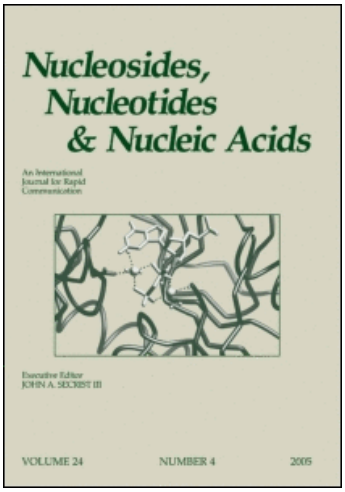

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SYNTHESIS OF 2′-([1,2,3]TRIAZOL-1-YL)-2′-DEOXYADENOSINES

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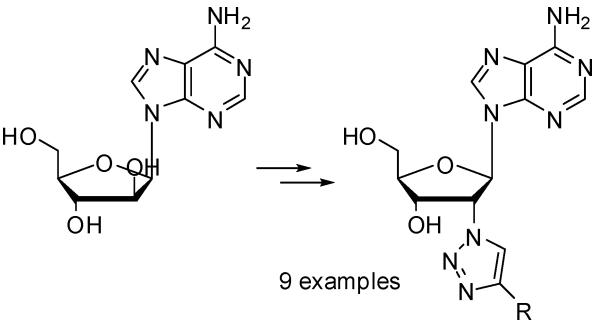
□ *A reliable and efficient protocol for the synthesis of 2′-([1,2,3]triazol-1-yl)-2′-deoxyadenosine derivatives from vidarabine is presented. Vidarabine was converted to 2′-azido-2′-deoxy-3′,5-O-(tetraisopropyldisiloxane-1,3-diyl)-adenosine. This azide was used as the starting material for the Cu^{I}-catalyzed parallel synthesis of 1,2,3-triazoles using a variety of alkynes. The reactions proceeded in good yield and gave almost exclusively the 1,4-disubstituted 1,2,3-triazoles.*



Keywords Nucleoside analogues; [3+2] cycloaddition

INTRODUCTION

Adenosine derivatives are of great importance in medicinal and biological chemistry, due to the abundance of adenosine-based species in living systems, such as the biologically crucial molecules RNA, ATP, cAMP, and NAD. It was recognized at an early stage that introducing diversity into the

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carbohydrate or base subunits of adenosine represent promising strategies to identify specific receptor ligands, enzyme inhibitors, or nucleoside function modifiers. Several naturally-occurring adenosine analogues demonstrate biological activities, such as protein synthesis inhibitors (puromycin)[1] and methyl transferase inhibitors (sinefungin).[2] Some synthetic analogues of nucleosides are prominent antiviral drugs owing to their ability to inhibit viral DNA polymerases and reverse transcriptases.[3] Many nucleoside analogues exhibit antiproliferative,[4] and antifungal properties.[5] Furthermore, a considerable number of nucleoside-based selective agonists and antagonists of adenosine receptors have been developed for potential therapeutic applications, including cardiovascular, inflammatory, and neurodegenerative diseases.[6]

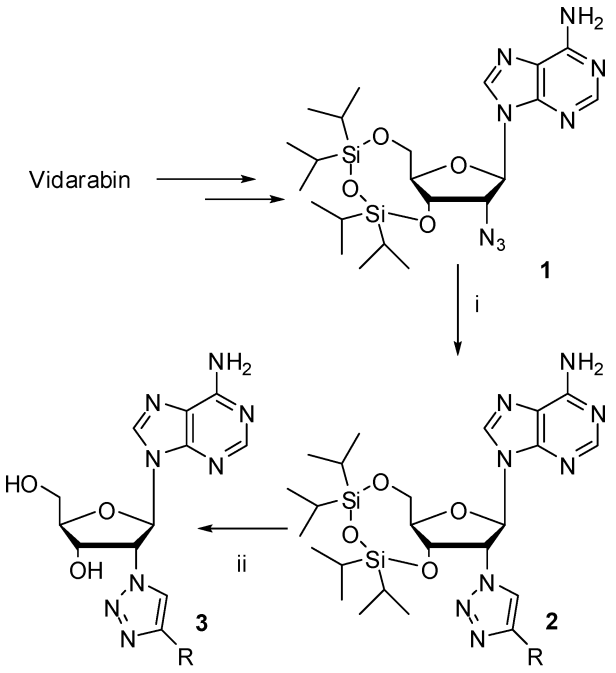
We have for some time been interested in designing enzyme inhibitors based on purine nucleosides, principally adenosine. For example, we have reported the synthesis of several enzymatically nonhydrolysable 5′-*O*-[N-(aminoacyl)-sulfamoyl]adenosine analogues of 5′-*O*-aminoacylphosphates that have been used in structural studies on a number of tRNA synthetases.[7] Recently, we have reported the preparation of 2′-aminoacylamino-2′-deoxyadenosine derivatives.[8] These compounds are nonhydrolysable isosteres of 2′-aminoacyladenosines and are of use in x-ray crystallographic studies of the elucidation of the editing mechanism of various tRNA synthetases.[9] Members of this class of adenosine derivatives have also been identified as potent inhibitors of trypanosomal glycosomal glyceraldehyde-3-phosphate dehydrogenase (GAPDH).[10]

Given the ubiquitous nature of the peptide linkage in biological molecules, replacement of the amide bond with isosteres in potential drug candidates has been a continual goal of many laboratories. Many surrogates have been introduced already,[11] yet the synthesis of many of these isosteres in a combinatorial way is difficult and requires several steps. Thus, the improved synthesis of peptide bond surrogates is an important endeavor that may open new opportunities for the study of amide-containing molecules and the development of compounds with novel physicochemical properties.

