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# 2′-Amino-2′-deoxy-$N^6$-(1-naphthylmethyl)adenosine as Novel Scaffold for a Polymer-Assisted Amidation Protocol

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**Abstract**—The synthesis of a novel scaffold for the simple and high-yielding polymer-assisted solution phase preparation of arrays of 2′-amido-2′-deoxy-$N^6$-(1-naphthylmethyl)adenosine derivatives **10a–h** as analogues of a known inhibitor of trypanosomatid glycosomal glyceraldehyde-3-phosphate dehydrogenase is described. 

## Introduction

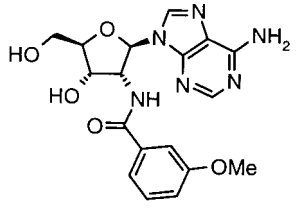
Enzymes, that are dependent on binding nucleoside derivatives to attain activity, represent attractive targets for rational drug design. Inhibitors of such enzymes can be generated by targeting the binding sites of these obligatory ligands rather than the actual active site. Thus, anti-trypanosomal drugs can be developed by inhibiting co-factor-dependent enzymes such as the glycosomal glyceraldehyde-3-phosphate dehydrogenase (GAPDH), which is prone to cause inhibition of the glycolytic flux in these parasites.[1]

## Results

The search for inhibitors of trypanosomatid GAPDH started from the assumption that adenosine derivatives should occupy the non-functional adenosine part of the $NAD^+$-binding site. This had led to the discovery of 2′-deoxy-2′-(3-methoxybenzamido)adenosine (**1**) (Fig. 1) as a lead structure by Van Calenbergh et al.[2]

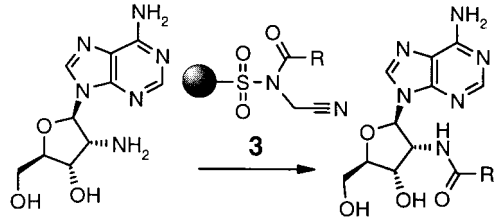
The 2′-amido substituent in **1** was designed to fill a so-called selectivity cleft that represents one of the major structural dissimilarities between the mammalian enzyme and the parasite homologue, as could be shown by Verlinde et al.[3] In order to access arrays of analogues of this lead, we designed a solid-phase-assisted synthesis for the selective acylation of the 2′-amino group of 2′-amino-2′-deoxyadenosine (**2**) by coupling carboxylic acids to the Kenner safety-catch linker.[4] After cyanomethylation, the polymer-bound activated carboxylic acids **3** could readily be transformed to target compounds **4** by addition of **2** in an appropriate solvent (Scheme 1).

Recently, Aronov et al. were successful in identifying inhibitors of glycosomal GAPDH with highly improved activity by introducing additional lipophilic substituents to the $N^6$-amino group of our original lead structure **1**, 1-naphthylmethyl being the most interesting group.[5] These findings resulted from exploration of the structural requirements of the adenosine part of the $NAD^+$-pocket by computational as well as synthetic methodologies.[6] In order to prove the versatility of the polymer-assisted




**1**

**Figure 1.**




**2** **4**

**Scheme 1.** Polymer-assisted amidation of the 2′-amino group in 2′-amino-2′-deoxyadenosine.

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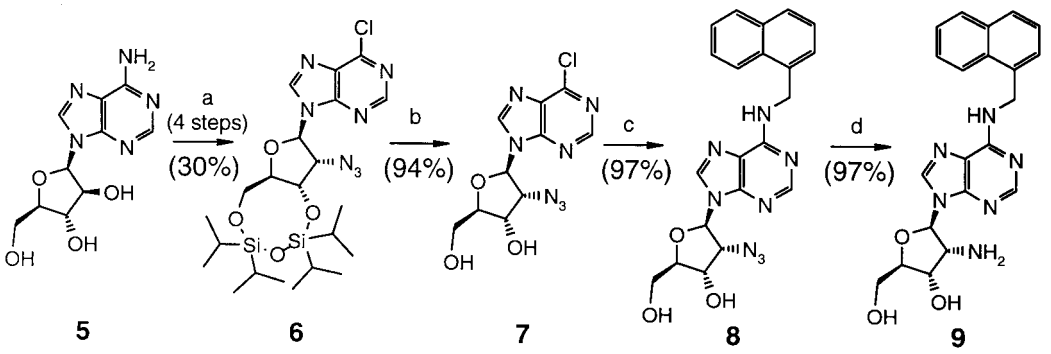
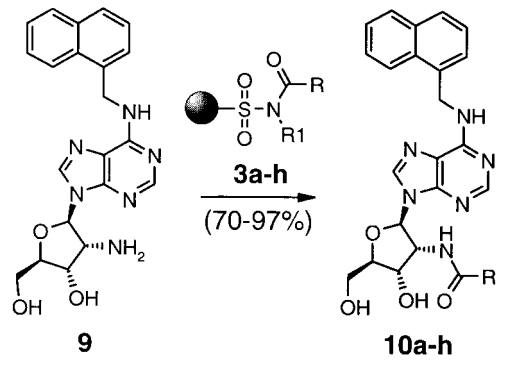



