b</td>
<td>37%</td>
<td>(97%)</td>
</tr>
<tr>
<td>23c</td>
<td>28%</td>
<td>(&gt;99%)</td>
</tr>
<tr>
<td>23d</td>
<td>32%</td>
<td>(99%)</td>
</tr>
<tr>
<td>23e</td>
<td>50%</td>
<td>(&gt;99%)</td>
</tr>
<tr>
<td>23f</td>
<td>46%</td>
<td>(98%)</td>
</tr>
<tr>
<td>23g</td>
<td>45%</td>
<td>(99%)</td>
</tr>
<tr>
<td>23h</td>
<td>30%</td>
<td>(94%)</td>
</tr>
<tr>
<td>23i</td>
<td>54%</td>
<td>(97%)</td>
</tr>
<tr>
<td>23j</td>
<td>44%</td>
<td>(98%)</td>
</tr>
<tr>
<td>23k</td>
<td>50%</td>
<td>(&gt;99%)</td>
</tr>
<tr>
<td>23l</td>
<td>34%</td>
<td>(92%)</td>
</tr>
<tr>
<td>23m</td>
<td>54%</td>
<td>(&gt;99%)</td>
</tr>
<tr>
<td>23n</td>
<td>50%</td>
<td>(99%)</td>
</tr>
<tr>
<td>23o</td>
<td>36%</td>
<td>(98%)</td>
</tr>
<tr>
<td>23p</td>
<td>42%</td>
<td>(94%)</td>
</tr>
<tr>
<td>23q</td>
<td>31%</td>
<td>(97%)</td>
</tr>
<tr>
<td>23r</td>
<td>32%</td>
<td>(95%)</td>
</tr>
<tr>
<td>23s</td>
<td>25%</td>
<td>(99%)</td>
</tr>
<tr>
<td>23t</td>
<td>19%</td>
<td>(99%)</td>
</tr>
</tbody>
</table>

$^a$Overall yield (purity) after HPLC purification.
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.

Scheme 3.9. Nitration of 6-chloropurine riboside 5'-carboxylic acid.

At first, 6-chloropurine 9 was nitrated in solution as is represented in Scheme 3.9. The carboxyl group was protected in situ with TFAA under formation of the mixed anhydride, 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 24 in high yield. At this point, the first amino diversity element was introduced

Scheme 3.10. (a) DIPEA, CH₂Cl₂, rt; (b) DIC, HOBT, DMF; (c) DIPEA, NMP, 80 °C; (d) TFA-HO(CH₂)₂OH-CH₂Cl₂, 5:1:5; (e) 0.5 equiv Cu(OAc)₂, THF.
in solution by 6-chloro displacement furnishing 6-aminopurine 25 (Scheme 3.10). Ensuing attachment to hydrazine resin 19 was brought about under standard acylation conditions, i.e. DIC in combination with HOBT. The use of the additive was allowed as no highly reactive electrophilic positions were present in purine 25. A bromophenol blue test confirmed quantitative formation of resin 26. Substitution of the 2-nitro group by nitrogen nucleophiles required gentle heating in NMP to obtain 2,6-diamino purine 27. Removal of the 2',3'-isopropylidene group under acidic conditions gave 28, 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,N5,N6-trisubstituted 5'-carboxamido-adenosine analogues 29.

Again, a small library was prepared to demonstrate the efficiency of the developed solid phase route. After oxidative cleavage from the resin, the copper salts were removed by solid phase extraction, using a silica gel cartridge, and products were obtained in 67-87% purity. Subsequent semi-preparative HPLC and lyophilisation afforded trisubstituted carboxamido-adenosine analogues 29a-h in 20-57% yield over four solid phase steps and high purity, ready for biological evaluation (see Table 3.3).

### Table 3.3. Library of 2,N5,N6-trisubstituted 5'-carboxamido-adenosine analogues.\(^a\)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>Purity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>29a</td>
<td>27%</td>
<td>(&gt;97%)</td>
</tr>
<tr>
<td>29b</td>
<td>26%</td>
<td>(96%)</td>
</tr>
<tr>
<td>29c</td>
<td>35%</td>
<td>(98%)</td>
</tr>
<tr>
<td>29d</td>
<td>35%</td>
<td>(99%)</td>
</tr>
<tr>
<td>29e</td>
<td>30%</td>
<td>(92%)</td>
</tr>
<tr>
<td>29f</td>
<td>57%</td>
<td>(91%)</td>
</tr>
<tr>
<td>29g</td>
<td>21%</td>
<td>(99%)</td>
</tr>
<tr>
<td>29h</td>
<td>38%</td>
<td>(91%)</td>
</tr>
</tbody>
</table>