In this article, we present the synthesis of 2′-([1,2,3]triazol-1-yl)-2′-deoxyadenosines as analogues of 2′-amino-2′-deoxyadenosines, with a 1,2,3-triazole ring used as a bioisostere of the amide bond. We have used a popular "click chemistry" reaction, the copper(I)-catalyzed azide-alkyne [3+2] cycloaddition[12] as a straightforward method for the preparation of 2′-([1,2,3]triazol-1-yl)-2′-deoxyadenosine derivatives.

2. RESULTS AND DISCUSSION

Azide **1** is available from vidarabine, according to a literature procedure.[13] 3′,5′-Diprotection of vidarabine with a tetraisopropyldisiloxy



3a:84%	**2a**:65 %	R= Ph
3b:81 %	**2b**:65 %	R= MeC(O)
3c:79 %	**2c**:61 %	R= $MeC(CH_2)$
3d:81 %	**2d**:70 %	R= $EtC(O)OCH_2$
3e:98 %	**2e**:68 %	R= $Cbz\text{-}NHCH_2$
3f: 87 %	**2f**:62 %	R= $HOCH_2$
3g:95 %	**2g**:65 %	R= $Me(CH_2)_3$
3h:86 %	**2h**:67 %	R= EtOC(O)
3i:84 %	**2i**:69 %	R= $MeC(O)OCH_2$

SCHEME 1 Synthesis of 2′-([1,2,3]triazol-1-yl)-2′-deoxyadenosine derivatives. i) TIPDS-Cl_2, pyridine, room temperature, 4 hours; ii) CF_3SO_2Cl, DMAP, DCM, 0°C, 1 hour; iii) NaN_3, DMF, room temperature, 5 hours; iv) 0.1 eq sodium ascorbate and 0.01 eq $CuSO_4$, 50% aqueous *t*-BuOH, room temperature, 12 hours; v) NH_4F, MeOH, room temperature, overnight.

group followed by 2′-*O*-triflation and subsequent nucleophilic displacement with sodium azide (with inversion of configuration) afforded azide **1** (Scheme 1). With the desired 2′-azido starting material **1** in hand, we were able to investigate the regioselective synthesis of the 1,2,3-triazole ring.

We previously have reported intra- and intermolecular 1,2,3-triazole ring formation at the 2′-position of adenosine to produce fluorescent nucleoside derivatives.[14] Using the same conditions as we have previously reported, the copper(I)-catalyzed [3+2]-cycloaddition reaction between azide **1** and various alkynes was carried out overnight at room temperature in a *t*-BuOH/H_2O solution, using catalytic amounts of sodium ascorbate and $CuSO_4 \cdot 5H_2O$. Other reported methods of producing copper(I) (e.g., by

the use of copper(0) wire and microwave irradiation)[12a] for this reaction failed to produce any of the desired products. The products were observed to precipitate from the reaction mixtures, but isolation by filtration led to low product recovery and thus a standard aqueous work-up procedure was used. However, omission of the aqueous workup prior to chromatographic purification led to no reduction in recovered yield or purity.

Good isolated yields were obtained for a variety of alkynes, including those with an aromatic moiety (**2a**), an alkane chain (**2g**), a ketone (**2b**), various esters (**2d**, **2h**, **2i**) in addition to both protected and unprotected heterofunctionalities (**2e** and **2f,** respectively). The 1,4-disubstituted 1,2,3-triazole was produced exclusively in most cases. However, when 2 metyl-1-buten-3-yne (entry 3) was used as the alkyne component, small amounts (<15% by ^{1}H NMR spectroscopy) of the 1,5-disubstituted 1,2,3-triazole was formed and 61% triazole **2c** was isolated by column chromatography. The 3′,5′-*O*-TIPDS group of compounds **2a–g** was removed using ammonium fluoride (10 equivalents) in methanol at room temperature.[15] Direct purification by flash chromatography afforded compounds **3a–i** in good yields.

Compounds **3a–i** can be regarded as non-hydrolysable isosteres of 2′-aminoacyladenosines that are intermediates in the enzymatic reaction of tRNA synthetases.[9] Work currently is underway to evaluate their potential use in X-ray crystallographic studies for the elucidation of the editing mechanism of various tRNA synthetases, and as potential tRNA synthetase inhibitors.

