Solid phase synthesis of C2,N^6-disubstituted adenosine analogues

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A 6-step solid phase sequence towards C2,N^6-disubstituted adenosine analogues was developed, which was validated by the construction of a small combinatorial library. Attachment of the 5′-OH of readily available 2′,3′-methoxymethylidene protected 6-chloropurine ribonucleoside onto carboxypolystyrene furnished the immobilised 6-chloropurine ribonucleoside. Nitration on the solid phase resulted in the formation of the 2-nitro-6-chloropurine nucleoside, a highly reactive difunctionalised species. Amines were selectively introduced at the 6-position by 6-chloro displacement at room temperature without affecting the 2-nitro group. Subsequent substitution of the 2-nitro group by amines was achieved at 80–90 °C. Removal of the methoxymethylidene group under mildly acidic conditions, followed by cleavage of the nucleosides from the resin, yielded the C2,N^6-disubstituted adenosine analogues.

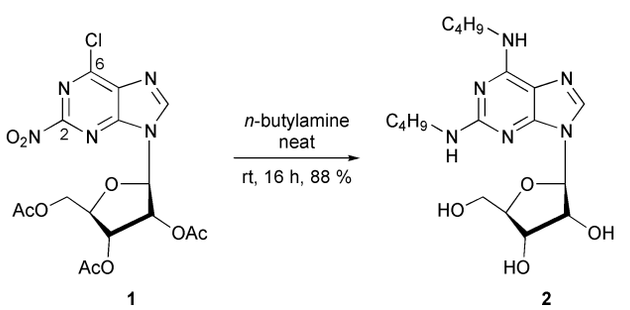
Introduction

The solid phase combinatorial synthesis of di- and trisubstituted purines, to obtain for instance cyclin-dependent kinase inhibitors, is well documented.[1] The occurrence of purine nucleosides on solid supports in the literature is restricted to the synthesis of DNA- and RNA-oligomers[2] and the more stable carbocyclic analogues.[3] General interest in the synthesis and application of adenosine analogues prompted us to fill this synthetic void and to develop a solid phase route towards the combinatorial substitution of purine ribonucleoside systems. We chose to introduce diversity elements onto the purine ring at the 2 and 6 positions, since several C2,N^6-disubstituted analogues of adenosine are described as potent adenosine receptor agonists[4–6] as well as inhibitors of *Trypanosoma brucei* phosphoglycerate kinase.[7] Moreover, adenosine analogues are potential therapeutic agents for malaria caused by drug-resistant *Plasmodium falciparum*.[8]

The introduction of amino substituents on the 2- and 6-positions is generally achieved *via* nucleophilic displacement of 2,6-dihalogenated purine systems. The halogen functionality at the 2 position is typically introduced by conversion of an amino group, as present in guanine or guanosine derivatives, *via* alkyl nitrite catalysed reactions.[9–11] A recently developed method involves 2-halogenation of 2-tributylstannyl-6-chloropurine ribonucleoside, which is obtained by lithiation–stannylation of 6-chloropurine ribonucleoside.[12]

The purine 6-position is the most reactive towards nucleophilic substitution and, although activated by the electron withdrawing effect of a halogen atom on C2, moderately elevated temperatures (25–80 °C) are usually applied in order to introduce aliphatic or aromatic amines to C6. Displacement of the halogen on the 2-position requires more forcing conditions (100–130 °C) and is restricted to aliphatic amines.[6,7,13] These harsh conditions are not favoured in automated solid phase synthesis.

Recently, we described the functionalisation of the 2-position in triacetyl-protected 6-chloropurine ribonucleoside by nitration with a mixture of tetrabutylammonium nitrate and trifluoroacetic acid anhydride (TBAN–TFAA).[14] The electrophilicity of the purine C6 was greatly enhanced by the nitro substituent, and introduction of amino substituents could be achieved at temperatures below 0 °C. Under these conditions the nitro and acetate groups were not affected. During ammonolysis of the acetate protecting groups undesired substitution of the nitro group was observed.[15] Intrigued by this nitro substitution, we dissolved 2-nitro-6-chloropurine ribonucleoside triacetate **1** in *n*-butylamine at room temperature, which offered 2,6-dibutylaminopurine ribonucleoside **2** in 88% yield (Scheme 1).



Scheme 1 6-Chloro and 2-nitro substitution with *n*-butylamine.

This preliminary result prompted us to explore the nitro displacement for beneficial use.

The nitro group is rarely encountered as a leaving group in S_NAr reactions; instead, it mainly serves as a precursor to an amino substituent *via* a reductive pathway. This is primarily due to the poor synthetic availability of nitrobenzenes containing *ortho* or *para* electron withdrawing substituents, which considerably facilitate aromatic nucleophilic substitution. Classical electrophilic nitration of aromatic rings containing one electron-withdrawing group predominantly results in the formation of *meta*-substituted products. In heterocyclic systems, such as pyridines and pyrimidines, α- and γ-nitrogen atoms are strongly activating towards S_NAr reactions. But again these electron poor positions cannot be nitrated using classical methods. In this respect, the introduction of a nitro group at the electrophilic 2-position on the purine ring is exceptional and most likely proceeds *via* a radical process, thus creating a highly activated nitro substituent.[14]

The nitro group acting as a leaving group has been reported to be particularly successful in activated aromatic systems,[16] in some cases even superior to fluorine.[17] In S_NAr reactions an approximate order of leaving-group ability is: F ≥ NO_2 > OTs > SOPh > Cl, Br, I.[18] Of course, this greatly depends on the

