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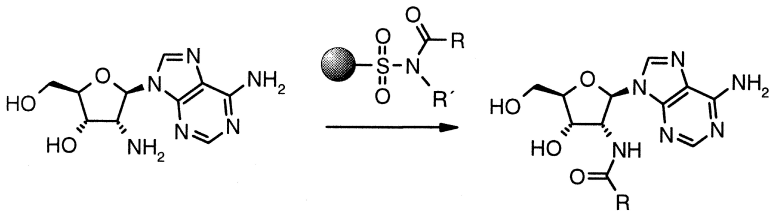

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Polymer-Assisted Solution-Phase Synthesis of 2′-Amido-2′-deoxyadenosine Derivatives Targeted at the NAD^+-Binding Sites of Parasite Enzymes†

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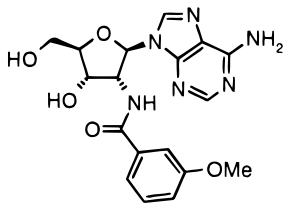
A polymer-assisted solution-phase (PASP) synthesis of lead structure analogues ready for biological testing without the demand for chromatographic purification is described. Carboxylic acids are coupled to the Kenner or Ellman safety catch linker, respectively, activated by methylation or cyanomethylation and subsequently transferred to the 2′-amino group of the 2′-amino-2′-deoxyadenosine scaffold (**5**). The chemoselective attack of weakly nucleophilic amino groups on the N-alkylated *N*-acyl sulfonamide linker allows for the synthesis of amides **6** in high yields without the need for protection of primary and secondary hydroxyl functions. Thus, the use of 4-sulfamylbenzoylaminomethyl polystyrene is reported for the construction of chemoselective polymer-supported acylating reagents instead of its known use as linker in solid-phase peptide or organic synthesis. This approach is demonstrated to be well suited to obtain 2′-amido-2′-deoxyadenosine derivatives **6** in parallel format. Biological evaluation of all compounds reported revealed no improvement over known lead structures.

Introduction

Adenosine binding motifs are associated with a broad array of targets of therapeutic importance in biological systems. Adenosine receptors, enzymes that utilize adenosyl-containing substrates such as *S*-adenosylmethionine, ATP, or NAD^+, not to mention nucleoside-related targets share the opportunity of the rational design of ligands starting from the adenosine scaffold. Thus, introducing diversity into either the carbohydrate and/or base subunits of adenosine represent promising strategies to identify receptor ligands, enzyme inhibitors, or nucleoside function modifiers. Because methods for generating carbohydrate-modified nucleoside-based combinatorial arrays or libraries are scarce, we were aiming at developing a custom-tailored procedure for the preparation of sugar-modified adenosine derivatives. The need for a simple and high yielding methodology for the synthesis of 2′-amido-2′-deoxyadenosines was revealed when the search for inhibitors of trypanosomal glycosomal glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was hampered by time-consuming classical organic synthesis in solution and subsequent individual chromatographic purification of analogues of the discovered lead compound 2′-deoxy-2′-(3-methoxybenzamido)adenosine (**1**).[1] Because synthetic strategies applying polymer supports as solubility control auxiliaries in order to facilitate the generation of molecular libraries have recently proven to be a powerful tool in drug discovery, the development of novel materials, and optimization of catalysts, we decided to initiate a program to test possible approaches for the synthesis of a set of lead structure analogues by polymer-supported or polymer-assisted protocols.[2−7]



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Synthesis

To rapidly address our specific synthetic problem, we assumed that for the production of arrays of 2′-amido-2′-deoxyadenosines (**6**) with no further substitution of the ribose moiety or the adenine part of the molecule, the single diversity element could be introduced most conveniently at the 2′-amino group of the scaffold **5** by PASP synthesis.[8] This technique can lead to undemanding product isolation since no cleavage reactions of the product from a polymer

† Dedicated to Prof. Dr. Dr. h.c. Wittko Francke on the occasion of his 60th birthday.

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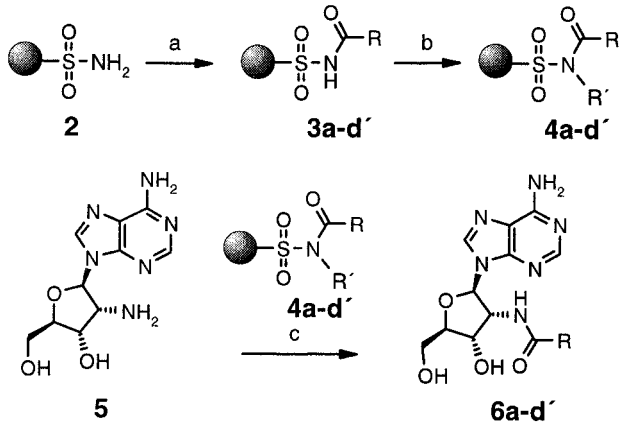
support are necessary. In addition, the danger of remaining traces of residual, potentially toxic cleavage reagents in biological assays is minimized. Thus, the synthesis of the common scaffold that does not bear variable elements was performed on a larger scale from the antiviral drug vidarabine in solution, following established procedures.[9,10] In this way we were able to take advantage of the straightforward chromatographic purification and highly developed analysis in solution. Due to the high cost of the starting material vidarabine, practically quantitative transformation to the final product in the PASP step was envisioned as one of the major objectives. Since scaffold **5** was used as a building block for all derivatives prepared in this series, the time-consuming preparation and purification was acceptable. Quite to the contrary, for the introduction of different acid residues in parallel, a fast and simple workup procedure was regarded as essential. What is more, we were aiming at the possibility of designing an approach in which no protecting groups would have to be removed at the end of the sequence and therefore no individual operation on every single test candidate would be necessary. Chromatographic separation of byproducts, impurities from protection strategies, or cleavage cocktails should therefore be avoided. Thus, we set up a polymer-assisted solution-phase synthesis designed for the selective acylation of the 2′-amino group of 2′-amino-2′-deoxyadenosine (**5**) by coupling the carboxylic acids to the Kenner safety catch linker **2** improved by Backes et al.[11] This linker was recently shown to be well suited for the high yielding acylation of amino groups in 4-(3-aminopropyl)-morpholine, morpholine, benzylamine, piperidine, cyclohexylamine, *tert*-butylamine, aniline, leucine methylester, 7-amino-4-methylcumarine, and for the synthesis of protected 'head-to-tail' cyclic peptides using a cleavage by cyclization approach.[12−14] The versatility of this linker for the synthesis of peptide C-terminal thioesters was recently demonstrated by Ingenito et al.[15] The use of multifunctional amino-deoxy-sugar moieties of nucleoside analogues had not been reported, but we were able to demonstrate the selectivity of the N-acylation in the presence of primary and secondary hydroxyl groups without formation of unintentionally formed esters on a limited series of compounds in a preliminary paper.[16] In this manner, resin aliquots **3a**−**d**′ were prepared from commercially available acids by amide bond forming procedures using in situ anhydride formation. Therefore, the selected acids were dissolved in THF, stirred with diisopropyl carbodiimide and Hünig's base, and then reacted with the polymer-bound linker **2** in the presence of catalytic DMAP. The success of the attachment reaction could be followed by the forming of an IR-absorption band at 1718 cm^{-1} and by carefully monitoring the increase in weight of the washed and dried resin samples **3a**−**d**′. Prior to the PASP reaction with scaffold **5**, polymer-bound acids **3a**−**d**′ had to be activated by N-alkylation as described by Backes et al. or by use of trimethylsilyldiazomethane, as introduced by nonquotable company advertisements and reported recently by Ingenito et al.[12,15] The resulting activated polymer-bound acids **4a**−**d**′ could easily be transformed to compounds **6a**−**d**′ by agitation with **5** in an appropriate solvent like THF at slightly elevated temperatures (Scheme 1, Table 1).