3. CONCLUSION

We have developed a reliable and efficient protocol for the synthesis of 2′-([1,2,3]triazol-1-yl-2′-deoxyadenosine derivatives from vidarabine. The method reported leads to the simple and high-yielding conversion of 2′-azidoadenosine **1** into 2′-([1,2,3]triazol-1-yl)-2′-deoxyadenosines.

4. EXPERIMENTAL

4. General Experimental Methods

All reactions were performed under a nitrogen atmosphere, except those not susceptible to moisture or air. Solvents were dried using standard procedures. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra recorded at 100 MHz using a JEOL Eclipse spectrometer, in the solvents specified. Spectra were referenced to residual nondeuterated solvent (^{1}H NMR: $CDCl_3$ 7.26 ppm, d_6-DMSO 2.55 ppm and ^{13}C NMR: $CDCl_3$ 77.2 ppm, d_6-DMSO 39.5 ppm). Coupling constant (J) values are quoted

in Hertz. Elemental analyses were performed by MikroKemi AB, Uppsala, Sweden. Mass spectra and high-resolution mass spectra were performed by Stenhagen Analyslab AB, Mölndal, Sweden, using a magnetic sector (VG7070) instrument with FAB ionization (Xe gun operating at 10 kV). The matrix used was 3-nitrobenzyl alcohol or glycerol. Acceleration voltage was 6 kV and scan time 5 seconds. Optical rotations were measured using a Perkin-Elmer 341 LC polarimeter and $[\alpha]_D$ values are given in 10^{-1}deg cm^2 g^{-1}. IR spectra were recorded as KBr plates using a Perkin-Elmer 16 PC FTIR spectrometer. Flash chromatography was performed using Merck Geduran Si 60 (0.063–0.200 mm) silica gel. Thin layer chromatography (TLC) was performed using Merck Silica Gel 60 F254 aluminum-backed plates and visualized using UV light (254 and/or 366 nm). The solvents used to determine R_f values are the same as used for chromatographic purification, unless otherwise stated.

General Procedure for Synthesis of the Triazoles (2a–2j)

The alkyne (1 eq) and 2′-azido-2′-deoxy-3′,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (**1**) (200 mg, 0.37 mmol) were suspended in 50% aqueous *t*-BuOH (3 mL). Sodium ascorbate (7.3 mg, 0.037 mmol) was added, followed by copper(II) sulfate pentahydrate (0.9 mg, 0.0037 mmol). The mixture was stirred at room temperature until TLC analysis (90:10 DCM/MeOH) indicated complete conversion. The solvents were removed under reduced pressure. The solid residue was dissolved in DCM (10 mL) and washed with water (3 × 10 mL) and dried over magnesium sulfate. Concentration and purification by flash chromatography (90:10 DCM/MeOH) afforded the final product.

***2′-(4-Phenyl-[1,2,3]triazol-1-yl)-2′-deoxy-3′,5′-O-(tetraisopropyldisiloxane-1,3-diyl)-adenosine* (2a).** Phenylacetylene (24.5 μl, 0.37 mmol) was reacted with 2′-azido-2′-deoxy-3′,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (**1**) according to the procedure above. ^{1}H NMR ($CDCl_3$): δ 8.32 (1H, s), 8.01 (1H, s), 7.9 (1H, s), 7.8–7.86 (2H, m), 7.34–7.49 (3H, m, 3), 6.85 (1H, d, J = 2.6 Hz), 5.88–5.94 (1H, m), 5.67 (2H, br s), 5.47 (1H, t, J = 7.7 Hz), 4.35–4.43 (1H, m), 4.19 (1H, dd, J = 12.8, 2.9 Hz), 4.07 (1H, dd, J = 12.8, 2.9 Hz), 1.30–0.78 (28H, m). ^{13}C NMR ($CDCl_3$): δ 156.0, 153.4, 149.3, 147.8, 140.5, 140.03, 130.5, 129.0, 128.4, 125.9, 121.8, 120.6, 86.8, 83.0, 70.3, 65.6, 61.3, 17.5, 17.49, 17.47, 17.40, 17.3, 16.93, 16.88, 13.4, 13.1, 12.9, 12.8. $[\alpha]_D$ = -128.6 (c = 0.0075, $CHCl_3$). HRMS [$C_{30}H_{44}N_8O_4Si_2$]: calcd. 637.551; found: 637.310. Elemental analysis: calcd. C, 56.52; H, 6.96; N, 17.58, Found C, 56.50; H, 6.86; N, 17.67.