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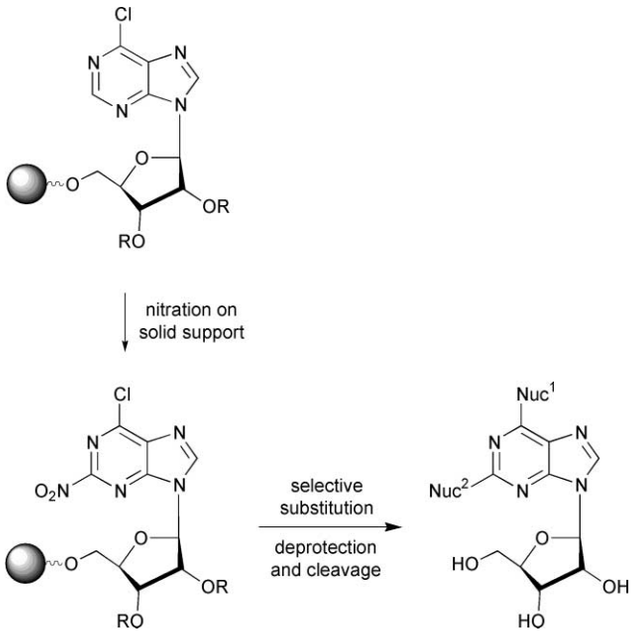
nature of the nucleophile and aromatic substrate. With translation of the substitution to the solid phase in mind, shown in Scheme 2, the 2-nitro displacement at room temperature is



Scheme 2 Strategy for the solid phase synthesis of C2,N^6-disubstituted adenosine analogues.

a considerable improvement compared with the 2-halogen substitutions, which require elevated temperatures even in solution.

Having established that the 6-chloro and the 2-nitro groups are promising handles for introducing structural diversity on the purine skeleton, we turned our attention to combinatorial solid phase synthesis. We wish to report here on the development of a solid phase route towards C2,N^6-disubstituted adenosine analogues, which is validated through the synthesis of a small combinatorial library.

Results and discussion

Synthesis

Solid phase modification of nucleosides was envisaged *via* coupling of the ribonucleoside 5′-OH to a polystyrene resin, leaving the purine system free for substitution (Scheme 2). Next, functionalisation of the solid supported 6-chloropurine ribonucleoside by TBAN–TFAA nitration would lead to the highly reactive 2-nitro-6-chloropurine system. This on-resin nitration offers considerable advantages over the coupling of a purine ribonucleoside already 2,6-difunctionalised: the attack of nucleophilic species on the activated electrophilic C6 in the nitrated system under coupling conditions is prevented,[19] and 6-chloropurine ribonucleoside is readily available. Introduction of diversity elements on the purine scaffold would provide, after deprotection and cleavage, the disubstituted purine ribonucleosides.

Carboxypolystyrene, the solid phase version of the benzoyl protecting group for alcohols, was selected as a solid support, since it is stable towards acidic and moderately basic–nucleophilic conditions. Alcohols are easily coupled to this resin by applying standard esterification reagents, *e.g.* diisopropylcarbodiimide (DIPCDI)–DMAP. For reasons of solubility and selectivity, 6-chloropurine ribonucleoside was 2′,3′-diol-protected prior to attachment to the solid support. Three 2′,3′-diol protecting groups were investigated: isopropylidene, TBDMS and methoxymethylidene groups (Scheme 3). The 2′,3′-isopropylidene protected 6-chloropurine ribonucleoside **3a**[20] was esterified to carboxypolystyrene in the presence of DIPCDI and DMAP. A malachite green test[21] after 16 h showed that no remaining COOH-groups were present on the resin.

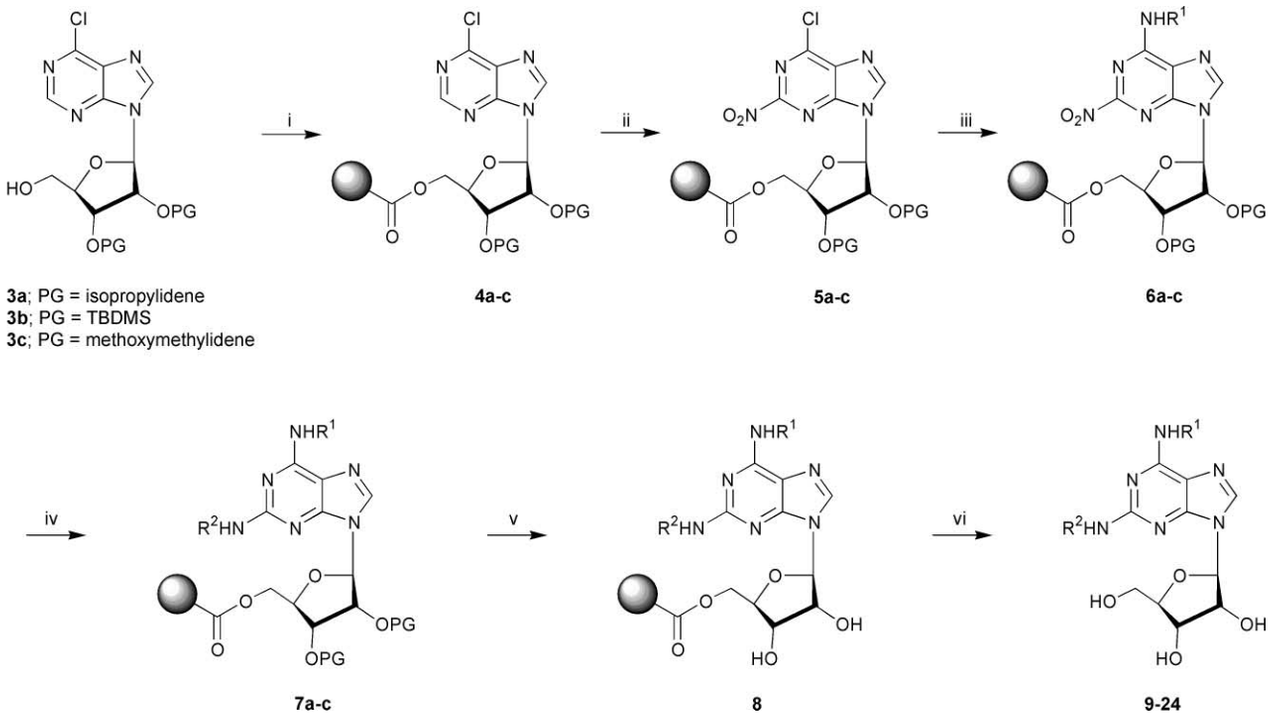
In solution the TBAN–TFAA nitration of 6-chloropurine ribonucleoside is performed at 0 °C.[14] For simplicity room temperature conditions are preferred in automated syntheses. The solid phase nitration of **4a** at room temperature was optimised to 90% using a 0.15 M solution of TBAN–TFAA (approx. 3 equiv.) in DCM. The conversion was determined by NMR and HPLC analysis of the crude mixture of products, obtained after cleaving the nucleosides from the resin using a NaOMe–MeOH–THF cocktail. Quantitative substitution of the chloro and nitro groups by methoxy groups was observed, providing mixtures of 6-methoxy and 2,6-dimethoxypurine ribonucleosides, corresponding to starting material and product respectively. It is noteworthy that no electrophilic nitration of the polystyrene matrix is observed,[22] thus supporting the radical mechanism of the TBAN–TFAA nitration.