\(^a\)Overall yield (purity) after HPLC purification.
3.4 CONCLUDING REMARKS

In summary, it was shown that the safety-catch approach towards di- and trisubstituted 5'-carboxamidoadenosine derivatives succeeded by application of the aryl hydrazide linker. Despite many efforts with Kenner’s sulfonamide linker we could not effect appreciable coupling of the nucleoside 5'-carboxylic acid to this linker, which was expected to be stable during solid supported nitration conditions. As the aryl hydrazide linker was not compatible with the TBAN-TFAA nitration, the solid phase synthesis of trisubstituted 5'-carboxamidoadenosine analogues required a combined solution-solid phase diversification procedure. The generation of two small combinatorial libraries demonstrated the validity of the aryl hydrazide resin supported syntheses leading to di- and trisubstituted 5'-carboxamidoadenosine derivatives 23a-t and 29a-h, respectively.

3.5 ACKNOWLEDGEMENTS

Vic Pinas is kindly acknowledged for the numerous experiments with the sulfonamide linkers. Remko Detz and Dr. Catia Lambertucci are greatly appreciated for the solid phase synthesis of the disubstituted 5'-carboxamido adenosine derivatives.

3.6 EXPERIMENTAL

General information. For experimental details see section 2.8. 4-Fmoc-hydrazinobenzoyl AM resin, 100-200 mesh, 0.98 mmol/g, was purchased from Novabiochem, N-(4-Sulfamoylbenzoyl)aminomethyl polystyrene, 200-400 mesh, 0.9 mmol/g, was purchased from Fluka, N-(4-Sulfamoylbutyryl)aminomethyl polystyrene, 200-400 mesh, 1.09 mmol/g, was a gift from Solvay Pharmaceuticals, Weesp. For the end-products 23 and 29 coupling constants $J$ of H-2', H-3' and H-4' were determined after mixing the sample with a drop of D$_2$O.

6-Chloro-(2,3-O-isopropylidene-5-carboxy-β-D-ribofuranosyl)-9H-purine (9). This compound was synthesised according to a modified literature procedure. A mixture of iodobenzene diacetate (6.72 g; 20.88 mmol), TEMPO (296 mg; 1.90 mmol) and 2',3'-isopropylidene protected 6-chloropurine riboside 8 (3.10 g; 9.49 mmol) in water-acetonitrile 1:1 (20 mL) was stirred for 4 h. The reaction mixture was carefully pured into 0.5 M aqueous NaHCO$_3$ (125 mL). After stirring for 10 min the mixture was washed with CH$_2$Cl$_2$ (3x40 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$_2$Cl$_2$-EtOH 95:5 (4x40 mL). Drying with Na$_2$SO$_4$ and coevaporation with toluene gave 5'-carboxylic acid 9 as a white solid (2.98 g; 8.74 mmol; 92%). $^1$H-NMR (d$_6$DMSO) δ 12.92 (bs, 1H, COOH), 8.84 and 8.78 (2xs, 2x1H, 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.
Attempted coupling of carboxylic acid 9 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 of DMF was added carboxylic acid 9 (153 mg; 0.45 mmol), DIC (70 µL; 0.45 mmol) and 1-methylimidazole (36 µL; 0.45 mmol). After 20 to 24 h the resulting resin was washed with the solvent of the reaction (3x), CH₂Cl₂ (3x), MeOH, CH₂Cl₂, MeOH, Et₂O, CH₂Cl₂, Et₂O, CH₂Cl₂ and dried in vacuo at 50 °C. No coupling was observed judging from the absence of a sulfonamide carbonyl vibration at v=1735 cm⁻¹. For other coupling conditions see Table 3.1.