***2′-(4-Carbomethyl-[1,2,3]triazol-1-yl)-2′-deoxy-3′,5′-O-(tetraisopropyldisiloxane-1,3-diyl)-adenosine* (2b).** 3-Butyn-2-one (28.9 μl, 0.37 mmol) was reacted with 2′-azido-2′-deoxy-3′,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (**1**) according to the procedure above. ^{1}H NMR ($CDCl_3$): δ 8.30

(1H, s), 8.20 (1H, s), 7.99 (1H, s), 6.77 (1H, d, $J = 2.6$ Hz), 5.89–5.94 (1H, m), 5.61 (2H, s), 5.46 (1H, t, $J = 7.9$ Hz), 4.29–4.36 (1H, m), 4.17 (1H, dd, $J = 12.8$, 4.0 Hz), 4.05 (1H, dd, $J = 13.0$, 3.1 Hz), 1.65 (3H, s), 1.15–0.79 (28H, m). ^{13}C NMR ($CDCl_3$): δ 192.8, 155.5, 153.1, 148.8, 147.5, 139.4, 127.4, 120.1, 86.4, 82.8, 69.7, 65.8, 60.8, 27.1, 17.2, 17.2, 17.1, 17.1, 17.0, 16.9, 16.6, 16.5, 13.1, 12.8, 12.6, 12.5. $[\alpha]_D = -85.5$ ($c = 0.014$, $CHCl_3$). HRMS [$C_{26}H_{42}N_8O_5Si_2$]: calcd. 603.508; found 603.293.

***2′-(4-Isopropenyl-[1,2,3]triazol-1-yl)-2′-deoxy-3′,5′-O-(tetraisopropyldisiloxane-1,3-diyl)-adenosine* (2c).** 2-Methyl-1-buten-3-yne (35 μl, 0.37 mmol) was reacted with 2′-azido-2′-deoxy-3′,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (**1**) according to the procedure above. ^{1}H NMR ($CDCl_3$): δ 8.25 (1H, s), 8.0 (1H, s), 7.62 (1H, s), 6.80 (1H, d, $J = 1.8$ Hz), 6.40 (2H, br s), 5.88–5.81 (1H, m), 5.69 (1H, s), 5.41 (1H, t, $J = 7.7$ Hz), 5.08 (1H, s), 4.34–4.25 (1H, m), 4.13 (1H, dd, $J = 12.6$, 6.4 Hz), 4.02 (1H, $J = 12.7$, 2.7 Hz), 2.09 (3H, s), 1.12–0.74 (28H, m). ^{13}C NMR ($CDCl_3$): δ 155.7, 153.3, 149.4, 148.7, 140.0, 133.3, 121.6, 120.6, 112.9, 86.7, 82.9, 70.3, 65.4, 61.3, 20.8, 17.5, 17.4, 17.4, 17.3, 17.2, 16.9, 16.8, 13.4, 13.1, 12.8, 12.7. HRMS [$C_{27}H_{45}N_8O_4Si_2$]: calcd. 601.310; found 601.310. Elemental analysis: calcd. C, 53.97; H, 7.38; N, 18.95, Found C, 53.92; H, 7.31; N, 18.89.

***2′-(4-Hydroxymethyl-[1,2,3]triazol-1-yl)-2′-deoxy-3′,5′-O-(tetraisopropyldisiloxane-1,3-diyl)-adenosine propionate* (2d).** Propargyl propionate (43 μl, 0.37 mmol) was reacted with 2′-azido-2′-deoxy-3′,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (**1**) according to the procedure above. ^{1}H NMR ($CDCl_3$): δ 8.30 (1H, s), 7.98 (1H, s), 7.74 (1H, s), 6.80 (1H, d, $J = 2.6$ Hz), 5.85 (1H, dd, $J = 7.1$, 2.4 Hz), 5.60 (2H, br s), 5.44 (1H, t, $J = 7.9$ Hz), 5.25 (2H, s), 4.28–4.35 (1H, m), 4.17 (1H, dd, $J = 12.8$, 4.0 Hz), 4.04 (1H, dd, $J = 12.8$, 2.9 Hz), 2.34 (2H, dd, $J = 7.5$, 15.2 Hz), 1.16–0.76 (31H, m). ^{13}C NMR ($CDCl_3$): δ 174.3, 156.0, 153.2, 149.2, 142.9, 139.9, 125.9, 120.5, 86.6, 82.8, 70.1, 65.5, 61.2, 57.5, 27.4, 17.4, 17.4, 17.3, 17.3, 17.1, 16.8, 16.8, 13.3, 13.0, 12.7, 12.7, 9.0. $[\alpha]_D = -74.4$ ($c = 0.01$, $CHCl_3$). HRMS [$C_{28}H_{46}N_8O_6Si_2$]: calcd. 646.886; found 647.3159.