Scheme 1. PASP Synthesis of Target Compounds[a]



[a] Reagents and conditions: (a) DIC, DIPEA, DMAP, THF, appropriate carboxylic acid; (b) $(CH_3)_3SiCHN_2$, THF or BrCHCN, NMP, DIPEA; (c) THF, 55 °C.

Table 1. Residues in Compounds **3**, **4**, or **6a**−**d**′, Purity and Isolated Yields for **6a**−**d**′

entry	R′ (in **4**)	R (in **3**, **4**, or **6**)	yield[a] (%)	purity[b] (%)
a	CH_3	3-fluorophenyl	95	98
b	CH_3	3-fluoro-4-methylphenyl	90	93
c	CH_3	3-(trifluoromethyl)phenyl	95	98
d	CH_3	3-(trifluoromethoxy)phenyl	92	89
e	CH_2CN	3,5-difluorophenyl	90	93
f	CH_2CN	4-fluoro-3-nitrophenyl	89	86
g	CH_2CN	3-chloro-4-fluorophenyl	89	91
h	CH_2CN	3,5-dichlorophenyl	91	96
i	CH_2CN	4-chloro-3-nitrophenyl	88	90
j	CH_2CN	4-nitrophenyl	95	88
k	CH_2CN	4-cyanophenyl	89	85
l	CH_2CN	4-iodophenyl	89	98
m	CH_2CN	3-iodophenyl	98	90
n	CH_2CN	4-(methylsulfonyl)phenyl	92	88
o	CH_2CN	4-(1-methylethyl)phenyl	89	85
p	CH_2CN	3-[4-phenyl(phenyl)]−3-oxopropyl	93	90
q	CH_2CN	(3-chlorophenyl)methyl	87	93
r	CH_2CN	(4-bromophenyl)methyl	93	96
s	CH_2CN	1-(2-phenyl)propyl (racemic)	85	88
t	CH_2CN	2-(4-methylphenyl)ethyl	93	93
u	CH_2CN	3-phenylpropyl	98	97
v	CH_2CN	3-(2-thienyl)propyl	96	99
w	CH_2CN	(2-thienyl)methyl	96	98
x	CH_2CN	3-oxo-3-phenylpropyl	94	96
y	CH_2CN	2-(3-indolyl)ethyl	98	95
z	CH_2CN	3-(3-indolyl)propyl	96	94
a′	CH_2CN	2-methylpropenyl	95	96
b′	CH_2CN	cyclohexen-4-yl	97	91
c′	CH_2CN	(3-cyclohexyl)propyl	92	96
d′	CH_2CN	3-(3,5-dichlorphenoxy)propyl	98	96

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

The reactions were terminated after TLC or HPLC analysis indicated consumption of the amino nucleoside **5**. Reaction monitoring was unambiguously possible, since in this PASP approach only the reactant to be consumed and the product formed were present in solution, whereas the reagent was polymer-bound and no additives such as cleavage reagents were applied. The only side products observed in some cases were traces of acids resulting from the hydrolysis of the activated polymer-bound acylation reagent. By excluding water traces, this side reaction could be minimized effectively.

Complex building blocks such as amino-deoxynucleosides synthesized in solution can be transformed to amide libraries by simple incubation with libraries of polymer-supported acids in a parallel format. The final library synthesis consists of a PASP protocol where a solution of the amine building block is treated with an excess of polymer-supported reagent leading to practically quantitative conversion of the amine to the desired amide. Workup includes parallel filtration and removal of the solvent by evaporation or freeze-drying, yielding the spatially separate target compounds in sufficient purity, ready for biological evaluation.

Results and Discussion

One special advantage of the selected linker with respect to the construction of amide libraries is the absence of reactivity toward primary or secondary hydroxyl functions. These functions do not attack the linker construct, even if a 10-fold excess of acylating agent is applied, thus enabling complete conversion of starting material without formation of accidentally acylated side products.

Interestingly, the potential use of this N-alkylated *N*-acylsulfonamide moiety as a chemoselective acylating agent was not derived from solution-phase synthesis and adapted to polymer-supported chemistry but, more or less, vice versa. The first reports on the use of, e.g., acylated 2-fluoro-*N*-mesylaniline as acylating species are from 1998.[17] Backes et al. recently demonstrated an elegant utilization of the safety-catch principle in solution using *N*-acyl-*tert*-butanesulfinamides for diastereoselective enolate alkylations. After a required chromatographic separation of diastereomeric mixtures, the N-alkylated *N*-acylsulfonamide moiety was generated by oxidation from a sulfinamide precursor.[18]

In preliminary investigations with other polymer supports for the generation of acylating agents, we were interested in the results obtainable with other activating anchor groups. Applying polymer-bound hydroxybenzotriazol as linker, we could observe a higher reactivity in terms of rapidity of conversion but, at the same time, a lack of chemoselectivity. Reactions with equimolar ratios of nucleophile could not be driven to completion. In cases where excess acylating agent was used, acylation at the 5′-OH group took place. Because the ester bond formed is less stable than the 2′-amido construct, selective cleavage of the ester bond is possible but leads to a necessary removal of the acid released by extraction or chromatography which is unconstructive for rapid parallel synthesis.