N-Benzyl-4-sulfamoyl-benzamide (12). 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-CH₂Cl₂ 1:1 (2 mL) was stirred for 2 h. Et₂O-EtOAc 1:1 (1 mL) and 5% aqueous KHSO₄ (1.5 mL) were added and after stirring for 5 min the mixture was washed with water (3x 2 mL). Drying with Na₂SO₄ and evaporation of the solvent yielded N-Benzyl-4-sulfamoyl-benzamide 12 as white crystalline solid (4.866 g; 19.0 mmol; 76%). ¹H-NMR (d₆-DMSO) δ 9.27 (t, J 6.0, 1H, NH), 8.07 (d, J 8.4, 2H, HCO₃), 7.92 (d, J 8.4, 2H, HCO₃), 7.50 (bs, 2H, NH₂), 7.37-7.32 (m, 4H, H₂Bn), 7.29-7.27 (m, 1H, H₂Bn), 4.52 (d, J 6.0, 2H, CH₂).

Attempted coupling of carboxylic acid 9 to sulfonamide 12 (13). In a typical experiment a mixture of carboxylic acid 9 (80 mg; 0.23 mmol), sulfonamide 12 (50 mg; 0.20 mmol), EDC (54 mg; 0.28 mmol) and DMAP (2.5 mg; 0.02 mmol) in DMA-CH₂Cl₂ 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.

Fmoc removal from 2-Fmoc-hydrazinobenzoyl AM resin 18 (19). A suspension of 2-Fmoc-hydrazinobenzoyl AM resin 18 (1.0 g; 0.98 mmol) in DMF-piperidine 4:1 (10 mL) was mixed by nitrogen flushing for 30 min. Resin 19 was washed with DMF (3x), CH₂Cl₂ (3x), MeOH, CH₂Cl₂, MeOH, Et₂O, CH₂Cl₂, Et₂O, CH₂Cl₂ and dried in vacuo at 50 °C.

Coupling of carboxylic acid 9 to hydrazinobenzoyl AM resin 19 (20). To a suspension of hydrazinobenzoyl AM resin 19 (0.78 g; 0.98 mmol) in DMF (10 mL) was added carboxylic acid 9 (0.84 g; 2.45 mmol) and DIC (384 µL; 2.45 mmol). The reaction was monitored with a bromophenolblue test. After 16 h the reaction was complete and resin 20 was washed with DMF (3x), CH₂Cl₂ (3x), MeOH, CH₂Cl₂, MeOH, Et₂O, CH₂Cl₂, Et₂O, CH₂Cl₂ and dried in vacuo at 50 °C.

General procedure for the amination by chloro substitution of resin-bound 6-chloropurines 20 (21). A suspension of resin-bound 6-chloropurine 20 (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 21 was washed with NMP (3x), CH₂Cl₂ (3x), MeOH, CH₂Cl₂, MeOH, Et₂O, CH₂Cl₂, Et₂O and CH₂Cl₂.

General procedure for the removal of the 2′,3′-isopropylidene group (22). The resin-bound isopropylidene protected riboside 21 (0.18 mmol) was washed with a solution of TFA-HO(CH₂)₂OH-CH₂Cl₂ 5:1:5 (2 mL). After subjecting to this solution (2 mL) for 18 h the resin was washed with CH₂Cl₂ (3x), CH₂Cl₂-DIPEA 9:1 (3x), CH₂Cl₂ (3x), MeOH, CH₂Cl₂, MeOH, CH₂Cl₂, Et₂O, CH₂Cl₂, Et₂O and CH₂Cl₂.

General procedure for oxidative cleavage of the nucleosides from the resin (23). A suspension of resin 22 (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. The resin was washed with THF (3×), MeOH, THF, MeOH, THF, MeOH, 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.

N^4-Cyclpentyl-5^'-N-methylcarboxamidoadenosine (23a). 28 mg; 0.077 mmol; 43%. 1H-NMR (d_6-DMSO) 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 (bs, 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, cyclpentyl), 1.77-1.72 (m, 2H, cyclpentyl), 1.72-1.54 (m, 4H, cyclpentyl). m/z 363.1789 (M^+H. C_{18}H_{23}N_{6}O_4 requires 363.1781).

N^4-Cyclpentyl-5^'-N-ethylcarboxamidoadenosine (23b). 25 mg; 0.067 mmol; 37%. 1H-NMR (d_6-DMSO) 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, cyclpentyl), 1.76-1.73 (m, 2H, cyclpentyl), 1.70-1.56 (m, 4H, cyclpentyl), 1.10 (t, J 7.0, 3H, CH_3). m/z 377.1927 (M^+H. C_{17}H_{25}N_{6}O_4 requires 377.1937).