***2′-(4-[N-Cbz-aminomethyl]-[1,2,3]triazol-1-yl)-2′-deoxy-3′,5′-O-(tetraisopropyldisiloxane-1,3-diyl)-adenosine* (2e).** Cbz-propargyl amine (65 mg, 0.37 mmol) was reacted with 2′-azido-2′-deoxy-3′,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (**1**) according to the procedure above. ^{1}H NMR ($CDCl_3$): δ 8.32 (1H, s), 8.01 (1H, s), 7.70 (1H, s), 7.40–7.30 (5H, m), 6.80–6.74 (1H, m), 5.88–5.80 (1H, m), 5.46–5.34 (1H, m), 5.10 (2H, s), 4.56–4.46 (1H, m), 4.36–4.26 (1H, m), 4.16 (1H, dd, $J = 12.6$, 3.7 Hz), 4.03 (1H, dd, $J = 12.6$, 2.8 Hz), 1.14–0.78 (28H, m). ^{13}C NMR ($CDCl_3$): δ 156.6, 156.0, 153.3, 149.1, 145.1, 140.2, 136.5, 128.6, 128.3, 128.2, 124.4, 120.4, 86.8, 82.9, 77.4, 70.4, 67.0, 65.6, 61.4, 36.3, 17.5, 17.44, 17.41, 17.36, 17.2, 16.9, 16.8, 13.3, 13.1, 12.8, 12.7. $[\alpha]_D = -27.2$ (c = 0.0035, $CHCl_3$). HRMS

$[C_{25}H_{41}N_8O_5Si_2]$: calcd. 724.342; found 724.343. Elemental analysis: calcd. C, 41.45; H, 5.72; N, 15.47, found C, 41.49; H, 5.69; N, 15.51.

2′-(4-Hydroxymethyl-[1,2,3]triazol-1-yl)-2′-deoxy-3′,5′-O-(tetraisopropyldisiloxane-1,3-diyl)-adenosine **(2f).** Propargyl alcohol (21.5 μl, 0.37 mmol) was reacted with 2′-azido-2′-deoxy-3′,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (**1**) according to the procedure above.[1]H NMR ($CDCl_3$): δ 8.28 (1H, s), 8.00 (1H, s), 7.68 (1H, s), 6.78 (1H, d, J = 2.6 Hz), 5.83 (1H, dd, J = 7.3, 2.2 Hz), 5.80 (2H, br s), 5.42 (1H, t, J = 7.7 Hz), 4.84 (2H, s), 4.37–4.30 (1H, m), 4.17 (1H, J = 12.8, 4.0 Hz), 4.05 (1H, J = 12.8, 2.9 Hz), 1.50–0.79 (28H, m). ^{13}C NMR (CD_3OD): δ 157.3, 153.9, 150.0, 148.8, 141.8, 125.8, 120.8, 88.2, 84.5, 72.4, 66.9, 63.4, 56.4, 17.9, 17.8, 17.8, 17.7, 17.6, 17.5, 17.2, 17.2, 14.3, 14.1, 14.0, 13.7. $[\alpha]_D$ = -84.6 (c = 0.01, $CHCl_3$). HRMS $[C_{25}H_{41}N_8O_5Si_2]$: calcd. 590.497; found 591.2899.

2′-(4-Butyl-[1,2,3]triazol-1-yl)-2′-deoxy-3′,5′-O-(tetraisopropyldisiloxane-1,3-diyl)-adenosine **(2g).** 1-Hexyne (42.5 μl, 0.37 mmol) was reacted with 2′-azido-2′-deoxy-3′,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (**1**) according to the procedure above. ^{1}H NMR ($CDCl_3$): δ 8.23 (1H, s), 7.98 (1H, s), 7.39 (1H, s), 6.78 (1H, d, J = 2.2 Hz), 6.54–6.36 (2H, br s), 5.82–5.76 (1H, m), 5.38 (1H, t, J = 7.7 Hz), 4.34–4.24 (1H, m), 4.12 (1H, dd, J = 12.8, 4.0 Hz), 4.0 (1H, dd, J = 12.8, 2.9 Hz), 2.62–2.27 (2H, m), 1.60 (2H, quintet, J = 7.5 Hz), 1.33 (2H, sextet, J = 7.4 Hz), 1.10–0.74 (31H, m). ^{13}C NMR ($CDCl_3$): δ 156.1, 153.2, 149.2, 148.2, 140.0, 120.5, 122.7, 86.7, 82.9, 70.2, 65.3, 61.3, 31.7, 25.3, 22.3, 17.5, 17.42, 17.39, 17.3, 17.2, 16.8, 13.9, 13.3, 13.1, 12.8, 12.7. $[\alpha]_D$ = -75.5 (c = 0.007, $CHCl_3$). HRMS $[C_{28}H_{48}N_8O_4Si_2]$: calcd. 617.530; found 617.3433. Elemental analysis: calcd. C, 54.46; H, 7.83; N, 18.15, found C, 54.38; H, 7.85; N, 18.08.