Chloro displacement of **5a** by aliphatic or aromatic amines, in the presence of diisopropylethylamine (DIPEA), occurred in DCM at room temperature without affecting the nitro group. These solid phase substitution reactions proceeded considerably more slowly as compared to those in solution, where nitro displacement was already observed at room temperature.

In the next step amine groups were introduced *via* nitro substitution of solid supported **6a**, which required elevated temperatures. *N*-Methyl-2-pyrrolidone (NMP) appeared to be a valuable solvent, as its resin swelling properties are excellent and a large temperature range can be applied.[23] Subjecting resin **6a** to an amine and DIPEA in NMP at 80–90 °C for 24 h led to the efficient formation of **7a**.[24] Undesired aminolysis of the ester linkage, resulting in cleavage of the nucleoside from the resin, was not observed.

At this point, removal of the 2′,3′-isopropylidene group from **7a** presented us with significant problems. Usually, this protecting group is removed in aqueous solutions containing AcOH.[25] These conditions, however, do not apply to polystyrene resins, since they do not swell in protic solvents. Trifluoroacetic or hydrochloric acid in DCM or THF were used instead. When applied to resin-bound **7a**, concomitant cleavage of the glycosidic bond was observed, while under milder acidic conditions removal of the isopropylidene group was incomplete. Therefore we focussed on the TBDMS-ether, which can be removed without the use of acid. 2′,3′-Di-TBDMS protected 6-chloropurine ribonucleoside **3b** was obtained in 96% yield by the efficient application of selective acid catalysed removal of the 5′-TBDMS–ether from a tri-TBDMS protected nucleoside.[26] Coupling of **3b** to the resin proceeded smoothly, but the nitration of resin-bound **4b** was sluggish. Furthermore, on-resin deprotection of **7b** with various fluoride salts (*e.g.* NH_4F, TBAF, $3HF{\cdot}Et_3N$) gave rise to incomplete removal of the silyl groups. Eventually, we switched to the 2′,3′-methoxymethylidene protecting group, a more acid labile variant of the isopropylidene moiety.[27] The nitration of **4c** provided a clean conversion to **5c** and following the amination steps, complete on-resin deprotection of **7c** was achieved under mild conditions (0.1 M *p*-TsOH in DCM–MeOH, 97 : 3) without affecting the glycosidic bond.

A small combinatorial library was synthesised in order to validate the developed solid phase sequence from methoxymethylidene protected 6-chloropurine ribonucleoside **3c** to adenosine analogues **9**–**24** (see Table 1). Most of the amines selected for substitution at the 2- and 6-positions are active pharmacophores known from adenosine receptor and trypanosome research (*e.g.* cyclopentylamine, 3-iodobenzylamine, diphenylethylamine, aniline and histamine). Compounds **9**–**24** were obtained in 64–97% purity after cleavage. Minor amounts of side-products could be traced back to incomplete nitration or nitro-substitution. In order to biologically evaluate the library higher purities were mandatory. Therefore, products



Scheme 3 *Reagents and conditions*: (i) DIPCDI, DMAP, DCM; (ii) TBAN, TFAA, DCM; (iii) R^1-NH_2, DIPEA, DCM; (iv) R^2-NH_2, DIPEA, NMP, 80–90 °C; (v) *p*TsOH·H_2O, DCM–MeOH (97 : 3); (vi) NaOMe, MeOH, THF.