N^4-Cyclpentyl-5^'-N-phenylcarboxamidoadenosine (23c). 21 mg; 0.050 mmol; 28%. 1H-NMR (d_6-DMSO) 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 (bs, 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, cyclpentyl), 1.77-1.32 (m, 12H, cyclpentyl). m/z 417.2247 (M^+H. C_{20}H_{29}N_{6}O_4 requires 417.2250).

N^4-Cyclpentyl-5^'-N-phe nylcarboxamidoadenosine (23d). 24 mg; 0.057 mmol; 32%. 1H-NMR (d_6-DMSO) δ 10.52 (s, 1H, CONH), 8.47 and 8.23 (2×s, 2×1H, H-2 and H-8), 7.91 (bs, 1H, N^6-H), 7.65 (d, J 7.7, 2H, H_2A), 7.40 (t, J 7.7, 2H, H_2A), 7.16 (t, J 7.7, 1H, H_2A), 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, cyclpentyl), 1.75-1.70 (m, 2H, cyclpentyl), 1.67-1.59 (m, 4H, cyclpentyl). m/z 425.1908 (M^+H. C_{21}H_{25}N_{6}O_4 requires 425.1937).

N^4-Benzyl-5^'-N-methylcarboxamidoadenosine (23e). 35 mg; 0.090 mmol; 50%. 1H-NMR (d_6-DMSO) δ 8.92 (q, J 4.6, 1H, CONH), 8.56 (bs, 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_2A), 7.23 (t, J 7.4, 1H, H_2A), 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×bs, 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_{6}O_4 requires 385.1624).

N^4-Benzyl-5^'-N-ethylcarboxamidoadenosine (23f). 33 mg; 0.083 mmol; 46%. 1H-NMR (d_6-DMSO) δ 8.90 (t, J 5.6, 1H, CONH), 8.56 (bs, 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_2A), 7.23 (t, J 7.2, 1H, H_2A), 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-1').
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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, CH2), 1.09 (t, J 7.2, 3H, CH3). m/z 399.1758 (M^+H. C_{19}H_{23}N_{6}O_{4} requires 399.1781).

N^6-Benzyl-5'-N-cyclopentylcarboxamidoadenosine (23g). 35 mg; 0.081 mmol; 45%. 1H-NMR (d_6- DMSO) δ 8.57-8.52 (m, 2H, CONH and N^6-H), 8.47 and 8.22 (2xs, 2x1H, 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 (2x prevail, 1H, CH2 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_{23}H_{27}N_{6}O_{4} requires 439.2094).

N^6-Benzyl-5'-N-phenylcarboxamidoadenosine (23h). 24 mg; 0.054 mmol; 30%. 1H-NMR (d_6-DMSO) δ 10.49 (s, 1H, CONH), 8.58 (bs, 1H, N^6-H), 8.52 and 8.23 (2xs, 2x1H, H-2 and H-8), 7.65 (d, J 8.1, 1H, H_Ar), 7.41-7.29 (m, 6H, H_Ar), 7.21-7.22 (m, 1H, H_Ar), 7.15 (t, J 7.3, 1H, H_Ar), 6.08 (d, J 7.0, 1H, H-1'), 5.90 (bs, 1H, OH), 5.70 (bs, 1H, OH), 5.17 and 4.76 (2fx prevail, 1H, CH2 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_{6}O_{4} requires 447.1871).

N^6-(3-Iodobenzyl)-5'-N-methylcarboxamidoadenosine (23i). 37 mg; 0.073 mmol; 54%. 1H-NMR (d_6-DMSO) δ 8.89 (q, J 4.7, 1H, CONH), 8.60 (bs, 1H, N^6-H), 8.47 and 8.32 (2xs, 2x1H, 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 (2fx prevail, 1H, CH2 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, CH3). m/z 511.0599 (M^+H. C_{18}H_{20}I_{2}N_{6}O_{4} requires 511.0591).

N^6-(3-Iodobenzyl)-5'-N-ethylcarboxamidoadenosine (23j). 31 mg; 0.059 mmol; 46%. 1H-NMR (d_6-DMSO) δ 8.86 (t, J 5.5, 1H, CONH), 8.61 (bs, 1H, N^6-H), 8.46 and 8.29 (2xs, 2x1H, 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 (2fx prevail, 1H, CH2 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, CH2), 1.09 (t, J 7.2, 3H, CH3). m/z 525.0752 (M^+H. C_{19}H_{22}I_{2}N_{6}O_{4} requires 525.0747).