2′-(4-Carboethoxy-[1,2,3]triazol-1-yl)-2′-deoxy-3′,5′-O-(tetraisopropyldisiloxane-1,3-diyl)-adenosine **(2h).** Ethyl propiolate (37.5 μl, 0.37 mmol) was reacted with 2′-azido-2′-deoxy-3′,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (**1**) according to the procedure above.[1]H NMR ($CDCl_3$): 8.29 (1H, s), 8.23 (1H, s), 8.00 (1H, s), 6.79 (1H, d, J = 2.6 Hz), 5.94 (1H, dd, J = 7.3, 2.2 Hz), 5.71 (2H, br s), 5.46 (1H, t, J = 7.7 Hz), 4.44 (2H, q, J 7.1 Hz), 4.33–4.27 (1H, m), 4.17 (1H, dd, J = 12.8, 4.0 Hz), 4.05 (1H, dd, J = 12.8, 2.9 Hz), 1.41 (3H, t, J = 7.1 Hz), 1.14–0.79 (28H, m). ^{13}C NMR ($CDCl_3$): δ 160.6, 155.9, 155.9, 153.1, 149.0, 139.9, 129.5, 120.1, 86.5, 82.8, 70.1, 65.9, 61.4, 61.2, 17.4, 17.3, 17.3, 17.2, 17.2, 17.0, 16.7, 16.7, 14.3, 13.2, 13.0, 12.7, 12.6. $[\alpha]_D$ = -105.8 (c = 0.008, $CHCl_3$). HRMS $[C_{27}H_{44}N_8O_6Si_2]$: calcd. 633.518; found 633.3014.

2′-(4-Carbomethoxy-[1,2,3]triazol-1-yl)-2′-deoxy-3′,5′-O-(tetraisopropyldisiloxane-1,3-diyl)-adenosine **(2i).** Methyl propiolate (33 μl, 0.37 mmol) was reacted with 2′-azido-2′-deoxy-3′,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (**1**) according to the procedure above. ^{1}H NMR ($CDCl_3$): δ 8.26 (1H, s), 8.21 (1H, s), 8.06 (1H, s), 6.79 (1H, s), 6.36 (2H, br s), 5.95 (1H, d, J = 7.0 Hz), 5.43 (1H, t, J = 7.9 Hz), 4.31–4.25 (1H, m), 4.15 (1H, dd,

J = 12.8, 3.7 Hz), 4.02 (1H, dd, J = 12.8, 2.9 Hz), 3.91 (3H, s), 1.10–0.77 (28H, m). ^{13}C NMR ($CDCl_3$): δ 161.0, 155.9, 153.1, 149.0, 139.9, 139.5, 129.6, 120.4, 86.6, 82.8, 70.0, 65.9, 61.1, 52.3, 17.41, 17.35, 17.31, 17.26, 17.2, 17.1, 16.8, 16.7, 13.2, 13.0, 12.8, 12.5, 12.4. $[\alpha]_D$ = -71.9 (c = 0.015, $CHCl_3$). HRMS [$C_{26}H_{42}N_8O_6Si_2$]: calcd. 619.507; found 619.283. Elemental analysis: calcd. C, 50.40; H, 6.85; N, 18.09, found C, 50.38; H, 6.86; N, 18.01.

General Procedure for the Synthesis of Compounds 3a–i

The 3′,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-protected compound **2** (1 eq) was suspended in methanol (10 mL). Ammonium fluoride (8.5 eq) was added and the mixture was stirred at room temperature until TLC analysis (90:10 DCM/MeOH) indicated that there was no starting material left, usually requiring overnight. Concentration under reduced pressure and purification by column chromatography (90:10 DCM/MeOH) afforded to product **3** as a white solid.

***2′-(4-Phenyl-[1,2,3]triazol-1-yl)- 2′-deoxy-adenosine* (3a).** Compound **2** (149 mg, 0.38 mmol) was treated with ammonium fluoride (119 mg, 3.21 mmol) according to the procedure above. ^{1}H NMR (CD_3OD) δ 8.57 (1H, s), 8.34 (1H, s), 8.18 (1H, s), 7.83–7.78 (2H, m), 7.45–7.30 (3H, m), 6.90 (1H, d, J = 8.1 Hz), 6.06 (1H, dd, J = .7, 5.5 Hz), 4.80 (1H, dd, J = 5.5, 2.2 Hz), 4.44–4.38 (1H, m), 3.99 (1H, dd, J = 12.8, 2.6 Hz), 3.86 (1H, dd, J = 12.7, 2.7 Hz). ^{13}C NMR (DMSO-d_6): δ 156.2, 152.7, 148.9, 146.1, 139.9, 130.5, 128.9, 127.9, 125.1, 122.2, 119.3, 86.9, 85.2, 70.3, 64.3, 61.4. $[\alpha]_D$ = -291.2 (c = 0.0055, MeOH). HRMS [$C_{18}H_{18}N_8O_3$]: calcd. 394.371; found 395.159. Elemental analysis: calcd. C, 54.82; H, 4.60; N, 28.41, found C, 54.73; H, 4.65; N, 28.33.