**Scheme 2.** Synthetic sequence leading to 2′-amino-2′-deoxy-$N^6$-(1-naphthylmethyl)adenosine from vidarabine. (a) i. TIPDSCl, pyridine; ii. TfCl, DMAP, $CH_2Cl_2$; iii. $NaN_3$, DMF; iv. $CCl_4$, isoamyl nitrite, 60°C. (b) TBAF, THF, 50°C, 5 h. (c) 1-Naphthylmethylamine, 1-propanol, 50°C, 16 h. (d) In/$NH_4Cl$, EtOH, $\Delta T$. Yields for isolated compounds.

protocol described above, we synthesized 2′-amino-2′-deoxy-$N^6$-(1-naphthylmethyl)adenosine (**9**) as a core building block and applied this technique to access another series of 2′-amido-2′-deoxyadenosine derivatives.

The synthesis of **9** started from the antiviral drug vidarabine (**5**). Vidarabine (**5**) was simultaneously protected at the 3′- and 5′-OH-functions using the Markiewicz reagent. Acylation at the 2′-hydroxyl group with triflic chloride and nucleophilic displacement with sodium azide was carried out following modified procedures originally presented by Robins and co-workers and Walcher and Pfleiderer.[7,8] Subsequent exchange of the 6-amino group for chlorine yielded compound **6**. Deprotection with TBAF and quantitative aminolysis using (1-naphtylmethyl)amine furnished compound **8**. A commonly used practice to afford reduction of this type of modified nucleoside is Pd-catalyzed hydrogenation, even though this reaction is reported to proceed slowly and incomplete, e.g. for 2′-azido-2′-deoxy-$N^6$-dimethyladenosine.[9] Considering the possible loss of the benzylic $N^6$-substituent, attempts to reduce the azido-function by this route were not undertaken. Instead, the recently introduced reagent couple indium/$NH_4Cl$ in ethanol was selected.[10] As anticipated, it led to a smooth and practically quantitative conversion of **8** to the desired novel scaffold **9** in an isolated yield of 97% without detectable loss of the $N^6$-(1-naphthylmethyl) group (Scheme 2).

Reaction of the title compound **9** with the polymer-supported activated carboxylic acids was performed with the purpose to evaluate the effectiveness of the reaction and to demonstrate the option to synthesize derivatives with structurally diverse residues on the 2′-amido substituent (Scheme 3).




**Scheme 3.** Synthesis of model analogues **10a**–**h** of lead structure **1**.

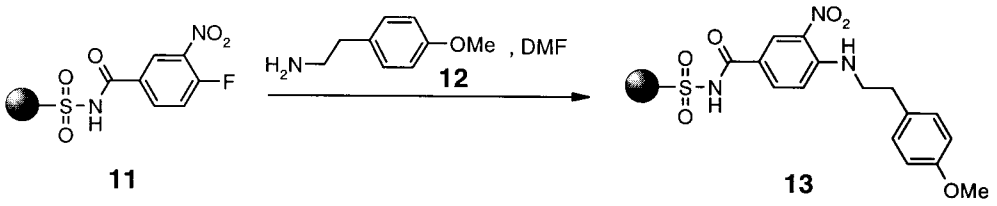
With the intention of widening the scope of the synthetic protocol, 4-fluoro-3-nitro-benzoic acid was attached to the sulfamoyl linker **11** and converted to the corresponding aniline derivative **13** by treatment with an excess amine (Scheme 4).

Similar transformations with different amines were already performed successfully and will be reported in the near future.

