Synthesis and Antiviral Activity of 2'-Deoxy-2'-fluoro-L-arabinofuranosyl 1,2,3-Triazole Derivatives

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Triazole Nucleosides, Anti-Viral Activity, Glycosyl Azides

The title compounds were prepared by building up the triazole ring at the anomeric position via the glycosyl azides 5a,b. The anomeric configurations of these nucleosides were assigned by using $^1$H, $^{13}$C and NOESY NMR spectroscopy. The synthesized nucleosides were evaluated against HIV-1 and HBV.

Introduction

Nucleosides incorporating five-membered heterocyclic rings such as imidazole, pyrrole, pyrazole, triazole etc. are common structural motifs in order to discover biologically active compounds. Imidazole nucleosides, AICA [5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide] and bredisin, are the most known compounds among the heterocyclic nucleosides [1–3].

Additionally, several C-nucleoside analogues, such as showdomycin and pyrazomycin, have been isolated and found to be potent antibiotics [4, 5]. The 1,2,4-triazole analogue, virazole (Fig. 1), is the first synthetic heterocyclic nucleoside which exhibits broad-spectrum antiviral activities [6, 7].

Most of nucleosides reported so far incorporating five-membered heterocyclic rings are riboside derivatives [8–10] and modifications at the carbohydrate moiety have not been well described in the literature. One of the most favored substituents in the carbohydrate moiety is a fluorine atom because of its similar van der Waals radius as that of hydrogen. The introduction of a fluorine atom has provided a variety of new compounds with enhanced antiviral activity and with a glycosidic bond stabilized to chemical and enzymatic hydrolysis [11].

We describe here the synthesis of 2'-deoxy-2'-fluoroarabinofuranosyl-1,2,3-triazole derivatives by the construction of the heterocyclic moiety from glycosyl azide templates. Therefore, it was of interest to develop a versatile method that allows us to access heterocyclic nucleosides and it was of interest to see whether any changes in biological activity resulted from this modification of the carbohydrate moiety with differently substituted triazoles.

Results

Generally, the synthesis of triazole nucleosides can be achieved by two methodologies [3]: (1) coupling of a triazole base with a glycosyl donor, and (2) construction of the heterocyclic moiety at the anomeric position via the glycosyl azide. The advantage of the latter method is that the triazole ring is constructed selectively and that compounds can be obtained which are not readily accessible by the direct condensation, although it generally takes a few more reaction steps than the first method.
Compound 3 was synthesized from commercially available 2-hydroxy-1,3,5-tri-O-benzoyl-α-L-ribofuranose (1) (Fig. 2), by using the procedure of Tann et al. [12] and then the fluorination method of Chou et al. [13]. Conversion of 3 to the glycosyl bromide [14] 4 followed by coupling with...
NaN\(_3\) in DMF [15] resulted in a mixture of glycosyl azide as anomers, which was previously synthesized by Stimac et al. [16]. The anomers were separated by silica gel column chromatography to give the individual isomers in a ratio of 3 : 1 (5b : 5a). The configurations of the azides were assigned based on the \(^1\)H NMR spectra. Due to the deshielding effect of the azido group, a higher chemical shift for 4'-H was observed for the \(\alpha\)-isomer 5a (\(\delta = 4.56\) ppm) than for the \(\beta\)-isomer 5b (\(\delta = 4.32\) ppm). In addition, the empirical rule reported by Mansuri et al. [17] can be extended to the glycosyl azide analogues, since \(^1\)C NMR spectra showed a \(J_{\text{C1}-\text{F}}\) of 17.1 Hz for the \(\beta\)-isomer, and of 35.0 Hz for the \(\alpha\)-isomer. The anomic assignment was also confirmed at the final nucleoside stage by NOESY NMR spectroscopy.

In order to synthesize the 1,2,3-triazole-5-carboxamide derivative, compound 6 was prepared by treatment of ethyl bromopyruvate with triphenylphosphine followed by NaHCO\(_3\) [18, 19]. Reaction of the \(\beta\)-azide 5b with 6 gave the protected nucleoside 7b as the only product (Fig. 2). The reaction carried out in refluxing xylene gave a low yield (29%), which was possibly due to the decomposition at this temperature, while using toluene as solvent resulted in a higher yield (60%). Deprotection with methanolic ammonia gave the free nucleoside 8b in 90% yield. The \(\alpha\)-isomer 8a was also obtained in a 72% yield by using similar methodology starting with the \(\alpha\)-azide 5a.