Table 1 Library of C2,N^6-disubstituted adenosine analogues

Product	R^1	R^2	Purity after cleavage (%)	Purity after prep-HPLC (%)	Yield after prep-HPLC (%)
9	Cyclopentyl	Cyclopentyl	73	99	26
10	Cyclopentyl	Tryptyl[a]	90	98	32
11	Cyclopentyl	$PhCH_2OCH_2CH_2$	80	96	31
12	Cyclopentyl	Histidyl[b]	—	98	38
13	Ph_2CHCH_2	Cyclopentyl	81	95	17
14	Ph_2CHCH_2	Tryptyl	91	95	33
15	Ph_2CHCH_2	$PhCH_2OCH_2CH_2$	66	97	27
16	Ph_2CHCH_2	Histidyl	—	96	68
17	3-I-$PhCH_2$	Cyclopentyl	66	91	56
18	3-I-$PhCH_2$	Tryptyl	69	98	31
19	3-I-$PhCH_2$	$PhCH_2OCH_2CH_2$	64	91	28
20	3-I-$PhCH_2$	Histidyl	—	98	61
21	Ph	Cyclopentyl	77	99	16
22	Ph	Tryptyl	72	95	24
23	Ph	$PhCH_2OCH_2CH_2$	76	94	20
24	Ph	Histidyl	97	99	33

[a] The IUPAC name for tryptyl is 2-(indol-3-yl)ethyl. [b] The IUPAC name for histidyl is 2-(imidazol-3-yl)ethyl.

9–**24** were purified using semi-preparative HPLC, furnishing the C2,N^6-disubstituted adenosine analogues in acceptable overall yields and high purity.

In conclusion, it was shown that resin bound 6-chloropurine ribonucleoside could be efficiently nitrated by the TBAN–TFAA mixture without affecting the polystyrene matrix. The resulting 2-nitro group on the purine ring not only activates the C6 position towards nucleophilic attack, but can also be easily substituted by nucleophiles. The solid phase sequence we developed opens the way to generate larger combinatorial libraries of disubstituted adenosine analogues. Biological evaluation of the synthesised adenosine analogues will be reported in due course. Further synthetic efforts addressing substitution reactions of the nitro purine system are currently underway.

Experimental

General

All reagents and solvents were used as commercially available, unless indicated otherwise. Peptide grade solvents were used for solid phase chemistry. Carboxypolystyrene (0.88 mmol g^{-1}) was purchased from Rapp Polymere, Tübingen, Germany. Flash chromatography refers to purification using the indicated eluents and Acros silica gel 60 (0.030–0.075 mm). Mps were measured with a Leitz melting point microscope and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR, attached proton test (APT)) spectra were determined in d_6-DMSO at 300 K using a Bruker ARX 400 (400 MHz) spectrometer, unless indicated otherwise. NH and OH signals were identified after mixing the sample with a drop of D_2O. 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 10000 (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% to 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 one of the following elution gradients: *method A*, linear gradient of 5% to 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}; *method B*, linear gradient of 5% to 95% aqueous CH_3CN over 15 min, then 95% aqueous CH_3CN for 6 min at 7.0 mL min^{-1}. Products were detected at $\lambda = 254$ nm.

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

2-*n*-Butylamino-N^6-*n*-butyladenosine 2

A solution of 2-nitro-6-chloro-9-(2,3,5-triacetyl-β-D-ribofuranosyl)-9*H*-purine (75 mg, 0.16 mmol) in *n*-butylamine (2 mL) was stirred under a nitrogen atmosphere for 16 h. The solution was evaporated to dryness and the residue was subjected to flash chromatography (EtOAc with 5 ⟶ 15% MeOH). Drying *in vacuo* at 55 °C for 16 h and trituration with Et_2O furnished **2** (55 mg, 88%) as a white solid, mp 141–142 °C. ^{1}H-NMR ($CDCl_3$) δ 7.88 (1H, s, 8-H), 7.29 (1H, br s, N^6-H), 6.19 (1H, br s, 2-NH), 5.73 (1H, d, *J* 6.1, 1′-H), 5.35 (1H, d, *J* 6.1, OH), 5.18 (1H, br s, OH), 5.10 (1H, d, *J* 4.6, OH), 4.60 (1H, m, 2′-H), 4.13 (2H, dd, *J* 8.1 and 4.6, 3′-H), 3.90 (1H, dd, *J* 7.2 and 3.7, 4′-H), 3.63 (1H, m, 5′-H^a), 3.52 (1H, m, 5′-H^b), 3.42 (2H, m, NCH_2), 3.24 (2H, m, NCH_2), 1.55 (4H, m, butyl), 1.34 (4H, m, butyl), 0.91 (6H, t, *J* 7.3, butyl); *m*/*z* 395.2415 (M^+ + H, $C_{18}H_{31}N_6O_4$ requires 395.2407).

6-Chloro-9-[2,3-bis-(*O*-*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-9*H*-purine 3b

To a stirred solution of 6-chloro-9-[2,3,5-tris-(*O*-*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-9*H*-purine[12] (3.75 g) in THF (75 mL) was added aqueous TFA (38 mL, TFA–H_2O, 1 : 1) at 0 °C. After stirring for 4.5 h at 0 °C, the reaction mixture was neutralised with saturated aqueous $NaHCO_3$ and diluted with ethyl acetate (200 mL). After separation, the organic phase was washed with H_2O and brine, dried over anhydrous Na_2SO_4 and evaporated at reduced pressure. The residue was subjected to flash chromatography (light petroleum–EtOAc, 1 : 1) to provide 2.98 g (96%) of **3b** as a white solid, mp 156–157 °C. The product was recrystallised from light petroleum–EtOAc prior to coupling to the resin. ^{1}H-NMR ($CDCl_3$) δ 8.78 (1H, s, 2-H), 8.19 (1H, s, 8-H), 5.88 (1H, d, *J* 7.8, 1′-H), 5.52 (1H, d, *J* 9.7, OH), 5.52 (1H, dd, *J* 7.8 and 4.6, 2′-H), 4.34 (1H, d, *J* 4.6, 3′-H), 4.19 (1H, m, 4′-H), 3.94 (1H, d, *J* 13.0, 5′-H^a), 3.73 (1H, dd, *J* 13.0 and 9.7, 5′-H^b), 0.95 and 0.74 (18H, 2 × s, 2 × *t*-Bu), 0.13, 0.12, −0.13, −0.65 (all 3H, s, $SiCH_3$).