N^6-(3-Iodobenzyl)-5'-N-cyclopentylcarboxamidoadenosine (23k). 38 mg; 0.068 mmol; 50%. 1H-NMR (d_6-DMSO) δ 8.61 (bs, 1H, N^6-H), 8.51 (d, J 7.1, 1H, CONH), 8.49 and 8.23 (2xs, 2x1H, 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 (2fx prevail, 1H, CH2 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}I_{2}N_{6}O_{4} requires 565.1060).

N^6-(3-Iodobenzyl)-5'-N-phenylcarboxamidoadenosine (23l). 26 mg; 0.046 mmol; 34%. 1H-NMR (d_6-DMSO) δ 10.47 (s, 1H, CONH), 8.61 (bs, 1H, N^6-H), 8.54 and 8.24 (2xs, 2x1H, H-2 and H-8), 7.75 (s, 1H, H_Ar), 7.65 (d, J 8.1, 2H, H_NHA), 7.61 (d, J 7.8, 1H, H_Ar), 7.41-7.31 (m, 3H, H_Ar and H_NHA), 7.17-7.11 (m, 2H, H_Ar and H_NHA), 6.09 (d, J 7.0, 1H, H-1'), 5.91 (bs, 1H, OH), 5.71 (bs, 1H, OH), 5.19 and 4.69-4.61 (2fx prevail, 2H, CH2 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}I_{2}N_{6}O_{4} requires 573.0747).
N^6-(2-Phenethyl)-5'-N-methylcarboxamidoadenosine (23m). 29 mg; 0.073 mmol; 54%. 1H-NMR (d_6-DMSO) δ 8.95 (q, 1H, CH, CONH), 8.42 and 8.36 (2×s, 2×1H, H-2 and H-8), 8.05 (bs, 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_{12}N_{4}O_4 requires 399.1781).

N^6-(2-Phenethyl)-5'-N-ethylcarboxamidoadenosine (23n). 28 mg; 0.068 mmol; 50%. 1H-NMR (d_6-DMSO) 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×bs, 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_{4}O_4 requires 413.1937).

N^6-(2-Phenethyl)-5'-N-cyclopentylcarboxamidoadenosine (23o). 22 mg; 0.049 mmol; 36%. 1H-NMR (d_6-DMSO) 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×bs, 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 (bs, 1H, OH), 5.59 (bs, 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'), 4.17-4.14 (m, 1H, CONH), 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_{4}O_4 requires 453.2250).

N^6-(2-Phenethyl)-5'-N-phenylcarboxamidoadenosine (23p). 26 mg; 0.057 mmol; 42%. 1H-NMR (d_6-DMSO) δ 10.46 (s, 1H, CONH), 8.48 and 8.26 (2×s, 2×1H, H-2 and H-8), 7.98 (bs, 1H, N^6-H), 7.65 (d, J 7.5, 2H, H_NHA), 7.40 (t, J 7.5, 2H, H_NHA), 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_{4}O_4 requires 461.1937).

N^6-(2,2-Diphenylethyl)-5'-N-methylcarboxamidoadenosine (23q). 26 mg; 0.056 mmol; 31%. 1H-NMR (d_6-DMSO) 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 (bs, 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 (bs, 1H, OH), 5.58 (bs, 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_{23}H_{17}N_{4}O_4 requires 475.2094).

N^6-(2,2-Diphenylethyl)-5'-N-ethylcarboxamidoadenosine (23r). 28 mg; 0.058 mmol; 32%. 1H-NMR (d_6-DMSO) δ 8.90 (t, J 5.6, 1H, CONH), 8.36 (s, 2H, H-2 and H-8), 7.96 and 7.76 (2×bs, 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 (bs, 1H, OH), 5.58 (bs, 1H, OH), 4.64-4.54 and 4.17-4.14 (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_{4}O_4 requires 489.2250).

N^6-(2,2-Diphenylethyl)-5'-N-cyclopentylcarboxamidoadenosine (23s). 24 mg; 0.045 mmol; 25%. 1H-NMR (d_6-DMSO) 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 (2xbs, 1H, N°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 (2xm, 6H, H-2', H-3', CH and CH2 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. C29H33N6O4 requires 529.2563).