## Discussion

In contrary to polymer-assisted solution phase (PASP) chemistry,[11] where only unchanged reagents are transferred to building blocks originating from solution-phase chemistry, diversity is achieved by on-bead modification of the attached residues. For this convergent assembly of 'solid-phase' modified and solution-phase building blocks we suggest the term convergent polymer-assisted solution phase (cPASP) amidation. This protocol represents a considerable advantage over strategies to access amide libraries by PASP synthesis making use of the catch-and-release linkers reported so far. Kim and Le recently described efficient *N*-acylation methods mediated by activated esters of polymer-supported 4-hydroxy-3-nitrobenzophenone, Masala and Taddei introduced a 2,4,6-trichloro[1,3,5]triazine based linker intended for the synthesis of amide libraries.[12,13] Using these PASP strategies, treatment with nucleophiles should afford amides without the option to selectively modify residues such as 4-fluoro-3-nitro-benzoic acid by aminolysis and therefore the desirable possibility of intermediate nucleophilic substitution of polymer-bound residues as a source for diversity in drug discovery is excluded.[14]

Alkylation with bromoacetonitrile or iodoacetonitrile as an activation step for the polymer-bound acid derivatives is known to give poor results for aromatic residues adjacent to the sulfamoyl attachment site.[15,16] Therefore, we employed the commercially available trimethylsilyldiazomethane as an activation reagent for the preparation of




**Scheme 4.** Formation of aniline derivative **13** from fluoro-analogue **11** on polymer support.

**Table 1.** Residues of polymer-supported compounds **3a–h** and target compounds **10a–h** with isolated yields of **10a–h**

| Entry | R1 (in **3**) | R (in **3** or **10**) | Yield[a] (%) | Purity[b] (%) |
|---|---|---|---|---|
| **a** | $CH_3$ | 3,5-difluorophenyl | 95 | 88 |
| **b** | $CH_3$ | 3-fluoro-4-methylphenyl | 91 | 86 |
| **c** | $CH_3$ | 4-[2-(4-methoxyphenyl)ethyl]amino-3-nitrophenyl | 70 | 85 |
| **d** | $CH_2CN$ | (3-thienyl)methyl | 96 | 95 |
| **e** | $CH_2CN$ | 2-(3-indolyl)ethyl | 97 | 98 |
| **f** | $CH_2CN$ | 3-(3-indolyl)propyl | 96 | 98 |
| **g** | $CH_2CN$ | 3-(3,5-dichlorophenoxy)propyl | 93 | 97 |
| **h** | $CH_2CN$ | 3-oxo-3-[(4-phenyl)phenyl]propyl | 95 | 92 |

[a] Isolated yields.
[b] Semi-preparative MPLC, 100% method, detection at 254 nm.

**10a–c**. Apparently, the resulting activation is less effective as compared to the electron withdrawing variant. This outcome is in accordance with theoretical considerations, but the yields of compounds **10a–c** are acceptable (Table 1). Alkylation of the aniline–nitrogen in **13** was not observed.

## Conclusion

In summary, we accomplished the synthesis of 2′-amino-2′-deoxy-$N^6$-(1-naphthylmethyl)adenosine (**9**) and demonstrated the versatility of a modification scheme for fast and optionally convergent polymer-assisted production of arrays of amido derivatives of **9** in solution.

## Experimental

Identity of all compounds was assigned by NMR spectroscopy. Sample purity was deduced from $^1$H NMR data as well as evaluated by MPLC. The purity of final products **10a–h** is reported as purity of crude products prior to purification (percentage of target compound contained in residue from evaporated reaction mixture). The yields for **10a–h** are reported as isolated material obtained by evaporation of purified product containing fractions. $^1$H NMR spectra were recorded on a Bruker AMX 400 spectrometer, using tetramethylsilane or hexamethyldisiloxane as an internal standard. MPLC simultaneous purity analyses/purifications were performed using a Büchi 681 pump (flow rate 10 mL, MeOH/$H_2O$ 70:30), 684 fraction collector, and UV-detector (254 nm) with Merck 310-25 Lobar-LiChroprep™-RP-18 column. Preparative column chromatography was performed using glass columns with varying dimensions given below on silica gel 100–200 active, 60 A, from ICN. TLC was performed on Macherey–Nagel Polygram™ Sil G/$UV_{254}$ precoated microplates, spots were visualized under UV-illumination. MS data (FAB) were obtained on a Finnigan MAT 311A instrument with *m*-nitrobenzylic alcohol as matrix. Infrared spectra of resin samples were recorded using KBr pellets on a Perkin–Elmer 1660 FTIR spectrometer; elemental compositions were calculated on the basis of microanalysis results obtained on a Heraeus CHN–O rapid instrument. Solvents were purified according to standard procedures and freshly distilled prior to use.[17] Standard glassware was oven dried at 150°C and kept in a desiccator or treated with trimethylsilylchloride to exclude water traces when indicated.