General procedure for the coupling of 2′,3′-diol protected 6-chloropurine ribonucleosides 3a–c to carboxypolystyrene

To a suspension of carboxypolystyrene (1.0 g, 0.88 mmol) in 10 mL of DCM was added the 2′,3′-diol protected 6-chloropurine ribonucleoside **3** (1.78 mmol), DIPCDI (0.28 mL, 1.78 mmol) and DMAP (43 mg, 0.35 mmol). The reaction was monitored with a malachite green test.[21] After 16 h the reaction was complete and resin **4** was washed with DCM (6×), MeOH, DCM, MeOH, Et_2O, DCM, Et_2O, DCM and dried *in vacuo* at 50 °C.

General procedure for the nitration of resins 4a–c

A 0.15 M nitrating mixture was prepared at 0 °C by adding TFAA (0.54 mL, 2.55 mmol) to a solution of tetrabutylammonium nitrate (TBAN, 0.77 g, 3 mmol) in dry DCM (17 mL) over a period of *ca*. 2 min. After stirring for 10 min this solution was added *via* syringe to resin **4** (0.88 mmol). After 2.5 h resin **5** was washed with DCM (6×), MeOH, DCM, MeOH, Et_2O, DCM, Et_2O, DCM and dried *in vacuo* at 50 °C.

General procedure for the amination of resins 5a–c

To a suspension of resin **5** (0.54 mmol) in DCM (8 mL) was added DIPEA (0.73 mL, 4.32 mmol) and cyclopentylamine (0.32 mL, 3.24 mmol). After 4 h resin **6** was washed with DCM (6×), MeOH, DCM, MeOH, Et_2O, DCM, Et_2O and DCM and dried *in vacuo* at 50 °C.

General procedure for the amination of resins 6a–c

To a suspension of resin **6** (0.10 mmol) in NMP (1.5 mL) was added DIPEA (0.14 mL, 0.8 mmol) and cyclopentylamine (60 μL, 0.6 mmol). After heating at 80–90 °C for 24 h resin **7** was washed with NMP (3×), DCM (3×), MeOH, DCM, MeOH, Et_2O, DCM, Et_2O and DCM.

General procedure for the removal of the 2′,3′-methoxymethylidene group from resin 7c

Resin **7c** (0.10 mmol) was washed twice with a solution of *p*-TsOH·H_2O (18 mg mL^{-1}) in DCM–MeOH (97 : 3). After subjection to this solution for 16 h resin **8** was washed with DCM–MeOH (97 : 3, 3×), DCM–DIPEA (90 : 10, 3×), DCM (3×), MeOH, DCM, MeOH, Et_2O, DCM, Et_2O and DCM.

General procedure for cleavage of the C2,N^6-disubstituted adenosine analogues from resin 8

To a suspension of resin **8** (0.10 mmol) in THF (1.5 mL) was added a solution of 5.24 M NaOMe in MeOH (76 μL, 0.40 mmol). After 1 h the resin was washed with THF (2×), MeOH, THF, MeOH, THF and MeOH. The washings were passed over a solid phase extraction (SPE) column (Supelco, packed with 1 g silica) and analysed using HPLC. The products **12**, **16**, **20** and **24** were purified *via* semi-preparative HPLC using method A. All other products were purified using method B. The products were isolated by lyophilisation furnishing the C2,N^6-disubstituted adenosine analogues **9**–**24**.

2-Cyclopentylamino-N^6-cyclopentyladenosine 9. ^{1}H-NMR δ 7.89 (1H, s, 8-H), 7.10 (1H, br s, N^6-H), 6.12 (1H, br s, 2-NH), 5.73 (1H, d, *J* 6.0, 1′-H), 5.36 (1H, d, *J* 4.7, OH), 5.12 (2H, m, 2 × OH), 4.59 (1H, br, 2′-H), 4.49 (1H, br, NCH), 4.15 (2H, m, NCH and 3′-H), 3.89 (1H, dd, *J* 7.5 and 3.9, 4′-H), 3.63 (1H, m, 5′-H^a), 3.53 (1H, m, 5′-H^b), 1.92 (4H, m, cyclopentyl), 1.66 (4H, m, cyclopentyl), 1.49 (8H, m, cyclopentyl); *m*/*z* 419.2416 (M^+ + H, $C_{20}H_{31}N_6O_4$ requires 419.2407).

2-[2-(Indol-3-yl)ethylamino]-N^6-cyclopentyladenosine 10. ^{1}H-NMR δ 10.80 (1H, s, indole NH), 7.92 (1H, s, 8-H), 7.62 (1H, d, *J* 7.8, indole 4-H), 7.35 (1H, d, *J* 7.9, indole 7-H), 7.18 (2H, br, N^6-H and indole 2-H), 7.08 (1H, t, *J* 7.9, indole 6-H), 7.00 (1H, t, *J* 7.8, indole 5-H), 6.28 (1H, br s, 2-NH), 5.79 (1H, d, *J* 6.0, 1′-H), 5.38 (1H, d, *J* 5.9, OH), 5.23 (1H, br s, OH), 5.12 (1H, d, *J* 4.4, OH), 4.61 (1H, m, 2′-H), 4.53 (1H, br, NCH), 4.15 (1H, m, 3′-H), 3.93 (1H, dd, *J* 6.9 and 3.5, 4′-H), 3.64 (1H, m, 5′-H^a), 3.42 (3H, m, 5′-H^b and NCH_2CH_2), 2.97 (2H, t,

J 7.5, NCH_2CH_2), 1.94 (2H, m, cyclopentyl), 1.69 (2H, m, cyclopentyl), 1.56 (4H, m, cyclopentyl); *m/z* 494.2489 (M^+ + H, $C_{25}H_{32}N_7O_4$ requires 494.2516).