N°-(2,2-Diphenylethyl)-5°-N-phenylcarboxamidoadenosine (23t). 18 mg; 0.034 mmol; 19%. 1H-NMR (d6-DMSO) δ 10.49 (s, 1H, CONH), 8.44 and 8.31 (2x2s, 2x1H, H-2 and H-8), 7.97 and 7.79 (2xbs, 1H, N°H rotamers), 7.65 (d, J 7.8, 2H, H NHa), 7.42-7.28 (m, 10H, H NHa and H Ar), 7.21-7.10 (m, 3H, H NHa and H Ar), 6.06 (d, J 6.9, 1H, H-1'), 5.88 (bs, 1H, OH), 5.68 (bs, 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, CH2). m/z 537.2259 (M^+H. C30H32N6O4 requires 537.2250).

2-Nitro-6-chloro-(2,3-O-isopropylidene-5-carboxy-D-ribofuranosyl)-9H-purine (24). TFAA (1.27 mL; 9.0 mmol) was added to a suspension of 6-chloropurine carboxylic acid 9 (1.07 g; 3.0 mmol) in dry CH2Cl2 (24 mL) at 0 °C and the mixture was stirred until a clear solution was obtained (30 min). TBAN (1.46 g; 4.8 mmol) was added and the reaction mixture was stirred for an additional 2h at 0 °C. The reaction mixture was divided between water (20 mL) and Et2O (75 mL) and the organic layer was washed with water (3x20 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 washed with water (30 mL). The combined water layers were washed with Et2O and the pH was adjusted to ≈2.3 with oxalic acid (0.54 g; 6.0 mmol). After extraction with EtOAc (40 mL; 15 mL, 15 mL) and washing of the combined organic layers with water (20 mL) the organic layer was dried with Na2SO4 and the solvent was evaporated. Nitrate product 24 was obtained as a yellow foam (1.09 g; 2.82 mmol; 94%). 1H-NMR (d6-DMSO) δ 12.97 (bs, 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, CH3), 1.40 (s, 3H, CH3).

2',3'-O-Isopropylidene-2-nitro-N°-cyclopentyladenosine 5°-carboxylic acid (25a). To a solution of 2'-nitro-6-chloropurine 24 (1.09 g; 2.82 mmol) in CH2Cl2 (15 mL) was 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 Et2O (50 mL) and the organic layer was extracted with water (2x20 mL). The combined water layers were washed with Et2O (25 mL) and the pH was adjusted to ≈2.3 with oxalic acid. The acidic water layer was extracted with EtOAc (3x30 mL) and the combined organic layers were washed with water (20 mL), dried with Na2SO4 and coevaporated with toluene (3x). Trituration with CH2Cl2 furnished adenosine carboxylic acid 25a as a yellow solid (0.70 g; 1.61 mmol; 57%). 1H-NMR (d6-DMSO) δ 12.78 (bs, 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 (2xm, 1H, CH rotamers), 2.01-1.96 (m, 2H, cyclopentyl), 1.75-1.55 (m, 6H, cyclopentyl), 1.54 (s, 3H, CH3), 1.39 (s, 3H, CH3).

2',3'-O-Isopropylidene-2-nitro-N°-(3-iodobenzyl)adenosine 5°-carboxylic acid (25b). This compound was prepared by the method described for 25a. After trituration with CH2Cl2 adenosine carboxylic acid 25b was obtained as a yellow solid (0.92 g; 1.58 mmol; 53%). 1H-NMR (d6-DMSO) δ 12.81 (bs, 1H, OH), 9.36 and 9.24 (2xt, J 6.1, 1H, NH rotamers), 8.60 (s, 1H, H-8), 7.85 and 7.78 (2xs, 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'),
General procedure for coupling of carboxylic acid 25 to hydrazinobenzoyl AM resin 19 (26). To a suspension of hydrazinobenzoyl AM resin 19 (0.78 g; 0.98 mmol) in DMF (5 mL) was added carboxylic acid 25 (1.47 mmol), HOBt (198 mg; 1.47 mmol) and DIC (230 µL; 1.47 mmol). After 16 h the reaction resin 26 was washed with DMF (3×), CH₂Cl₂ (3×), MeOH, CH₂Cl₂, MeOH, Et₂O, CH₂Cl₂, Et₂O, CH₂Cl₂ and dried in vacuo at 50 °C.

General procedure for the amination by nitro substitution of resin-bound 2-nitropurines 26 (27). A suspension of resin-bound 2-nitropurine 26 (200 mg; 0.16 mmol) and the amine (0.71 mmol) in NMP (22 mL) was gently stirred at 80 °C. After 24 h resin 27 was washed with NMP (3×), CH₂Cl₂ (3×), MeOH, CH₂Cl₂, MeOH, Et₂O, CH₂Cl₂, Et₂O and CH₂Cl₂.