Another strong implication of using the Kenner safety-catch linker in PASP chemistry besides chemoselectivity for N-nucleophiles is the opportunity to modify resin-bound residues prior to the PASP synthesis by solid-phase organic synthesis (SPOS). This possibility represents a considerable advantage over strategies reported thus far to access amide libraries by PASP synthesis making use of catch-and-release linkers. 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.[19,20] 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. Therefore, the highly desirable possibility of intermediate nucleophilic substitution of polymer-bound residues as a source for diversity in drug discovery is excluded in these approaches.[21] This opportunity will further be exploited by our group and reported in due course. Possible nucleophilic attack of the amino group of **5** on the activated halide substituent in polymer-bound activated acid **4f** similar to the reaction described by Yeh and Sun was not observed in initial experiments, most likely due to the weak nucleophilic character of the 2′-amino group in **5**.[22]

The compounds **6a**−**d**′ were evaluated using an enzyme-based assay reported previously or in a parasite-based assay and did not show any improvement over compounds obtained before.[23] The candidates **6a**−**h,j**−**p,w**−**d**′ were tested in the enzyme-based assay and showed no inhibition of GAPDH from *Trypanosoma brucei* or *Trypanosoma cruzei* greater than 20% when tested at a concentration of 150 μM. Compounds **6a**−**d,i,q**−**v** were tested in a parasite-based assay at Tibotec, Mechelen, Belgium, and no inhibition of *T. brucei* was observed at concentrations smaller than 25 μM.

These results can be interpreted in a way that 3-methoxybenzoyl and 3-chlorobenzoyl residues are already very close to being optimal, and especially that space filling substituents are not tolerated by the enzyme region near the 2′-OH of the adenosine part of NAD^+. These findings are in accordance with experimental data derived from X-ray crystallography and with recent insights gained from theoretical calculations.[24] As could already be shown by Aronov et al., additional modification of the N^6-position of the adenine ring is beneficial for binding affinity, leading to compounds with submicromolar affinity.[23] As to be expected, the measured effects of substitution in the 2′-region and on the N^6-nitrogen atom cannot easily be correlated. Therefore, for optimization of the lead structure **1,** a combinatorial approach allowing for the synthesis of all possible combinations of an array of selected modifications is an interesting objective to be addressed by further synthetic work.

Conclusion

We demonstrated the versatility of the Kenner linker modified by Ellman and his group for PASP synthesis for the rapid parallel modification of aminodeoxynucleosides to provide amide libraries. We reached our synthetic goals in that the method reported leads to the simple and high yielding parallel conversion of unprotected amino sugars. The procedure was shown to be reliable and efficient. The other advantage of the use of the Kenner linker lies in its potential to modify acids attached to the polymer support and build up diversity by its original use in SPOS. This linker tolerates strongly basic or acidic conditions prior to activation, and thus its use greatly widens the scope of the acid residues accessible. The necessary activation with toxic, alkylating agents requiring large numbers of thorough washing steps afterward, represents a considerable disadvantage that is only tolerable when diversity is to be achieved on the resin, but makes this method inferior if this is not desirable. On-bead

modifications of acids attached to the Kenner linker might become a valuable source of diversity for other adenosine derived targets, and this will be studied by our group.

Experimental Section

General Remarks. Identity of all compounds was assigned by ^{1}H NMR spectroscopy. Sample purity was deduced from ^{1}H NMR data as well as evaluated by MPLC. The purity of final products **6a**−**d′** is reported as purity of crude products prior to purification (percentage of target compound contained in residue from evaporated reaction mixture). Yields for **6a**−**d′** 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 as 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. Purity was calculated from the peak ratio according to the 100% method. TLC was performed on Macherey-Nagel Polygram Sil G/UV_{254} precoated microplates; spots were visualized under UV-illumination at 254 nm. MS data (FAB) were obtained on a Finnigan MAT 311A instrument with *m*-nitrobenzylic alcohol or thioglycerol as matrix using a Kratos Concept IH mass spectrometer. 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. Standard glassware was oven dried at 150 °C and kept in a desiccator.

General Procedure for the Synthesis of Polymer-Bound Acids 4a−**d′**. 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, batch number A20540) 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 of dry THF and preactivated via in situ anhydride formation by adding 780 μL (5 mmol) of *N*,*N*-diisopropylcarbodiimide. After addition of 580 μL of Hünig's base (3.4 mmol) and 15 mg (0.12 mmol) of 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 (two times 5 mL), methanol (two times 5 mL), and THF (two times 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 A: the sulfonamide linker of 200 mg (approximately 0.2 mmol) of **3** was activated for cleavage by alkylation with 260 μL (3.2 mmol) of bromoacetonitrile and 290 μL (1.7 mmol) of Hünig's base in 3 mL of 1-methylpyrrolidone overnight and washed with dry dimethyl sulfoxide (five times 3 mL) and THF (five times 5 mL). Activation method B: 200 mg (approximately 0.2 mmol) of resins **3** were swollen in THF and treated with 2.0 mL (trimethylsilyl)diazomethane of 1 M solution in hexanes (2.0 mmol) purchased from Aldrich for 24 h and washed with THF (5 mL), methanol (three times 5 mL), and THF (5 mL).

General Procedure for the Synthesis of 2′-Amido-2′-deoxy-adenosines 6a−**d′**. The polymer-supported activated acids **4 a**−**d′** were transferred to the amino group of 2.76 mg (10 μmol) of 2′-amino-2′-deoxy-adenosine (**5**) by shaking at 55 °C in 5 mL of THF. The reaction was monitored by TLC and terminated when the starting material was quenched (6−96 h). Polymer beads and particulates were removed by filtration, the beads where extracted exhaustively with dry, hot THF, and the combined THF fractions were evaporated to furnish **6a**−**d′**. ^{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 starting material or acid hydrolyzed from the resin.