2-(2-Benzyloxyethylamino)-*N*^{6}-cyclopentyladenosine 11. ^{1}H-NMR δ 7.91 (1H, s, 8-H), 7.35 (4H, m, Ar-H), 7.29 (1H, m, Ar-H), 7.21 (1H, br s, N^6-H), 6.17 (1H, br s, 2-NH), 5.74 (1H, d, *J* 6.1, 1′-H), 5.36 (1H, d, *J* 5.9, OH), 5.23 (1H, br s, OH), 5.13 (1H, d, *J* 4.3, OH), 4.59 (1H, m, 2′-H), 4.52 (2H, s, $PhCH_2$), 4.45 (1H, br, NCH), 4.13 (1H, m, 3′-H), 3.91 (1H, m, 4′-H), 3.57 (6H, m, 5′-H, NCH_2CH_2, NCH_2CH_2), 1.94 (2H, m, cyclopentyl), 1.64 (2H, m, cyclopentyl), 1.53 (4H, m, cyclopentyl); *m/z* 485.2507 (M^+ + H, $C_{24}H_{33}N_6O_5$ requires 485.2512).

2-[2-(Imidazol-3-yl)ethylamino]-*N*^{6}-cyclopentyladenosine 12. ^{1}H-NMR δ 8.21 (1H, br s, Im-2-H), 7.90 (1H, s, 8-H), 7.59 (1H, br s, Im-NH), 7.15 (1H, br s, N^6-H), 6.86 (1H, br s, Im-4-H), 6.31 (1H, br s, 2-NH), 5.74 (1H, d, *J* 5.6, 1′-H), 4.63 (1H, m, 2′-H), 4.48 (1H, br, NCH), 4.25 (1H, m, 3′-H), 3.91 (1H, dd, *J* 7.8 and 3.9, 4′-H), 3.65 (1H, m, 5′-H^a), 3.51 (3H, m, 5′-H^b and NCH_2CH_2), 2.73 (2H, m, NCH_2CH_2), 1.92 (2H, m, cyclopentyl), 1.66 (2H, m, cyclopentyl), 1.52 (4H, m, cyclopentyl); *m/z* 445.2299 (M^+ + H, $C_{20}H_{29}N_8O_4$ requires 445.2312).

2-Cyclopentylamino-*N*^{6}-(2,2-diphenylethyl)adenosine 13. ^{1}H-NMR δ 7.84 (1H, s, 8-H), 7.31 (8H, m, Ar-H), 7.19 (3H, m, Ar-H and N^6-H), 6.28 (1H, br s, 2-NH), 5.71 (1H, d, *J* 5.2, 1′-H), 5.36 (1H, br s, OH), 5.11 (2H, br s, 2 × OH), 4.62 (1H, m, 2′-H), 4.55 (1H, m, Ph_2CH), 4.22 (1H, br, NCH), 4.12 (1H, m, 3′-H), 4.03 (2H, m, Ph_2CHCH_2), 3.88 (1H, m, 4′-H), 3.64 (1H, m, 5′-H^a), 3.51 (1H, m, 5′-H^b), 1.93 (2H, m, cyclopentyl), 1.69 (2H, m, cyclopentyl), 1.51 (4H, m, cyclopentyl); *m/z* 531.2723 (M^+ + H, $C_{29}H_{35}N_6O_4$ requires 531.2720).

2-[2-(Indol-3-yl)ethylamino]-*N*^{6}-(2,2-diphenylethyl)adenosine 14. ^{1}H-NMR δ 10.82 (1H, s, indole NH), 7.89 (1H, s, 8-H), 7.63 (1H, d, *J* 7.5, indole 4-H), 7.36 (1H, d, *J* 8.0, indole 7-H), 7.23 (12H, m, Ar-H, N^6-H and indole 2-H), 7.08 (1H, m, indole 6-H), 6.98 (1H, m, indole 5-H), 6.49 (1H, br s, 2-NH), 5.77 (1H, m, 1′-H), 4.59 (2H, m, 2′-H and Ph_2CH), 4.13 (1H, m, 3′-H), 4.03 (3H, m, 4′-H and Ph_2CHCH_2), 3.49 (4H, m, 5′-H and NCH_2CH_2), 2.98 (2H, m, NCH_2CH_2); *m/z* 606.2822 (M^+ + H, $C_{34}H_{36}N_7O_4$ requires 606.2829).

2-(2-Benzyloxyethylamino)-*N*^{6}-(2,2-diphenylethyl)adenosine 15. ^{1}H-NMR δ 7.86 (1H, s, 8-H), 7.36–7.26 (14H, m, Ar-H and N^6-H), 7.19 (2H, m, Ar-H), 6.35 (1H, br s, 2-NH), 5.72 (1H, d, *J* 5.6, 1′-H), 5.35 (1H, d, *J* 6.0, OH), 5.22 (1H, br s, OH), 5.12 (1H, d, *J* 4.4, OH), 4.61 (1H, m, 2′-H), 4.56 (1H, m, Ph_2CH), 4.53 (1H, s, $PhCH_2$), 4.12 (1H, m, 3′-H), 4.03 (2H, m, Ph_2CHCH_2), 3.88 (1H, m, 4′-H), 3.58 (6H, m, 5′-H, NCH_2CH_2, NCH_2CH_2); *m/z* 597.2846 (M^+ + H, $C_{33}H_{37}N_6O_5$ requires 597.2825).