**9-[3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxan-1,3-diyl)-β-D-arabinofuranosyl]adenine (5).** An amount of 5.53 g (20 mmol) vidarabine was suspended in absolute pyridine (70 mL) in a silylated and oven dried 100 mL flask, and repeatedly evaporated by vacuum to remove the crystal water of vidarabine. The dry vidarabine was resuspended in 70 mL absolute pyridine and cooled to −25°C. To this suspension was added 6.4 mL (20 mmol) 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane. After allowing the slurry to warm to room temperature and stirring for 18 h, the mixture was heated to 50°C and stirred for an additional 30 min. The clear solution was evaporated and the residue partitioned between EtOAc (200 mL) and $H_2O$ (100 mL). The organic layer was washed with 0.2 M HCl (100 mL), saturated $NaHCO_3$ solution (100 mL) and brine (100 mL), dried by means of $MgSO_4$ and evaporated. Purification by column chromatography (4×15 cm, dichloromethane) gave 9.40 g (92%) of colorless foam, Ref. 18 87%. $^1$H NMR (400 MHz, [$D_6$]-DMSO) δ (ppm)=8.11 (s, 1H, 8H), 8.04 (s, 1H, 2H), 7.29 (bs, 2H, $NH_2$), 6.21 (d, 1H, 1′H, *J*=6.61 Hz), 5.83 (bs, 1H, 2′OH), 4.62–4.56 (m, 1H, 2′H), 4.52–4.49 (m, 1H, 3′H), 4.15–4.07 (m, 1H, 5′H), 3.95–3.88 (m, 1H, 5′H), 3.82–3.75 (m, 1H, 4′H), 1.20–0.99 (m, 28H, TIPDS). Identical to those of the reported data.[19]

**2′-Azido-6-chloro-2′-deoxyadenosine (7).** Nitrogen was bubbled through a solution of 3.99 g (7.46 mmol)

2′-azido-2′-deoxy-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)adenosine[20] in 70 mL $CCl_4$. To this solution was added 3.0 mL isoamyl nitrite (22 mmol) and stirred at 60°C overnight (TLC, EtOAc). The solvent was subsequently removed under reduced pressure, the residue was dissolved in 50 mL THF and tetrabutylammonium fluoride (15 mL, 1 M in THF) was added. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the purification via column chromatography (4.5×15 cm) gave 1.31 g as pale yellow viscous mass (55.6% over both steps). $^1$H NMR (400 MHz, [$D_6$]-DMSO) $\delta$ (ppm)=8.95 (s, 1H, 8H), 8.84 (s, 1H, 2H), 6.16 (d, 1H, 1′H, *J*=5.09 Hz), 6.09 (d, 1H, 3′OH, *J*=5.09 Hz), 5.16 (t, 1H, 5′OH, *J*=4.58 Hz), 4.71 (m, 1H, 2′H), 4.61 (m, 1H, 3′H), 4.02 (m, 1H, 4′H), 3.71 (m, 1H, 5′H), 3.62 (m, 1H, 5′H); $^{13}$C NMR (101 MHz, [$D_6$]-DMSO) $\delta$ (ppm)=151.81, 145.40, 85.88, 70.45, 64.79, 60.27, 57.42.

