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Practical method for the parallel synthesis of 2′-amido-2′-deoxyadenosines

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Abstract

A new synthetic strategy for the simple and high yielding preparation of arrays of 2′-amido-2′-deoxyadenosine derivatives ready for biological testing without the need for chromatographic purification is described. Acids are coupled to the Kenner or Ellman safety catch linker, respectively, activated by cyanomethylation and subsequently transferred to the 2′-amino group of 2′-amino-2′-deoxyadenosine.

Keywords: Amino sugars; Combinatorial chemistry; Nucleosides; Supported reagents/reactions.

Introducing diversity into the carbohydrate subunits of nucleosides is a promising strategy to identify receptor ligands and enzyme inhibitors. Therefore methods for generating carbohydrate-modified nucleoside based combinatorial arrays or libraries are highly demanded. In our group the need for a simple and high yielding methodology to build molecular diversity around a carbohydrate nucleus arose, when the search for inhibitors of trypanosomal glycosomal glyceraldehyde-3-phosphate dehydrogenase was hampered by time consuming protection and deprotection schemes and necessary individual chromatographic purification of analogues of the discovered lead compound 2′-deoxy-2′-(3-methoxybenzamido)adenosine [1]. Consequently we set up a solid-phase assisted synthesis designed for the acylation of the 2′-amino group of 2′-amino-2′-deoxyadenosine (**2**) by coupling the selected acids to the Kenner safety catch linker improved by Ellman et al. [2]. In this way different resin aliquots were prepared from commercially available acids by standard amide bond forming procedures and activated for cleavage as described by Ellman. The resulting highly activated polymer bound acids **1a-j** could easily be transformed to compounds **3a-j** by stirring with **2** in an appropriate solvent (scheme 1, table 1).

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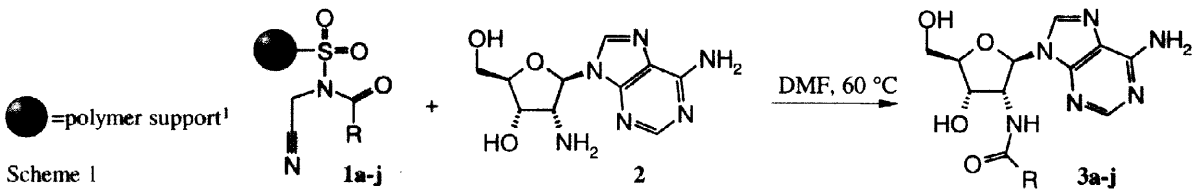

Scheme 1

Table 1
Compounds **3a-j** prepared from resins **1a-j**

	R	Equivalents of Resin Applied	Yield (%)	Purity[2] (%)
a	4-ethylphenyl	1.8	98	96
b	4-(methylethyl)phenyl	5.8	98	89
c	4-ethoxyphenyl	8.3	quantitative	91
d	benzo[*d*]1,3-dioxol-5-yl	5.5	94	88
e	3-chloro-4-fluorophenyl	9.3	92	89
f	3,4-difluorophenyl	5.9	92	84
g	(4-bromophenyl)methyl	10.0	quantitative	91
h	2-(4-methylphenyl)ethyl	1.7	99	95
i	3-oxo-3-phenylpropyl	8.7	quantitative	82
j	3-phenoxypropyl	1.4	quantitative	97

[2] C-18 RP HPLC, diode array detection 200-360 nm, for 100% method 260 nm; eluent methanol/water 40/60. ^{1}H NMR: Example: (**3h**) 500 MHz, [D_6]-DMSO, TMS, δ (ppm) = 2.19 (s, 3H, CH_3), 2.31-2.36 (m, 2H, 3′CH_2), 2.55-2.68 (m, 2H, 2′CH_2), 3.54-3.61 (m, 1H, 5′CH_2), 3.64-3.70 (m, 1H, 5′CH_2), 4.02-4.05 (m, 1H, 4′CH), 4.21 (d, 1H, 3′CH, *J*=5.0 Hz), 5.08-5.13 (m, 1H, 2′CH), 5.51-5.56 (m, 1H, 5′OH), 5.67 (s, 1H, 3′OH), 5.92 (d, 1H, 1′CH, *J*=8.2 Hz), 6.90 (s, 4H, aromatic tolyl H), 7.34 (s, 2H, NH_2), 7.94 (d, 1H, 2′NH, *J*=8.2 Hz), 8.13 (s, 1H, adenine H), 8.24 (s, 1H, adenine H); no indication of possible O- and N-acylated side products detected. FAB MS in accordance.

The reactions were terminated after TLC or HPLC analysis indicated practically complete consumption of the amino nucleoside. After filtration of the beads, removal of the solvent afforded **3a-j** in excellent to quantitative yield pure enough for biological testing. As a result, we set up a new modification scheme for aminodeoxynucleosides likely to be well suited for combinatorial approaches[4], especially for the fast production of arrays of amido nucleosides.

Acknowledgement

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References

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[2] Backes B, Virgilio AA, Ellman JA. J. Am. Chem. Soc. 1996; 118: 3055-3056.

[1] Novabiochem® very high load aminomethylated polystyrene resin with 4-sulfamylbenzoic acid or 4-sulfamylbutanoic acid as linker.

[4] In order to improve achievable diversity Fmoc-protected γ-aminobutyric acid was attached to the sulfamyl group on solid support, deprotected and subsequently acetic acid and 3-methoxy benzoic acid respectively were coupled to the free amino terminus. Activation for cleavage and stirring with a limiting amount of **2** yielded the expected compounds as determined by NMR and FAB MS (calculated for $C_{16}H_{23}N_7O_5$ $[M-H]^-$ 392.17, found 392.2; calculated for $C_{22}H_{27}N_7O_6$ $[M+H]^+$ 486.21, found 486.2).