General procedure for the removal of the 2′,3′-isopropylidene group (28). See general procedure for 22.

General procedure for oxidative cleavage of the nucleosides from the resin (29). See general procedure for 23.

2-Cyclopentylamino-5′-2′-cyclopentyl-5′-N-ethylcarboxamidoadenosine (29a). 20 mg; 0.043 mmol; 27%. ¹H-NMR (d₆-DMSO) δ 8.14 (bs, 1H, CONH), 8.00 (s, 1H, H-8), 7.18 (bs, 1H, N⁶-H), 6.16 (bs, 1H, 2-NH), 5.84 (d, J 6.8, 1H, H-1′), 5.59 (bs, 1H, OH), 5.51 (d, J 5.7, 1H, OH), 4.74-4.70 (m, 1H, H-2′), 4.50-4.44 (m, 1H, N⁶-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, HCH), 3.22-3.11 (m, 1H, HCH), 1.95-1.89 (m, 12H, cyclopentyl). m/z 460.2685 (M⁺+H. C₂₂H₃₄N₇O₄ requires 460.2672).

2-Cyclopentylamino-5′-2′-cyclopentyl-5′-N-cyclopentylcarboxamidoadenosine (29b). 21 mg; 0.042 mmol; 26%. ¹H-NMR (d₆-DMSO) δ 8.05 (s, 1H, H-8), 7.88 (d, J 7.1, 1H, CONH), 7.13 (bs, 1H, N⁶-H), 6.21 (bs, 1H, 2-NH), 5.87 (d, J 6.8, 1H, H-1′), 5.53 (d, 2H, 2xOH), 4.66-4.62 (m, 1H, H-2′), 4.53-4.45 (m, 1H, N⁶-CH), 4.27 (s, 1H, H-4′), 4.22 (m, 1H, H-3′), 4.21-4.15 (m, 1H, 2-NHCH), 4.05-4.00 (m, 1H, CONHCH), 1.94-1.33 (m, 24H, cyclopentyl). m/z 500.2982 (M⁺+H. C₂₅H₃₈N₇O₄ requires 500.2985).

2-(2-Phenethylamino)-5′-2′-cyclopentyl-5′-N-ethylcarboxamidoadenosine (29c). 28 mg; 0.056 mmol; 35%. ¹H-NMR (d₆-DMSO) δ 8.11 (bs, 1H, CONH), 8.03 (s, 1H, H-8), 7.33-7.18 (m, 6H, N⁶-H and H₆A), 6.35 (bs, 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, N⁶-CH), 4.27 (s, 1H, H-4′), 4.19 (m, 1H, H-3′), 3.53-3.43 (m, 2H, 2-NHC H₂), 3.22-3.16 (m, 1H, HCH), 3.14-3.07 (m, 1H, HCH), 2.89-2.86 (m, 2H, PHCH₂), 1.99-1.96 (m, 2H, cyclopentyl), 1.75-1.71 (m, 2H, cyclopentyl), 1.68-1.51 (m, 4H, cyclopentyl), 1.00 (s, J 7.2, 3H, CH₃). m/z 496.2686 (M⁺+H. C₂₅H₃₄N₇O₄ requires 496.2672).

2-(2-Phenethylamino)-5′-2′-cyclopentyl-5′-N-cyclopentylcarboxamidoadenosine (29d). 30 mg; 0.056 mmol; 35%. ¹H-NMR (d₆-DMSO) δ 8.09 (s, 1H, H-8), 7.91 (d, J 7.0, 1H, CONH), 7.31-7.20 (m, 6H, N⁶-H and H₆A), 6.41 (bs, 1H, 2-NH), 5.89 (d, J 5.7, 1H, H-1′), 5.53 (bs, 2H, 2xOH), 4.67-4.63 (m, 1H, H-2′), 4.53-4.49 (m, 1H, N⁶-CH), 4.29 (s, 1H, H-4′), 4.21 (m, 1H, H-3′), 4.04-4.00 (m, 1H, CON-
2-Cyclopentylamino-\(N^6\)-(3-iodobenzyl)-5'-N-ethylcarboxamidoadenosin (29e). 30 mg; 0.045 mmol; 30%. \(^1\)H-NMR (\(d_6\)-DMSO) \(\delta\) 8.15-7.99 (m, 3H, CONH, H-8 and N\(^6\)-H), 7.77 (s, 1H, H\(_{A}\)), 7.59 (d, J 7.7, 1H, H\(_{A}\)), 7.40 (d, J 7.7, 1H, H\(_{A}\)), 7.13 (t, J 7.7, 1H, H\(_{A}\)), 6.20 (bs, 1H, 2-NH), 5.86 (d, J 6.8, 1H, H-1'), 5.45 (bs, 2H, 2xOH), 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').