**2′-Azido-2′-deoxy-$N^6$-(1-naphthylmethyl)adenosine (8).** An amount of 330 mg (1.06 mmol) **7** was dissolved in 20 mL 1-propanol. To this solution were added 200 mg (1.27 mmol) (1-naphthylmethyl)amine and 250 μL (1.50 mmol) Hünig's base. The reaction mixture was stirred at 50°C for 16 h. Evaporation of the solvent and purification via column chromatography (4.5×15 cm, *n*-hexane/EtOAc 1:1) gave 430 mg (97%) of a pale yellow foam. IR (KBr): 2112 $cm^{-1}$ ($N_3$). $^1$H NMR (400 MHz, [$D_6$]-DMSO) $\delta$ (ppm)=8.56 (bs, 1H, NH), 8.44 (s, 1H, 8H), 8.24 (s, 2H, overlapping 2H and $H_{aromat.}$), 7.99–7.41 (m, 6H, $H_{aromat.}$), 6.09 (d, 1H, 1′H, *J*=6.10 Hz), 6.06 (d, 1H, 3′OH, *J*=5.09 Hz), 5.27 (bs, 1H, 5′OH), 5.19 (bs, 2H, $CH_{2\ naphthyl}$), 4.46 (m, 1H, 2′H), 4.55 (m, 1H, 3′H), 4.00 (m, 1H, 4′H), 3.67–3.59 (m, 2H, 5′$H_2$); HRMS (FAB) calcd. 433.1738[M+1] found: 433.1738.

**2′-Amino-2′-deoxy-$N^6$-(1-naphthylmethyl)adenosine (9).** A solution of 350 mg (0.81 mmol) **8**, 93 mg (0.81 mmol) indium and ammonium chloride 45 mg (0.81 mmol) in 6 mL ethanol was refluxed for 3 h. The reaction was monitored by TLC (EtOAc). Evaporation of the solvent and purification over silica gel (1.5×15 cm, EtOAc) and Dowex™ 2×OH (4.5×15 cm, MeOH/$H_2O$ 70:30) sequentially gave 320 mg (97%) of the title compound. IR (KBr): 3289 $cm^{-1}$ ($NH_2$). $^1$H NMR (400 MHz, [$D_6$]-DMSO) $\delta$ (ppm)=8.52 (bs, 1H, $N^6$-H,) 8.25 (s, 1H, $H_{adenosine}$), 8.23 (s, 1H, $H_{aromat.}$), 8.21 (s, 1H, 2H), 7.96–7.42 (m, 6H, $H_{aromat.}$), 5.77 (d, 1H, 1′H, *J*=5.09 Hz), 5.66 (bs, 1H, 5′OH), 3.64–3.55 (m, 2H, 5′$H_2$), 4.10–4.00 (m, 3H, 4′H overlapping 3′H and 2′H), 5.19 (bs, 2H, $H_{2\ naphtylmethyl}$), 5.47 (bs,1H, 3′OH), 1.7 (bs, 2′$NH_2$, not clearly detectable due to peak width); HRMS (FAB) calcd. 407.1832 [M+1] found: 407.1853.

*General procedure A for the synthesis of the polymer supported acids **3a–h**:* To a flask containing 2.0 g of dry 4-sulfamylbenzoylaminomethyl polystyrene with an initial loading level of 1.24 mmol/g as determined by elemental analysis (prepared from very high load aminomethylated polystyrene, purchased from Novabiochem™, Switzerland) was added 20 mL of THF. The resin was allowed to swell at room temperature for 2 h. In another flask, 10 mmol of the appropriate acid was dissolved in 10–20 mL dry THF and preactivated via in situ anhydride formation by adding 780 μL (5 mmol) *N*,*N*-diisopropylcarbodiimide. CAUTION: may lead to severe allergic reactions, strictly avoid skin contact. After addition of 580 μL Hünig's base (3.4 mmol) and 15 mg (0.12 mmol) 4-(dimethylamino)-pyridine as catalyst, to the swollen resin, the coupling mixture was added. The resulting reaction mixture was agitated at room temperature for 24 h. The resin beads were filtered off and washed exhaustively with THF (2×5 mL), methanol (2×5 mL), and THF (2×5 mL). After careful drying the increase in weight and elemental composition were determined. The success of the reaction could be followed by IR spectroscopy, too: the acylation of the sulfonamide linker leads to a decrease of the intensity of the sulfonamide absorption at 3340 $cm^{-1}$ while a new carbonyl stretch at 1718 $cm^{-1}$ is formed. Activation method A1: 200 mg (approximately 0.2 mmol) of resin were subsequently swollen in THF and treated with 2.0 mL (trimethylsilyl)diazomethane 1 M solution in hexanes (2.0 mmol) purchased from Aldrich for 24 h and washed with THF (5 mL), methanol (3×5 mL), and THF (5 mL). Activation method A2: the sulfonamide linker of 200 mg (approximately 0.2 mmol) resin was activated for cleavage by alkylation with 260 μL (3.2 mmol) bromoacetonitrile (CAUTION: alkylating agent, strictly avoid skin contact), 290 μL (1.7 mmol) Hünig's base in 3 mL 1-methylpyrrolidone overnight and washed with dry dimethylsulfoxide (5×3 mL) and THF (5×5 mL).