***2′-(4-Carbomethyl-[1,2,3]triazol-1-yl)- 2′-deoxy-adenosine* (3b).** Compound **2** (123 mg, 0.34 mmol) was treated with ammonium fluoride (107 mg, 2.89 mmol) according to the procedure above.^{1}H NMR (CD_3OD): δ 8.77 (1H, s), 8.32 (1H, s), 8.18 (1H, s), 6.86 (1H, d, J = 7.7 Hz), 6.10 (1H, dd, J = 7.3, 5.5 Hz), 4.78 (1H, dd, J = 5.5, 2.2 Hz), 4.41–4.36 (1H, m), 3.98 (1H, dd, J = 12.8, 2.6 Hz), 3.84 (1H, dd, J = 12.6, 2.7 Hz), 2.59 (3H, s). ^{13}C NMR (DMSO-d_6): δ 191.6, 156.2, 152.7, 148.8, 146.8, 139.9, 128.1, 119.3, 86.8, 85.2, 70.2, 64.4, 61.4, 27.1. $[\alpha]_D$ = -166.9 (c = 0.007, MeOH). HRMS [$C_{14}H_{16}N_8O_4$]: calcd. 360.306; found 361.138. Elemental analysis. Calcd: C, 46.66; H, 4.48; N, 31.10, Found: C, 46.57; H, 4.50; N 31.07.

***2′-(4-isopropenyl-[1,2,3]triazol-1-yl)- 2′-deoxy-adenosine* (3c).** Compound **2** (80 mg, 0.23 mmol) was treated with ammonium fluoride (73 mg, 1.97 mmol) according to the procedure above.^{1}H NMR: (CD_3OD) δ 8.32 (1H, s), 8.31 (1H, s), 8.27 (1H, s), 6.84 (1H, d, J = 8.1 Hz), 6.00 (1H, dd, J = 7.7, 5.5 Hz), 5.66 (1H, s), 5.10 (1H, s), 4.75 (1H, dd, J = 5.5, 2.2 Hz), 4.40–4.36 (1H, m), 3.97 (1H, dd, J = 12.8, 2.6 Hz), 3.84 (1H, dd, J = 12.6, 2.7 Hz), 2.01 (3H, s). ^{13}C NMR (DMSO-d_6): 156.2, 152.6, 148.9, 147.2, 139.9, 133.5, 128.1,

122.1, 119.3, 111.7, 86.9, 85.2, 70.3, 64.1, 61.4, 48.6, 20.3. $[\alpha]_D = -118.3$ (c = 0.005, MeOH).

***2′-(4-Hydroxymethyl-[1,2,3]triazol-1-yl)-2′-deoxy-adenosine propionate* (3d).** Compound **2** (190 mg, 0.47 mmol) was treated with ammonium fluoride (148 mg, 3.99 mmol) according to the procedure above.[1]H NMR (CD_3OD): δ 8.31 (1H, s), 8.26 (1H, s), 8.17 (1H, s), 6.82 (1H, d, J = 7.7 Hz), 6.01 (1H, dd, J = 7.7, 5.5 Hz), 5.17 (2H, s), 4.74 (1H, dd, J = 5.3, 2.4 *Hz*), 4.39–4.34 (1H, m), 3.96 (1H, dd, J = 12.4, 2.6 Hz), 3.83 (1H, dd, J = 2.7, 12.6 Hz), 2.33 (2H, q, J = 7.6 Hz), 1.08 (3H, t, J = 7.5 Hz). ^{13}C NMR (DMSO-d_6): δ 173.3, 156.2, 152.7, 148.9, 141.7, 139.8, 125.5, 119.2, 86.9, 85.1, 70.2, 64.2, 61.4, 57.0, 26.6, 8.9. $[\alpha]_D = -116.3$ (c = 0.006, MeOH). HRMS [$C_{16}H_{20}N_8O_5$]: calcd. 404.354; found 405.162. Elemental analysis: calcd. C, 47.53; H, 4.99; N, 27.71, found C, 47.58; H, 5.06; N, 27.63.

***2′-(4-Carboethoxy-[1,2,3]triazol-1-yl)-2′-deoxy-adenosine* (3e).** Compound **2** (95 mg, 0.20 mmol) was treated with ammonium fluoride (63 mg, 1.70 mmol) according to the procedure above. ^{1}H NMR (DMSO-d_6): δ 8.39 (1H, s), 8.14 (1H, s), 8.09 (1H, s), 7.42–7.27 (5H, m), 6.74 (1H, d, J = 7.3), 6.06 (1H, dd, J = 7.4, 5.9 Hz), 5.99 (1H, d, J = 5.1 Hz), 5.50 (1H, dd, J = 6.6, 5.1 Hz), 5.03 (2H, s), 4.64–4.61 (1H, m), 4.25–4.11 (3H, m), 3.82–3.77 (1H, m), 3.68–3.63 (1H, m). ^{13}C NMR (DMSO-d_6): δ 156.8, 153.3, 149.5, 145.6, 140.4, 137.6, 128.9, 128.3, 124.1, 119.8, 87.5, 85.7, 70.9, 66.0, 64.6, 62.0, 36.6. $[\alpha]_D$ = -99.4 (c = 0.004, MeOH). HRMS [$C_{21}H_{24}N_9O_5$]: calcd. 482.190; found 482.191. Elemental analysis. Calcd: C, 52.27; H, 5.03; N, 26.13, Found: C, 52.31; H, 5.05; N 26.17.