2-Cyclopentylamino-\(N^6\)-(3-iodobenzyl)-5'-N-ethylcarboxamidoadenosine (29f). 55 mg; 0.086 mmol; 57%. \(^1\)H-NMR (\(d_6\)-DMSO) \(\delta\) 8.10 (s, 1H, H-8), 7.99 (bs, 1H, N\(^6\)-H), 7.87 (d, J 6.9, 1H, CONH), 7.75 (s, 1H, H\(_{A}\)), 7.59 (d, J 7.8, 1H, H\(_{A}\)), 7.38 (d, J 7.8, 1H, H\(_{A}\)), 7.13 (t, J 7.8, 1H, H\(_{A}\)), 6.30 (d, J 7.3, 1H, 2-NH), 5.87 (d, J 6.5, 1H, H-1'), 5.52-5.49 (m, 2H, 2xOH), 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'), 4.14-4.11 (m, 1H, 2-NHCH\(_3\)), 3.24-3.10 (m, 1H, CONHCH\(_3\)), 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\(_7\)O\(_4\) requires 608.1482).

2-(2-Phenethylamino)-\(N^6\)-(3-iodobenzyl)-5'-N-ethylcarboxamidoadenosin (29g). 20 mg; 0.032 mmol; 21%. \(^1\)H-NMR (\(d_6\)-DMSO) \(\delta\) 8.14-8.00 (m, 3H, CONH, H-8 and N\(^6\)-H), 7.77 (s, 1H, H\(_{A}\)), 7.60 (d, J 7.8, 1H, H\(_{A}\)), 7.39 (d, J 7.8, 1H, H\(_{A}\)), 7.28 (t, J 7.3, 2H, H\(_{Ph}\)), 7.24-7.10 (m, 4H, H\(_{A}\) and H\(_{Ph}\)), 6.49 (bs, 1H, 2-NH), 5.89 (d, J 6.9, 1H, H-1'), 5.51 (bs, 2H, 2xOH), 4.72-4.62 (m, 3H, H-2' and N\(^6\)-CH\(_2\)), 4.29 (d, J 2.1, 1H, H-4'), 4.21 (s, 1H, H-3'), 3.51-3.33 (m, 2H, 2-NHCH\(_3\)), 3.23-3.16 (m, 1H, HCHCH\(_3\)), 3.14-3.08 (m, 1H, HCHCH\(_3\)), 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\(_{35}\)IN\(_7\)O\(_4\) requires 644.1482).

2-(2-Phenethylamino)-\(N^6\)-(3-iodobenzyl)-5'-N-cyclopentylcarboxamidoadenosin (29h). 39 mg; 0.057 mmol; 38%. \(^1\)H-NMR (\(d_6\)-DMSO) \(\delta\) 8.14 (s, 1H, H-8), 8.06 (bs, 1H, N\(^6\)-H), 7.92 (d, J 7.3, 1H, CONH), 7.75 (s, 1H, H\(_{A}\)), 7.59 (d, J 7.7, 1H, H\(_{A}\)), 7.38 (d, J 7.7, 1H, H\(_{A}\)), 7.30 (t, J 7.1, 2H, H\(_{Ph}\)), 7.20-7.09 (m, 4H, H\(_{A}\) and H\(_{Ph}\)), 6.47 (bs, 1H, 2-NH), 5.90 (d, J 6.7, 1H, H-1'), 5.54 (m, 2H, 2xOH), 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, CONHCH\(_3\)), 3.45-3.33 (m, 2H, 2-NHCH\(_3\)), 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\(_7\)O\(_4\) requires 684.1795).

3.7 REFERENCES

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29. The use of DIC in combination with 1-methylimidazole is described in the synthesis notes of the Novabiochem 2000 Catalogue.
31. 4-Fmoc-hydrazinobenzoyl AM resin is commercially available from Novabiochem.