*General procedure B for the synthesis of 2′-amido-2′-deoxy-$N^6$-(1-naphthylmethyl)adenosines* **10a–h***:* The polymer supported activated acids **3a–h** were transferred to the amino group of 4.06 mg (10 μmol) of 2′-amino-2′-deoxy-$N^6$-(1-naphthylmethyl)adenosine (**9**) by shaking at 55°C in 5 mL THF. The reaction was monitored by TLC and terminated when the starting material was quenched (6–24 h). Polymer beads and particulates were removed by filtration, the beads were washed exhaustively with dry THF and the combined THF fractions were evaporated. $^1$H NMR experiments of the crude material obtained as well as MPLC analyses revealed high purity of the compounds and the absence of impurities in detectable quantities other than traces of the starting material or acid hydrolyzed from the resin.

**2′-Deoxy-2′-(3,5-difluorobenzamido)-$N^6$-(1-naphthylmethyl)adenosine (10a).** Compound **10a** was prepared from resin **3a** synthesized by general procedure A, activation method A1. Following the general procedure B 5.2 mg (95%) white product was obtained. $^1$H NMR (400 MHz, [$D_6$]-DMSO) $\delta$ (ppm)=8.55 (bs, 1H, $N^6$-H), 8.46 (s, 1H, 8H), 8.27 (2s, 2H, $2H_{adenine}$ overlapping $H_{aromat.}$), 7.95 (d, 1H, 2′NH, *J*=7.16 Hz),), 7.82–6.66 (m, 10H, $H_{aromat.}$), 6.22 (s, 1H, 1′H), 5.64 (m, 1H, 5′OH), 5.55 (m, 1H, 3′OH), 5.20–5.18 (m, 3H, $CH_{2\ naphthylmethyl}$ and 2′H), 4.32 (m, 2H, 3′H, 4′H), 3.61 (m, 2H, 5′$H_2$) MPLC purity: 88%. HRMS (FAB) calcd. 547.1905 [M+1] found: 547.1880 [M+1].

**2′-Deoxy-2′-(3-fluoro-4-methylbenzamido)-$N^6$-(1-naphthylmethyl)adenosine (10b).** Compound **10b** was prepared from resin **3b** synthesized by the general procedure A, activation method A1. Following the general procedure B 4.90 mg (91%) white product was obtained. $^1$H NMR (400 MHz, [$D_6$]-DMSO) $\delta$ (ppm)=8.47 (bs, 1H, $N^6$-H),

8.39 (s, 1H, 8H), 8.20 (2s, 2H, $2H_{adenine}$ overlapping $H_{naphthyl}$), 7.90 (d, 1H, 2′NH, $J$=7.12 Hz), 7.80–7.31 (m, 9H, $H_{aromat.}$), 6.16 (d, 1H, 1′H, $J$=3.05 Hz), 5.58–5.53 (m, 1H, 5′OH), 5.51–5.45 (m, 1H, 3′OH), 5.20–5.13 (m, 1H, 2′H), 4.28–4.21 (m, 1H, 3′H), 3.65–3.52 (m, 3H, 4′H overlapping $5'H_2$), 2.31 (s, 3H, $CH_3$) MPLC purity: 86%. HRMS (FAB) calcd. 543.2157 [M+1] found: 543.2185 [M+1].