2-[2-(Imidazol-3-yl)ethylamino]-*N*^{6}-(2,2-diphenylethyl)adenosine 16. ^{1}H-NMR δ 8.18 (1H, br s, Im-2-H), 7.85 (1H, s, 8-H), 7.62 (1H, br s, Im-NH), 7.29 (9H, m, Ar-H and N^6-H), 7.19 (2H, m, Ar-H), 6.85 (1H, br s, Im-4-H), 6.48 (1H, br s, 2-NH), 5.72 (1H, d, *J* 5.0, 1′-H), 4.61 (2H, m, 2′-H and Ph_2CH), 4.23 (1H, m, 3′-H), 4.03 (2H, m, Ph_2CHCH_2), 3.90 (1H, m, 4′-H), 3.58 (4H, m, 5′-H and NCH_2CH_2), 2.85 (2H, m, NCH_2CH_2); *m/z* 557.2641 (M^+ + H. $C_{29}H_{33}N_8O_4$ requires 557.2625).

2-Cyclopentylamino-*N*^{6}-(3-iodobenzyl)adenosine 17. ^{1}H-NMR δ 7.97 (1H, br s, N^6-H) 7.94 (1H, s, 8-H), 7.74 (1H, s, Ph 2-H), 7.59 (1H, d, *J* 7.7, Ph 4-H), 7.37 (1H, d, *J* 7.7, Ph 6-H), 7.12 (1H, t, *J* 7.7, Ph 5-H), 6.21 (1H, br s, 2-NH), 5.74 (1H, d, *J* 6.0, 1′-H), 5.36 (1H, d, *J* 6.0, OH), 5.11 (2H, m, 2 × OH), 4.57 (3H, m, 2′-H and N^6-CH_2), 4.12 (2H, m, 3′-H and NCH), 3.89 (1H, dd, *J* 7.5 and 3.9, 4′-H), 3.65 (1H, m, 5′-H^a), 3.54 (1H, m, 5′-H^b), 1.84 (2H, m, cyclopentyl), 1.64 (2H, m, cyclopentyl), 1.45 (4H, m, cyclopentyl); *m/z* 567.1216 (M^+ + H, $C_{22}H_{28}N_6O_4I$ requires 567.1217).

2-[2-(Indol-3-yl)ethylamino]-*N*^{6}-(3-iodobenzyl)adenosine 18. ^{1}H-NMR δ 10.79 (1H, s, indole NH), 8.01 (1H, br s, N^6-H), 7.96 (1H, s, 8-H), 7.75 (1H, s, Ph 2-H), 7.57 (2H, m, indole 4-H and Ph 4-H), 7.36 (2H, m, indole 7-H and Ph 6-H), 7.09 (3H, m, indole 2-H, indole 6-H and Ph 5-H), 6.98 (1H, m, indole 5-H), 6.36 (1H, br s, 2-NH), 5.79 (1H, d, *J* 5.6, 1′-H), 5.39 (1H, d, *J* 6.1, OH), 5.19 (1H, br s, OH), 5.12 (1H, d, *J* 4.7, OH), 4.62 (3H, m, 2′-H and N^6-CH_2), 4.15 (1H, m, 3′-H), 3.92 (1H, dd, *J* 7.3 and 3.8, 4′-H), 3.65 (1H, m, 5′-H^a), 3.52 (3H, m, 5′-H^b and NCH_2CH_2), 2.93 (2H, t, *J* 7.4, NCH_2CH_2); *m/z* 642.1337 (M^+ + H, $C_{27}H_{29}N_7O_4I$ requires 642.1326).

2-(2-Benzyloxyethylamino)-*N*^{6}-(3-iodobenzyl)adenosine 19. ^{1}H-NMR δ 8.01 (1H, br s, N^6-H), 7.95 (1H, s, 8-H), 7.73 (1H, s, Ph 2-H), 7.58 (1H, d, *J* 7.9, Ph 4-H), 7.32 (6H, m, $C_6H_5CH_2O$ and Ph 6-H), 7.10 (1H, t, *J* 7.9, Ph 5-H), 6.26 (1H, br s, 2-NH), 5.74 (1H, d, *J* 5.9, 1′-H), 5.37 (1H, d, *J* 5.8, OH), 5.22 (1H, br s, OH), 5.13 (1H, d, *J* 4.4, OH), 4.54 (3H, m, 2′-H and N^6-CH_2), 4.46 (2H, s, $PhCH_2$), 4.13 (1H, m, 3′-H), 3.91 (1H, m, 4′-H), 3.65 (1H, m, 5′-H^a), 3.52 (5H, m, 5′-H^b, NCH_2CH_2, NCH_2CH_2); *m/z* 633.1298 (M^+ + H, $C_{26}H_{30}N_6O_5I$ requires 633.1322).