2′-Deoxy-2′-(3-fluorobenzamido)adenosine (6a). Compound **6a** was prepared from resin **4a** as obtained from **3a** via activation method A. ^{1}H NMR (400 MHz, [D_6] DMSO) δ (ppm) = 8.41 (s, 1H, 8H), 8.18 (s,2 H, 2H), 7.81 (d, 1H, aromat., J = 7.81), 7.69 (d, 1H, aromat., J = 9.67), 7.64−7.56 (m, 1H, aromat.), 7.53−7.44 (m, 1H, aromat.), 7.37 (bs, 2H, NH_2), 6.19 (d, 1H, 1′H, J = 3.06), 5.63−5.55 (m, 1H, 5′OH), 5.54−5.49 (m, 1H, 3′OH), 5.25−5.15 (m, 1H, 2′H), 4.30−4.23 (m, 1H, 3′H), 3.66−3.56 (m, 3H, 4′H, 5′H). HRFAB-MS $[M + H]^+$ calc = 389.1373;; found = 389.1371. MPLC purity = 98%. Yield = 95%.

2′-Deoxy-2′-(3-fluoro-4-methylbenzamido)adenosine (6b). Compound **6b** was prepared from resin **4b** as obtained from **3b** via activation method A. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.40 (s, 1H, 8H), 8.17 (s, 1H, 2H), 7.69 (d, 1H, aromat., J = 6.20), 7.62 (d, 1H, aromat., J = 8.65), 7.46 (t, 1H, aromat., J = 8.65), 7.36 (bs, 2H, NH_2), 6.17 (d, 1H, 1′H, J = 3.05), 5.58−5.53 (m, 1H, 5′OH), 5.51−5.45 (m, 1H, 3′OH), 5.17 (t, 1H, 2′H, J = 5.59), 4.27−4.21 (m, 1H, 3′H), 3.63−3.55 (m, 3H, 4′H, 5′H), 2.32 (s, 3H, methyl). HRFAB-MS $[M + H]^+$ calc = 403.1530; found = 403.1511. MPLC purity = 93%. Yield = 90%.

2′-Deoxy-2′-(4-trifluoromethylbenzamido)adenosine (6c). Compound **6c** was prepared from resin **4c** as obtained from **3c** via activation method A. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.41 (s, 1H, 8H), 8.25 (d, 1H, aromat., J = 7.62), 8.18 (s, 2 H, 2H, aromat. overlaped), 8.03 (d, 1H, aromat., J = 8.14), 7.81 (dd, 1H, aromat., J = 8.14, J = 7.63), 7.37 (bs, 2H, NH_2), 6.20 (d, 1H, 1′H, J = 2.54), 5.64−5.57 (m, 1H, 5′OH), 5.55−5.49 (m, 1H, 3′OH), 5.25−5.17 (m, 1H, 2′H), 4.33−4.25 (m, 1H, 3′H), 3.69−3.55 (m, 3H, 4′H, 5′H). HRFAB-MS $[M + H]^+$ calc = 439.1341; found = 439.1363. MPLC purity = 98%. Yield = 95%.

2′-Deoxy-2′-(4-trifluoromethoxybenzamido)adenosine (6d). Compound **6d** was prepared from resin **4d** as obtained from **3d** via activation method A. ^{1}H NMR (400 MHz, [D6]

DMSO) δ (ppm) = 8.69 (d, 1H, 2′NH, J = 8.65), 8.27 (s, 1H, 8H), 8.14 (s, 1H, 2H), 7.88 (d, 1H, aromat., J = 7.63), 7.79 (s, 1H, aromat.), 7.65−7.49 (m, 2H, aromat.), 7.37 (bs, 2H, NH_2), 6.25 (d, 1H, 1′H, J = 8.65), 5.68−5.46 (bs and m, 2H, 5′OH, 3′OH, overlapped), 5.38−5.28 (m, 1H, 2′H), 4.38−4.33 (m, 1H, 3′H), 4.14−4.08 (m, 1H, 4′H), 3.77−3.58 (m, 2H, 5′H_2). HRFAB-MS $[M + H]^+$ calc = 455.1291; found = 455.1286. MPLC purity = 89%. Yield = 92%.

2′-Deoxy-2′-(3,5-difluorobenzamido)adenosine (6e). Compound **6e** was prepared from resin **4e** as obtained from **3e** via activation method A. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.40 (s, 1H, 8H), 8.18 (s, 1H, 2H), 7.63−7.54 (m, 3H, aromat.), 7.36 (bs, 2H, NH_2), 6.18 (d, 1H, 1′H, J = 3.1), 5.64−5.59 (m, 1H, 5′OH), 5.55−5.49 (m, 1H, 3′OH), 5.21−5.16 (m, 1H, 2′H), 4.30−4.24 (m, 1H, 3′H), 3.63−3.54 (m, 3H, 4′H, 5′H_2). HRFAB-MS $[M + H]^+$ calc = 407.1279; found = 407.1286. MPLC purity = 93%. Yield = 90%.

2′-Deoxy-2′-(4-fluoro-3-nitrobenzamido)adenosine (6f). Compound **6f** was prepared from resin **4f** as obtained from **3f** via activation method A. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.59−8.55 (m, 1H, aromat.), 8.40 (s, 1H, 8H), 8.18 (s, 1H, 2H), 7.95 (s, 1H, aromat), 7.39−7.35 (m, 3H, NH_2, aromat.), 6.20 (d, 1H, 1′H, J = 2.54), 5.64−5.60 (m, 1H, 5′OH), 5.58−5.54 (m, 1H, 3′OH), 5.22−5.17 (m, 1H, 2′H), 4.32−4.27 (m, 1H, 3′H), 3.63−3.57 (m, 3H, 4′H, 5′H). HRFAB-MS $[M + H]^+$ calc = 434.1146; found = 434.1150. MPLC purity = 86%. Yield = 89%.

2′-(3-Chloro-4-fluorobenzamido)-2′-deoxy-adenosine (6g). Compound **6g** was prepared from resin **4g** as obtained from **3g** via activation method A. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.26 (s, 1H, 8H), 8.14 (s, 1H, 2H), 8.10−8.04 (m, 1H, aromat.), 7.87−7.80 (m, 1H, aromat.), 7.56−7.44 (m, 1H, aromat.), 7.36 (bs, 2H, NH_2), 6.20 (d, 1H, 1′H, J = 8.7), 5.73 (d, 1H, 5′OH, J = 4.1), 5.68−5.61 (m, 1H, 3′OH), 5.38−5.24 (m, 1H, 2′H), 4.37−4.31 (m, 1H, 3′H), 4.12−4.04 (m, 1H, 4′H), 3.78−3.54 (m, 2H, 5′H). HRFAB-MS $[M + H]^+$ calc = 423.0906; found = 423.0901. MPLC purity = 91%. Yield = 89%.