**2′-Deoxy-2′-{4-[2-(4-methoxyphenyl)ethyl]amino-3-nitrobenzamido}-$N^6$-(1-naphthylmethyl)adenosine (10c).** Compound **10c** was prepared from resin **3c** as described in the general procedure B. First, resin **11** was generated via the coupling of 4-fluoro-3-nitrobenzoic acid to the sulfamoyl group of the linker following general procedure A. Resin **13** was prepared from resin **11** by subsequent treatment with 300 mg (2 mmol) 2-(4-methoxyphenyl)ethylamine in 5 mL DMF for 12 h and washing with DMF (3×3 mL) and THF (5×2 mL). Activation from **13** to **3c** followed the activation method A1. Transfer to scaffold **9** furnished 5.02 mg (70%) yellow product. $^1$H NMR (400 MHz, [$D_6$]-DMSO) $\delta$ (ppm)=8.55 (s, 1H, NH), 8.50 (bs, 1H, $N^6$H), 8.40 (s, 1H, 8H), 8.20 (2s, $2H_{overlapping}$, 2H, $1H_{naphthyl}$), 7.95 (d, 1H, 2′NH, $J$=7.12 Hz), 7.95–7.34 (m, 13H, $H_{aromat.}$), 6.15 (d, 1H, 1′H, $J$=8.14 Hz), 5.56–5.50 (m, 1H, 5′OH), 5.48–5.43 (m, 1H, 3′OH), 5.21–5.10 (m,3H, 2′H, $CH_{2\ naphthylmethyl}$), 4.05–4.00 (m, 1H, 3′H), 3.99–3.90 (m, 3H, 4′H,$5'H_2$), 3.73 (s, 3H, $OCH_3$), 3.69–3.62 (m, 2H, $H_{ethyl}$), 2.93–2.85 (m, 2H, $H_{ethyl}$) MPLC purity: 85%.

**2′-Deoxy-$N^6$-(1-naphthylmethyl)-2′-(3-thienyl)acetamidoadenosine (10d).** Compound **10d** was prepared from resin **3d** synthesized by the general procedure A, activation method A2. Following the general procedure B 5.10 mg (96%) off-white product was obtained. $^1$H NMR (400 MHz, [$D_6$]-DMSO) $\delta$ (ppm)=8.48 (bs, 1H, $N^6$-H), 8.33 (s, 1H, 8H), 8.24 (2s, 2H, $2H_{adenine}$ overlapping $1H_{aromat.}$), 7.98 (d, 1H 2′NH, $J$=7.12 Hz), 7.82–7.32 (m, 6H, $H_{naphthyl.}$) 7.11–6.86 (m, $3H_{thienyl}$) 6.05 (d, 1H, 1′H, $J$=8.14 Hz), 5.97 (d, 1H, 5′OH, $J$=4.58 Hz), 5.71 (bs, 1H, 3′OH), 5.18–5.13 (m, 3H, $CH_{2\ naphthylmethyl}$ overlapping 2′H), 4.38–4.21 (m, 3H, 4′H, $5'H_2$), 3.73 (s, 2H, $CH_{2\ acetyl}$) MPLC purity: 95%. HRMS (FAB) calcd. 531.1815 [M+1] found: 531.1813 [M+1].

**2′-Deoxy-2′-[3-(3-indolyl)propanamido]-$N^6$-(1-naphthylmethyl)adenosine (10e).** Compound **10e** was prepared from resin **3e** synthesized by the general procedure A, activation method A2. Following the general procedure B 5.62 mg (97%) off-white product was obtained. $^1$H NMR (400 MHz, [$D_6$]-DMSO) $\delta$ (ppm)=10.69 (s, 1H, $NH_{indole}$), 8.52 (bs, 1H, $N^6$-H), 8.32 (s, 1H, 8H), 8.23 (2s, 2H, $2H_{adenine}$ overlapping $1H_{aromat.}$), 8.05 (d, 1H 2′NH, $J$=8.65 Hz), 7.95–6.93 (m, 12H, $H_{aromat.}$), 6.00 (d, 1H, 1′H, $J$=8.14 Hz), 5.71 (bs, 1H, 5′OH), 5.54–5.51 (m, 1H, 3′OH), 5.19–5.02 (m, 3H, $CH_{2\ naphthylmethyl}$, 2′H), 4.29–4.25 (m, 1H, 3′H), 4.08–4.04 (m, 1H, 4′H), 3.68–3.59 (m, 2H, $5'H_2$), 2.77 (m, 2H, $H_{prop.}$), 2.47 (m, 2H, $H_{prop.}$), MPLC purity: 98%. HRMS (FAB) calcd. 578.2516 [M+1] found: 578.2481 [M+1].