2-[2-(Imidazol-3-yl)ethylamino]-*N*^{6}-(3-iodobenzyl)adenosine 20. ^{1}H-NMR δ 8.17 (1H, br s, Im-2-H), 7.99 (1H, br s, N^6-H), 7.94 (1H, s, 8-H), 7.75 (1H, s, Ph 2-H), 7.58 (2H, m, Ph 4-H and Im-NH), 7.38 (1H, d, *J* 7.7, Ph 6-H), 7.10 (1H, t, *J* 7.7, Ph 5-H), 6.81 (1H, br s, Im-4-H), 6.40 (1H, br s, 2-NH), 5.75 (1H, d, *J* 5.6, 1′-H), 5.02 (3H, br, 3 × OH), 4.62 (3H, m, 2′-H and N^6-CH_2), 4.24 (1H, m, 3′-H), 3.90 (1H, m, 4′-H), 3.67 (1H, m, 5′-H^a), 3.51 (3H, m, 5′-H^b, NCH_2CH_2), 2.73 (2H, m, NCH_2CH_2); *m/z* 593.1116 (M^+ + H, $C_{22}H_{26}N_8O_4I$ requires 593.1122).

2-Cyclopentylamino-*N*^{6}-phenyladenosine 21. ^{1}H-NMR δ 9.51 (1H, br s, N^6-H), 8.07 (1H, s, 8-H), 8.05 (2H, d, *J* 7.7, Ph 2-H), 7.29 (2H, t, *J* 7.7, Ph 2-H), 6.99 (1H, t, *J* 7.7, Ph 4-H), 6.61 (1H, br s, 2-NH), 5.80 (1H, d, *J* 6.0, 1′-H), 5.41 (1H, d, *J* 6.1, OH), 5.15 (1H, d, *J* 4.7, OH), 5.05 (1H, br s, OH), 4.64 (1H, m, 2′-H), 4.18 (2H, m, 3′-H and NCH), 3.91 (1H, dd, *J* 7.8 and 4.2, 4′-H), 3.67 (1H, m, 5′-H^a), 3.56 (1H, m, 5′-H^b), 1.94 (2H, m, cyclopentyl), 1.70 (2H, m, cyclopentyl), 1.53 (4H, m, cyclopentyl); *m/z* 427.2117 (M^+ + H, $C_{21}H_{27}N_6O_4$ requires 427.2094).

2-[2-(Indol-3-yl)ethylamino]-*N*^{6}-phenyladenosine 22. ^{1}H-NMR δ 10.82 (1H, s, indole NH), 9.46 (1H, br s, N^6-H), 8.10 (1H, s, 8-H), 8.03 (2H, d, *J* 7.7, Ph 2-H), 7.63–7.59 (1H, m, indole 4-H), 7.35 (1H, d, *J* 8.1, indole 7-H), 7.25 (2H, t, *J* 7.7, Ph 3-H), 7.20 (1H, s, indole 2-H), 7.08 (1H, m, indole 6-H), 6.99 (2H, m, indole 5-H and Ph 4-H), 6.74 (1H, br s, 2-NH), 5.85 (1H, d, *J* 4.9, 1′-H), 5.43 (1H, d, *J* 6.0, OH), 5.15 (1H, d, *J* 4.7, OH), 5.11 (1H, m, OH), 4.64 (1H, m, 2′-H), 4.18 (1H, m, 3′-H), 3.95 (1H, dd, *J* 7.5 and 4.0, 4′-H), 3.60 (4H, m, 5′-H and NCH_2CH_2), 2.93 (2H, t, *J* 7.6, NCH_2CH_2); *m/z* 502.2236 (M^+ + H, $C_{26}H_{28}N_7O_4$ requires 502.2203).

2-(2-Benzyloxyethylamino)-*N*^{6}-phenyladenosine 23. ^{1}H-NMR δ 9.47 (1H, br s, N^6-H), 8.09 (1H, s, 8-H), 8.01 (2H, d, *J* 8.0, Ph 2-H), 7.30 (7H, m, $C_6H_5CH_2O$ and Ph 3-H), 6.99 (1H, t, *J* 7.3, Ph 4-H), 6.65 (1H, br s, 2-NH), 5.81 (1H, d, *J* 6.0, 1′-H), 5.41 (1H, d, *J* 6.0, OH), 5.16 (1H, d, *J* 4.8, OH), 5.12 (1H, br s, OH), 4.63 (1H, m, 2′-H), 4.53 (2H, s, $PhCH_2$), 4.16 (1H, m, 3′-H), 3.93 (1H, m, 4′-H), 3.59 (6H, m, 5′-H, NCH_2CH_2,

NCH_2CH_2); *m*/*z* 493.2209 (M^+ + H, $C_{25}H_{29}N_6O_5$ requires 493.2199).

2-[2-(Imidazol-3-yl)ethylamino]-*N*^{6}-phenyladenosine 24. ^{1}H-NMR δ 9.45 (1H, br s, N^6-H), 8.20 (1H, br s, Im-NH), 8.08 (1H, s, 8-H), 8.03 (2H, d, *J* 7.6, Ph 2-H), 7.59 (1H, s, Im-2-H), 7.28 (2H, t, *J* 7.6, Ph 3-H), 6.99 (1H, t, *J* 7.6, Ph 4-H), 6.86 (1H, s, Im-4-H), 6.77 (1H, br s, 2-NH), 5.81 (1H, d, *J* 5.7, 1′-H), 5.22 (3H, band, 3 × OH), 4.64 (1H, m, 2′-H), 4.27 (1H, m, 3′-H), 3.93 (1H, m, 4′-H), 3.67 (1H, m, 5′-H^a), 3.51 (3H, m, 5′-H^b, NCH_2CH_2), 2.81 (2H, m, NCH_2CH_2); *m*/*z* 453.2011 (M^+ + H, $C_{21}H_{25}N_8O_4$ requires 453.1999).

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