2′-(3,5-Dichlorobenzamido)-2′-deoxy-adenosine (6h). Compound **6h** was prepared from resin **4h** as obtained from **3h** via activation method A. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.40 (s, 1H, 8H), 8.18 (s, 1H, 2H), 7.95−7.92 (m, 1H, aromat.), 7.91−7.87 (m, 2H, aromat.), 7.37 (bs, 2H, NH_2), 6.18 (d, 1H, 1′H, J = 3.05), 5.63−5.57 (m, 1H, 5′OH), 5.55−5.49 (m, 1H, 3′OH), 5.25−5.17 (m, 1H, 2′H), 4.31−4.25 (m, 1H, 3′H), 3.64−3.56 (m, 3H, 4′H, 5′H_2). HRFAB-MS $[M + H]^+$ calc = 439.0688; found = 439.0695. MPLC purity = 96%. Yield = 91%.

2′-(4-Chloro-3-nitrobenzamido)-2′-deoxy-adenosine (6i). Compound **6i** was prepared from resin **4i** as obtained from **3i** via activation method A. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.55−8.50 (m, 1H, aromat.), 8.41 (s, 1H, 8H), 8.23−8.19 (m, 1H, aromat.), 8.18 (s, 1H, 2H), 7.96 (d, 1H, aromat., J = 8.64), 7.38 (bs, 2H, NH_2), 6.20 (d, 1H, 1′H, J = 2.55), 5.67−5.60 (m, 1H, 5′OH), 5.59−5.50 (m, 1H, 3′OH), 5.24−5.19 (m, 1H, 2′H), 4.33−4.26 (m, 1H, 3′H), 3.69−3.55 (m, 3H, 4′H, 5′H_2). HRFAB-MS $[M + H]^+$ calc = 450.0929; found = 450.0933. MPLC purity = 90%. Yield = 88%.

2′-Deoxy-2′-(4-nitrobenzamido)adenosine (6j). Compound **6j** was prepared from resin **4j** as obtained from **3j** via activation method A. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.41 (s, 1H, 8H), 8.38−8.35 (m, 2 H, aromat.), 8.20−8.16 (m, 3H, 2H, aromat.), 7.35 (bs, 2H, NH_2), 6.21 (d, 1H, 1′H, J = 3.06), 5.67−5.61 (m, 1H, 5′OH), 5.58−5.52 (m, 1H, 3′OH), 5.22−5.19 (m, 1H, 2′H), 4.31−4.28 (m, 1H, 3′H), 3.65−3.58 (m, 3H, 4′H, 5′H_2). HRFAB-MS $[M + H]^+$ calc = 416.1318; found = 416.1360. MPLC purity = 88%. Yield = 95%.

2′-(4-Cyanobenzamido)-2′-deoxy-adenosine (6k). Compound **6k** was prepared from resin **4k** as obtained from **3k** via activation method A. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.40 (s, 1H, 8H), 8.18 (s, 1H, 2H), 8.14−7.99 (m, 5H, 2′NH, aromat.), 7.37 (bs, 2H, NH_2), 6.19 (d, 1H, 1′H, J = 2.54), 5.65−5.59 (m, 1H, 5′OH), 5.56−5.48 (m, 1H, 3′OH), 5.22−5.16 (m, 1H, 2′H), 4.29−4.25 (m, 1H, 3′H), 3.65−3.57 (m, 3H, 4′H, 5′H). HRFAB-MS $[M + H]^+$ calc = 396.1420; found = 396.1418. MPLC purity = 85%. Yield = 89%.

2′-Deoxy-2′-(4-iodobenzamido)adenosine (6l). Compound **6l** was prepared from resin **4l** as obtained from **3l** via activation method A. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.39 (s, 1H, 8H), 8.17 (s,1H, 2H), 7.97−7.89 (m, 2H, aromat.), 7.73−7.67 (m, 2H, aromat.), 7.36 (bs, 2H, NH_2), 6.17 (d, 1H, 1′H, J = 2.55), 5.57−5.52 (m, 1H, 5′OH), 5.50−5.46 (m, 1H, 3′OH), 5.21−5.16 (m, 1H, 2′H), 4.26−4.20 (m, 1H, 3′H), 3.65−3.54 (m, 3H, 4′H, 5′H). HRFAB-MS $[M + H]^+$ calc = 497.0434; found = 497.0416. MPLC purity = 98%. Yield = 89%.

2′-Deoxy-2′-(3-iodobenzamido)adenosine (6m). Compound **6m** was prepared from resin **4m** as obtained from **3m** via activation method A. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.40 (s, 1H, 8H), 8.25−8.22 (m, 1H, aromat.), 8.18 (s, 1H, 2H), 8.00 (d, 1H, 2′NH, J = 8.1), 7.96 (d, 1H, aromat., J = 8.13), 7.37 (bs, 2H, NH_2), 7.35−7.32 (m, 2H, aromat.), 6.16 (d, 1H, 1′H, J = 2.54), 5.59−5.54 (m, 1H, 5′OH), 5.51−5.44 (m, 1H, 3′OH), 5.21−5.16 (m, 1H, 2′H), 4.29−4.22 (m, 1H, 3′H), 3.62−3.55 (m, 3H, 4′H5′H). HRFAB-MS $[M + H]^+$ calc = 497.0434; found = 497.0443. MPLC purity = 90%. Yield = 98%.

2′-Deoxy-2′-(3-methylsulfonylbenzamido)adenosine (6n). Compound **6n** was prepared from resin **4n** as obtained from **3n** via activation method A. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.81 (d, 1H, aromat., J = 8.2), 8.37 (s, 1H, 8H), 8.28 (s, 1H, 2H), 8.15−8.10 (m, 2 H, aromat.), 8.06 (d, 1H, 2′NH, J = 8.1), 7.37 (bs, 2H, NH_2), 6.24 (d, 1H, 1′H, J = 2.54), 5.81−5.78 (m, 1H, 5′OH), 5.68−5.62 (m, 1H, 3′OH), 5.40−5.34 (m, 1H, 2′H), 4.40−4.32 (m, 1H, 3′H), 4.18−4.10 (m, 1H, 4′H), 3.78−3.55 (m, 2H, 5′H), 3.20 (s, 3H, CH_3). HRFAB-MS $[M + H]^+$ calc = 449.1165; found = 449.1170. MPLC purity = 88%. Yield = 92%.