**2′-Deoxy-2′-[4-(3-indolyl)butanamido]-$N^6$-(1-naphthylmethyl)adenosine (10f).** Compound **10f** was prepared from resin **3f** synthesized by the general procedure A, activation method A2. Following the general procedure B 5.68 mg (96%) off-white product was obtained. $^1$H NMR (400 MHz, [$D_6$]-DMSO) $\delta$ (ppm)=10.73 (s, 1H, $NH_{indole}$), 8.50 (bs, 1H, $N^6$-H), 8.32 (s, 1H, 8H), 8.21 (2s, 2H, $2H_{adenine}$ overlapping $1H_{aromat.}$), 8.00 (d, 1H, 2′NH, $J$=8.14 Hz), 7.80–6.94 (m, 12H, $H_{aromat.}$), 6.00 (d, 1H, 1′H, $J$=8.13 Hz), 5.71 (bs, 1H, 5′OH), 5.46–5.41 (m, 1H, 3′OH), 5.18–5.01 (m, 3H, $CH_{2\ naphthylmethyl}$ overlapping 2′H), 4.26–4.22 (m, 1H, 3′H), 4.05 (bs, 1H, 4′H), 3.68–3.59 (m, 2H, $5'H_2$), 2.15 (m, 2H, $H_{but.}$), 1.76 (m, 2H, $H_{but.}$), 0.86 (m, 2H, $H_{but.}$) MPLC purity: 98%. HRMS (FAB) calcd. 592.2672 [M+1] found: 592.2616 [M+1].

**2′-[4-(3,5-Dichlorophenoxy)butanamido]-2′-deoxy-$N^6$-(1-naphthylmethyl)adenosine (10g).** Compound **10g** was prepared from resin **3g** synthesized by the general procedure A, activation method A2. Following the general procedure B 5.93 mg (93%) off-white product was obtained. $^1$H NMR (400 MHz, [$D_6$]-DMSO) $\delta$ (ppm)=8.49 (bs, 1H, $N^6$-H), 8.30 (s, 1H, 8H), 8.24 (s, 1H, $H_{naphthyl}$), 8.19 (s, 1H, 2H), 8.06 (d, 1H, 2′NH, $J$=8.65 Hz), 8.01–6.97 (m, 9H, $H_{aromat.}$), 5.99 (d, 1H, 1′H, $J$=8.14 Hz), 5.72 (d, 1H, 5′OH, $J$=4.07 Hz), 5.54–5.48 (m, 1H, 3′OH), 5.17 (bs, 2H, $CH_{2\ naphthylmethyl}$), 5.09–5.05 (m, 1H, 2′H), 4.27–4.21 (m, 1H, 3′H), 4.07–4.0 (m, 1H, 4′H), 3.73–3.51 (m, 2H, $5'H_2$), 3.12–3.00 (m, 2H, $H_{but.}$), 2.33–2.18 (m, 2H, $H_{but.}$), 1.86–1.77 (m, 2H, Hbut.) MPLC purity: 97%. HRMS (FAB) calcd. 637.1733 [M+1] found: 637.1694 [M+1].

**2′-Deoxy-$N^6$-(1-naphthylmethyl)-2′-{4-oxo-4-[(4-phenyl)-phenyl]butanamido}adenosine (10h).** Compound **10h** was prepared from resin **3h** synthesized by the general procedure A, activation method A2. Following the general procedure B 6.10 mg (95%) off-white product was obtained. $^1$H NMR (400 MHz, [$D_6$]-DMSO) $\delta$ (ppm)=8.54 (bs, 1H, $N^6$-H), 8.32 (s, 1H, 8H), 8.25 (ds, 2H, $H_{naphthyl}$ overlapping 2H), 8.04 (d, 1H, 2′NH, $J$=8.65 Hz), 8.02–7.33 (m, 16H, $H_{aromat.}$), 6.00 (d, 1H, 1′H, $J$=4.07 Hz,), 5.74 (s. 1H, 5′OH), 5.58–5.52 (m,1H, 3′OH), 5.19 (bs, 2H, $H_{2\ naphthylmethyl}$), 5.15–5.10 (m, 1H, 2′H), 4.27 (s, 1H, 3′H), 4.07 (s, 1H, 4′H), 3.57–3.54 (m, 2H, $5'H_2$), 3.20–3.10 (m, 2H, $H_{but.}$), 2.61–2.40 (m, 2H, $H_{but.}$ overlapped by DMSO signal) MPLC purity: 92%. HRMS (FAB) calcd. 643.2669 [M+1] found: 643.2654 [M+1].

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