***2′-(4-Hydroxymethyl-[1,2,3]triazol-1-yl)-2′-deoxy-adenosine* (3f).** Compound **2** (156 mg, 0.45 mmol) was treated with ammonium fluoride (142 mg, 3.83 mmol) according to the procedure above.[1]H NMR (CD_3OD): δ 8.31 (1H, s), 8.19 (1H, s), 8.11 (1H, s), 6.80 (1H, d, J = 8.0 Hz), 6.04 (1H, dd, J = 7.9, 5.3 Hz), 4.74 (1H, dd, J = 5.5, 2.2 Hz), 4.66 (2H, s), 4.39–4.36 (1H, m), 3.97 (1H, dd, J = 12.8, 2.6 Hz), 3.84 (1H, dd, J = 12.8, 2.6 Hz). ^{13}C NMR (DMSO-d_6): δ 156.8, 153.3, 149.5, 148.3, 140.5, 124.0, 119.8, 87.6, 85.7, 70.9, 64.5, 62.0, 55.5. $[\alpha]_D = -176.9$ (c = 0.006, MeOH). HRMS [$C_{13}H_{16}N_8O_4$]: calcd.- 349.137; found 349.136.

***2′-(4-Butyl-[1,2,3]triazol-1-yl)-2′-deoxy-adenosine* (3g).** Compound **2** (142 mg, 0.41 mmol) was treated with ammonium fluoride (129 mg, 3.48 mmol) according to the procedure above. ^{1}H NMR (CD_3OD): δ 8.31 (1H, s), 8.16 (1H, s), 7.98 (1H, s), 6.80 (1H, d, J = 7.7 Hz), 5.98–5.92 (1H, m), 4.72 (1H, dd, J = 5.5, 2.2 Hz), 4.39–4.35 (1H, m), 3.96 (1H, dd, J = 12.5, 2.6 Hz), 3.83 (1H, dd, J = 12.6, 2.8 Hz,), 2.7 (2H, t, J = 7.5 Hz), 1.62 (2H, quintet, J = 7.6 Hz), 1.35 (2H, sextet, J = 7.5 Hz), 0.92 (3H, t, J = 7.5 Hz). ^{13}C NMR (DMSO-d_6) δ 156.2 152.6, 148.9, 146.6, 139.7, 122.5, 119.2, 87.0, 85.1, 70.4, 64.1, 61.5, 30.9, 24.6, 21.6, 13.7. $[\alpha]_D = -206.0$ (c = 0.007, MeOH). HRMS [$C_{13}H_{16}N_8O_4$]: calcd. 348.370; found 348.377.

***2′-(4-Carboethoxy-[1,2,3]triazol-1-yl)-2′-deoxy-adenosine* (3h).** Compound **2** (145 mg, 0.38 mmol) was treated with ammonium fluoride (119 mg, 3.21 mmol) according to the procedure above. ^{1}H NMR (CD_3OD): δ 8.79 (1H, s), 8.33 (1H, s), 8.18 (1H, s), 6.85 (1H, d, $J = 7.7$ Hz), 6.12–6.08 (1H, m), 4.81–4.76 (1H, m), 4.42–4.42 (3H, m), 1.37 (3H, t, $J = 7.1$ Hz). ^{13}C NMR (DMSO-d_6) δ 160.1, 156.2, 152.6, 148.8, 139.9, 138.7, 129.9, 119.3, 86.8, 85.2, 70.2, 64.5, 61.4, 60.6, 14.2. $[\alpha]_D$ = -27.1 ($c = 0.005$, MeOH). HRMS [$C_{15}H_{18}N_8O_5$]: calcd. 390.327; found 391.146. Elemental analysis: calcd. C, 46.15; H, 4.65; N, 28.71, found: C, 46.06; H, 4.58; N, 28.59.

***2′-(4-Carbomethoxy-[1,2,3]triazol-1-yl)-2′-deoxy-adenosine* (3i).** Compound **2** (149 mg, 0.40 mmol) was treated with ammonium fluoride (126 mg, 3.40 mmol) according to the procedure above. ^{1}H NMR: (CD_3OD) δ 8.8 (1H, s), 8.30 (1H, s), 8.18 (1H, s), 6.85 (1H, d, $J = 7.3$ Hz), 6.12–6.06 (1H, m), 4.77 (1H, dd, $J = 5.5$, 2.6 Hz), 4.40–4.35 (1H, m), 3.97 (1H, dd, $J = 18.8$, 2.6 Hz), 3.91 (3H, s), 3.84 (1H, dd, $J = 12.6$, 2.7 Hz). ^{13}C NMR (DMSO-d_6): δ 160.6, 156.2, 125.6, 148.8, 139.9, 138.4, 130.0, 119.3, 86.8, 85.2, 70.2, 64.5, 61.4, 51.8 $[\alpha]_D$ = -225.2 ($c = 0.005$, MeOH). HRMS [$C_{14}H_{16}N_8O_5$]: calcd. 377.300; found: 377.134. Elemental analysis. Calcd: C, 44.69; H, 4.29; N, 29.78, Found: C, 44.56; H, 4.34; N 29.62.

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