2′-Deoxy-2′-[4-(1-methylethyl)benzamido]adenosine (6o). Compound **6o** was prepared from resin **4o** as obtained from **3o** via activation method A. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.40 (s, 1H, 8H), 8.18 (s, 1H, 2H), 8.14−7.99 (m, 5H, 2′NH, aromat.), 7.37 (bs, 2H, NH_2), 6.19 (d,

1H, 1′H, J = 2.54), 5.65−5.59 (m, 1H, 5′OH), 5.56−5.48 (m, 1H, 3′OH), 5.22−5.16 (m, 1H, 2′H), 4.29−4.25 (m, 1H, 3′H), 3.65−3.57 (m, 3H, 4′H, 5′H). HRFAB-MS $[M + H]^+$ calc = 396.1420; found = 396.1418. MPLC purity = 85%. Yield = 89%.

2′-{4-[4-Phenyl(phenyl)]-4-oxo-butanamido}-2′-deoxy-adenosine (6p). Compound **6p** was prepared from resin **4p** as obtained from **3p** via activation method A. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.24 (s, 1H, 8H), 8.13 (s, 1H, 2H), 8.05 (d, 1H, 2′NH, J = 8.64), 7.98−7.40 (9H, aromat.), 7.35 (bs, 2H, NH_2), 5.97 (d, 1H, 1′H, J = 8.6), 5.71 (d, 1H, 5′OH, J = 4.07), 5.61−5.55 (m, 1H, 3′OH), 5.12−5.04 (m, 1H, 2′H), 4.27−4.21 (m, 1H, 3′H), 4.08−4.02 (m, 1H, 4′H), 3.70−3.55 (m, 2H, 5′H), 3.16−3.09 (m, 2H, aliphat.), 2 H missing due to overlapping with DMSO signal. HRFAB-MS $[M + H]^+$ calc = 503.2043; found = 503.2028. MPLC purity = 90%. Yield = 93%.

2′-[2-(3-Chlorophenyl)acetamido]-2′-deoxy-adenosine (6q). Compound **6q** was prepared from resin **4q** as obtained from **3q** via activation method A. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.31 (d, 1H, 2′NH, J = 8.65), 8.25 (s, 1H, 8H), 8.13 (s, 1H, 2H), 7.32 (bs, 2H, NH_2), 7.23−7.14 (m, 3H, aromat.), 7.03−6.97 (m, 1H, aromat.), 6.00 (d, 1H, 1′H, J = 8.65), 5.58 (bs, 1H, 5′OH), 5.60−5.51 (m, 1H, 3′OH), 5.09−5.01 (m, 1H, 2′H), 4.26−4.20 (m, 1H, 3′H), 4.09−4.03 (m, 1H, 4′H), 3.73−3.54 (m, 2H, 5′H), 3.54 (s, 2H, CH_2). HRFAB-MS $[M + H]^+$ calc = 419.1234; found = 419.1191. MPLC purity = 93%. Yield = 87%.

2′-[2-(4-Bromophenyl)acetamido]-2′-deoxy-adenosine (6r). Compound **6r** was prepared from resin **4r** as obtained from **3r** via activation method B. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.29−8.21 (m, 2H, 2′NH, 8H, overlapped), 8.13 (s, 1H, 2H), 7.41−7.27 (m, 4H, NH_2, aromat., overlapped), 7.01 (d, 2H, aromat., J = 8.14), 5.98 (d, 1H, 1′H, J = 8.64), 5.85−5.78 (m, 1H, 5′OH), 5.59−5.52 (m, 1H, 3′OH), 5.08−5.00 (m, 1H, 2′H), 4.25−4.19 (m, 1H, 3′H), 4.08−4.03 (m, 1H, 4′H), 3.72−3.53 (m, 2H, 5′H), 3.42 (d, 2H, CH_2, J = 8.14). HRFAB-MS $[M + H]^+$ calc = 463.0729; found = 463.0763. MPLC purity = 96%. Yield = 93%.

2′-Deoxy-2′-(2-phenyl)butanamido]adenosine (1:1 mixture of two diastereomers) (6s). Compound mixture **6s** was prepared from racemic resin **4s** as obtained from **3s** via activation method B. ^{1}H NMR of mixture of two diastereomers (400 MHz, [D6] DMSO) δ (ppm) = 8.27 (s, 1H, 8H), 8.12 (s, 1H, 2H),8.10 (s, 1H, 8H), 8.09 (d, 1H, 2′NH, J = 8.64), 8.04 (s, 1H, 2H), 8.03 (d, 1H, 2′NH, J = 8.64) 7.33 (bs, 2H, NH_2), 7.28 (bs, 2H, NH_2), 7.26−6.95 (m, 10H, aromat.), 5.97 (d, 1H, 1′H, J = 8.65), 5.88−5.80 (bs, 2H, 5′OH), 5.85 (d, 1H, 1′H, J = 8.14) 5.59 (bs, 2H, 3′OH), 5.11−5.02 (m, 2H, 2′H), 4.28−4.21 (m, 1H, 3′H), 4.13−4.08 (m, 1H, 3′H), 4.06−4.01 (m, 2H, 4′H), 3.70−3.63 (m, 2H, benzylic), 3.61−3.45 (m, 4H, 5′H_2), 1.86−1.30 (m, 4H, aliphat.), 0.76 (t, 3H, aliphat., J = 7.12), 0.42 (t, 3H, aliphat., J = 7.13). HRFAB-MS $[M + H]^+$ calc = 413.1937; found = 413.1956. MPLC purity = 88% (mixture of two diastereomers, no chromatographic separation determined). Yield = 85% (mixture of two diastereomers).

2′-Deoxy-2′-[3-(4-methylphenyl)propanamido]adenosine (6t). Compound **6t** was prepared from resin **4t** as obtained from **3t** via activation method B. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.25 (s, 1H, 8H), 8.12 (s, 1H, 2H), 7.94 (d, 1H, 2′NH, J = 8.7), 7.34 (bs, 2H, NH_2), 7.26−7.00 (m, 5H, aromat.), 5.95 (d, 1H, 1′H, J = 8.7), 5.70 (bs, 1H, 5′OH), 5.62−5.52 (m, 1H, 3′OH), 5.13−5.05 (m, 1H, 2′H), 4.25−4.18 (m, 1H, 3′H), 4.06−4.01 (m, 1H, 4′H), 3.72−3.53 (m, 2H, 5′H_2), 2.42−2.32 (m, 2H, aliphat.), 2.14−2.02 (m, 2H, aliphat.), 1.24 (s, 3H, CH_3). HRFAB-MS $[M + H]^+$ calc = 413.1937; found = 413.1908. MPLC purity = 93%. Yield = 93%.

2′-Deoxy-2′-(4-phenylbutanamido)adenosine (6u). Compound **6u** was prepared from resin **4u** as obtained from **3u** via activation method B. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.26 (s, 1H, 8H), 8.11 (s, 1H, 2H), 7.94 (d, 1H, 2′NH, J = 8.6), 7.34 (bs, 2H, NH_2), 7.26−7.00 (m, 5H, aromat.), 5.96 (d, 1H, 1′H, J = 8.6), 5.72 (bs, 1H, 5′OH), 5.60−5.54 (m, 1H, 3′OH), 5.13−5.05 (m, 1H, 2′H), 4.25−4.18 (m, 1H, 3′H), 4.06−4.01 (m, 1H, 4′H), 3.71−3.53 (m, 2H, 5′H_2), 2.39−2.32 (m, 2H, aliphat.), 2.11−2.04 (m, 2H, aliphat.), 1.70−1.57 (m, 2H, aliphat.). HRFAB-MS $[M + H]^+$ calc = 413.1937; found = 413.1908. MPLC purity = 97%. Yield = 98%.

2′-Deoxy-2′-[4-(2-thienyl)butanamido]adenosine (6v). Compound **6v** was prepared from resin **4v** as obtained from **3v** via activation method B. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.25 (s, 1H, 8H), 8.12 (s, 1H, 2H), 7.95 (d, 1H, 2′NH, J = 8.65), 7.34 (bs, 2H, NH_2), 7.27 (d, 1H, aromat., J = 4.57), 6.91−6.85 (m, 1H, aromat.), 6.72 (s, 1H, aromat.), 5.95 (d, 1H, 1′H, J = 8.13), 5.70 (d, 1H, 5′OH, J = 4.07), 5.61−5.54 (m, 1H, 3′OH), 5.12−5.03 (m, 1H, 2′H), 4.26−4.18 (m, 1H, 3′H), 4.06−4.01 (m, 1H, 4′H), 3.75−3.52 (m, 2H, 5′H_2), 2.64−2.56 (m, 2H, aliphat.), 2.18−2.07 (m, 2H, aliphat.), 1.75−1.61 (m, 2H, aliphat.). HRFAB-MS $[M + H]^+$ calc = 419.1501; found = 419.1512. MPLC purity = 99%. Yield = 96%.

2′-Deoxy-2′-[2-(3-thienyl)acetamido]adenosine (6w). Compound **6w** was prepared from resin **4w** as obtained from **3w** via activation method B. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.26 (s, 1H, 8H), 8.15 (bs, 1H, 2′NH), 8.13 (s, 1H, 2H), 7.37−7.30 (m, 3H, NH_2, aromat.), 7.06 (d, 1H, aromat., J = 2.03), 6.10 (d, 1H, aromat., J = 6.83), 5.98 (d, 1H, 1′H, J = 8.64), 5.80 (d, 1H, 5′OH, J = 4.58), 5.59−5.52 (m, 1H, 3′OH), 5.10−5.02 (m, 1H, 2′H), 4.27−4.20 (m, 1H, 3′H), 4.06−4.03 (m, 1H, 4′H), 3.71−3.55 (m, 2H, 5′H_2), 3.42 (s, 2H, CH_2). HRFAB-MS $[M + H]^+$ calc = 391.1189; found = 391.1196 MPLC purity: 98%. Yield = 96%.

2′-Deoxy-2′-(4-oxo-4-phenylbutanamido)adenosine (6x). Compound **6x** was prepared from resin **4x** as obtained from **3x** via activation method B. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.24 (s, 1H, 8H), 8.12 (s, 1H, 2H), 8.04 (d, 1H, 2′NH, J = 8.6), 7.98 (d, 1H, aromat., J = 7.1), 7.88 (d, 1H, aromat., J = 7.6), 7.68−7.58 (m, 1H, aromat.), 7.58−7.47 (m, 2H, aromat.), 7.35 (bs, 2H, NH_2), 5.96 (d, 1H, 1′H, J = 8.6), 5.70 (d, 1H, 5′OH, J = 2.8), 5.64−5.56 (m, 1H, 3′OH), 5.12−5.03 (m, 1H, 2′H), 4.28−4.22 (m, 1H, 3′H), 4.08−4.02 (m, 1H, 4′H), 3.70−3.55 (m, 2H, 5′H_2), 3.21 (t,

2H, aliphat., $J = 6.1$), 2.68 (t, 2H, aliphat., $J = 6.1$). HRFAB-MS $[M + H]^+$ calc = 426.1652; found = 426.1658. MPLC purity = 96%. Yield = 94%.

2′-Deoxy-2′-[3-(3-indolyl)propanamido]adenosine (6y). Compound **6y** was prepared from resin **4y** as obtained from **3y** via activation method B. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 10.68 (s, 1H, NH_{indol}), 8.25 (s, 1H, 8H), 8.14 (s, 1H, 2H), 8.02 (d, 1H, 2′NH, $J = 8.14$), 7.45 (d, 1H, aromat., $J = 7.63$), 7.35 (bs, 2H, NH_2), 7.31 (d, 1H, aromat., $J = 8.14$), 7.08−6.89 (m, 3H, aromat.), 5.95 (d, 1H, 1′H, $J = 8.65$), 5.72 (d, 1H, 5′OH, $J = 4.07$), 5.65−5.57 (m, 1H, 3′OH), 5.16−5.07 (m, 1H, 2′H), 4.27−4.22 (m, 1H, 3′H), 4.07−4.02 (m, 1H, 4′H), 3.37−3.54 (m, 2H, 5′H_2), 2.82−2.72 (m, 2H, aliphat.), 2.47−2.39 (m, 2H, aliphat.). HRFAB-MS $[M + H]^+$ calc = 438.1890; found = 438.1877. MPLC purity = 95%. Yield = 98%.

2′-Deoxy-2′-[4-(3-indolyl)butanamido]adenosine (6z). Compound **6z** was prepared from resin **4z** as obtained from **3z** via activation method B. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 10.71 (s, 1H, NH_{indol}), 8.25 (s, 1H, 8H), 8.11 (s, 1H, 2H), 7.91 (d, 1H, 2′NH, $J = 8.64$), 7.40 (d, 1H, aromat., $J = 8.14$), 7.33 (bs, 2H, NH_2), 7.13 (d, 1H, aromat., $J = 8.13$), 7.07−6.90 (m, 3H, aromat.), 5.95 (d, 1H, 1′H, $J = 8.65$), 5.69 (d, 1H, 5′OH, $J = 4.07$), 5.60−5.53 (m, 1H, 3′OH), 5.14−5.05 (m, 1H, 2′H), 4.25−4.19 (m, 1H, 3′H), 4.06−4.01 (m, 1H, 4′H), 3.72−3.53 (m, 2H, 5′H_2), 2.17−2.08 (m, 2H, aliphat.), 1.76−1.68 (m, 2H, aliphat.). HRFAB-MS $[M + H]^+$ calc = 452.2046; found = 452.2052. MPLC purity = 94%. Yield = 96%.

2′-Deoxy-2′-(3-methylbut-2-enamido)adenosine (6a′). Compound **6a′** was prepared from resin **4a′** as obtained from **3a′** via activation method B. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.25 (s, 1H, 8H), 8.13 (s, 1H, 2H), 7.82 (d, 1H, 2′NH, $J = 8.65$), 7.34 (bs, 2H, NH_2), 5.95 (d, 1H, 1′H, $J = 8.65$), 5.72 (s, 1H, aliphat.), 5.69 (d, 1H, 5′OH $J = 4.07$), 5.58−5.52 (m, 1H, 3′OH), 5.17−5.08 (m, 1H, 2′H), 4.24−4.19 (m, 1H, 3′H), 4.06−4.01 (m, 1H, 4′H), 3.72−3.52 (m, 2H, 5′H_2), 1.96 (s, 3H, aliphat.), 1.72 (s, 3H, aliphat.). HRFAB-MS $[M + H]^+$ calc = 349.1624; found = 349.1648. MPLC purity = 96%. Yield = 95%.

2′-(Cyclohex-3-en-1-ylcarbonamido)-2′-deoxy-adenosine (6b′). Compound **6b′** was prepared from resin **4b′** as obtained from **3b′** via activation method A. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.23 (s, 1H, 8H), 8.12 (s, 1H, 2H), 7.58 (d, 1H, 2′NH, $J = 8.64$), 7.33 (bs, 2H, NH_2), 5.95 (d, 1H, 1′H, $J = 8.64$), 5.73−5.67 (m, 1H, 5′OH), 5.64−5.52 (m, 3H, 3′OH, 2H, aliphat.), 5.08−4.99 (m, 1H, 2′H), 4.25−4.18 (m, 1H, 3′H), 4.07−4.02 (m, 1H, 4′H), 3.73−3.53 (m, 2H, 5′H_2), 2.45−2.35 (m, 3H, aliphat.), 2.02−1.78 (m, 3H, aliphat.). HRFAB-MS $[M + H]^+$ calc = 375.1781; found = 375.1768. MPLC purity = 91%. Yield = 97%.

2′-(4-Cyclohexylbutanamido)-2′-deoxy-adenosine (6c′). Compound **6c′** was prepared from resin **4c′** as obtained from **3c′** via activation method B. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.23 (s, 1H, 8H), 8.11 (s, 1H, 2H), 7.86 (d, 1H, 2′NH, $J = 8.65$), 7.31 (bs, 2H, NH_2), 5.94 (d, 1H, 1′H, $J = 8.64$), 5.68 (d, 1H, 5′OH, $J = 4.07$), 5.55−5.50 (m, 1H, 3′OH), 5.12−5.04 (m, 1H, 2′H), 4.21−4.17 (m, 1H, 3′H), 4.04−4.00 (m, 1H, 4′H), 3.70−3.56 (m, 2H, 5′H_2), 2.05−1.98 (m, 2H, aliphat.), 1.61−1.45 (m, 5H, aliphat.), 1.37−1.27 (m, 2 H, aliphat.), 1.17−0.80 (m, 6H, aliphat.), 0.70−0.60 (m, 2H, aliphat.). HRFAB-MS $[M + H]^+$ calc = 419.2407; found = 419.2347. MPLC purity = 96%. Yield = 92%.

2′-[4-(3,5-Dichlorophenoxy)butanamido]-2′-deoxy-adenosine (6d′). Compound **6d′** was prepared from resin **4d′** as obtained from **3d′** via activation method B. ^{1}H NMR (400 MHz, [D6] DMSO) δ (ppm) = 8.25 (s, 1H, 8H), 8.11 (s, 1H, 2H), 8.00 (d, 1H, 2′NH, $J = 8.65$ Hz), 7.54 (d, 1H, H_{aromat}, $J = 2.54$ Hz), 7.34 (bs, 2H, NH_2), 7.32 (d, 1H, H_{aromat}, $J = 2.54$),7.01 (d, 1H,H_{aromat}, $J = 8.64$), 5.95 (d, 1H, 1′H, $J = 8.64$), 5.70 (d, 1H, 5′OH, $J = 4.07$), 5.57−5.54 (m, 1H, 3′OH), 5.10−5.04 (m, 1H, 2′H), 4.24−4.21 (m, 1H, 3′H), 4.06−4.01 (m, 1H, 4′H), 3.95−3.92 (m, 2H, aliphat.), 3.72−3.55 (m, 2H, 5′H_2), 2.29−2.20 (m, 2H, aliphat.), 1.85−1.79 (m, 2H, aliphat.). HRFAB-MS $[M + H]^+$ calc = 497.1108; found = 497.1120. MPLC purity: 96%.Yield = 98%.

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