The \(^1\)H NMR spectra of these 5-carbonyl substituted 1,2,3-triazoles show unusually low-field chemical shifts for the anomeric protons (\(\delta = 7.0-7.4\) ppm). This is observed for both the \(\alpha\) and \(\beta\) anomers at both protected and deprotected stages. A possible explanation may be due to the deshielding effect of the 5-carbonyl group, since neither the 5-NH\(_2\) substituted nor the 5-unsubstituted analogues exhibit this low-field chemical shift.

The synthesis of 1,2,3-triazole-4-carboxamide was achieved by 1,3-dipolar cycloaddition of the \(\beta\)-azide 5b with ethyl propiolate in refluxing toluene [20] (Fig. 2). Two regio-isomers (9b and 7b) were obtained with the desired product (9b) precipitating from the reaction mixture after cooling to 20°C. Separation of the mixture from the mother liquor gave a total yield of 97% in a ratio of 3 : 1 (9b : 7b). The same total yield (97%) was also obtained for the \(\alpha\)-isomers with a ratio of 2.3 : 1 for 9a and 7a. Deprotection in methanolic ammonia gave the 1,2,3-triazole-4-carboxamides 10b and 10a, respectively.

The anomic configurations of 10b and 10a were assigned based on the NOESY spectra. For 10b, a correlation between 1'-H and 4'-H was observed, indicating that they are on the same side. The \(\beta\)-configuration was also confirmed by the correlation of 3'-H and 5'-OH with 5-H of the heterocyclic ring. On the other hand, the \(\alpha\)-configuration of 10a was confirmed based on the observation that 5-H of the heterocycle showed cross peaks with 2'-H, 3'-OH and 4'-H, respectively, while no correlation between 1'-H and 4'-H was observed.

The 5-amino-1,2,3-triazole-4-carboxamide derivatives 11b and 11a were synthesized by treatment of glycosyl azide 5b and 5a, respectively, with ethyl cyanoacetate in DMF in the presence of KOH at 20 °C [21] (Fig. 2). Due to partial debenzylation, a complex reaction mixture was obtained. Therefore, it was treated with NaOMe/MeOH to ensure a full deprotection and purified on a silica gel column to give 11b and 11a in 50% and 76% yield, respectively. In addition to the NMR spectroscopy, the products have also been characterized by microanalysis (see Table 1), mass spectrometry, IR, UV and optical rotation.

**Biological evaluation.** The synthesized nucleosides were evaluated against HIV-1 and HBV. Compound 10b showed a 50% inhibition at >1 \(\mu\)M against HIV. The other analogues did not show any significant antiviral activity against HIV at concentrations up to 100 \(\mu\)M. No significant activity against HBV was found for the synthesized nucleosides.

**Experimental**

Melting points were determined on a Mel-temp II and are uncorrected. \(^1\)H NMR spectra were recorded on a Bruker 400 AMX spectrometer for 400 MHz, with Me\(_4\)Si as internal standard. Chemical shifts (\(\delta\) values) are reported in parts per million (ppm), and signals are reported as s (singlet), \(\delta\) (doublet), t (triplet), q (quartet), m (multiplet) or br s (broad singlet). Mass spectra were recorded on a Micromass Autospec high resolution mass spectrometer. IR Spectra were measured on a Nicolet 510P FT-IR spectrometer. Optical rotations were performed on a Jasco DIP-370 Digital Pola-
Table 1. NMR data of compounds 5–11.

<table>
<thead>
<tr>
<th>Compd.</th>
<th>1'-H</th>
<th>2'-H</th>
<th>3'-H</th>
<th>4'-H</th>
<th>5'a,b-H</th>
<th>4-H or 5-H</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a*</td>
<td>5.66 (bd, 1H, (J_{1',F} = 12.5) Hz)</td>
<td>4.96 (bd, 1H, (J_{2',F} = 49.0) Hz)</td>
<td>5.45 (dd, 1H, (J_{2',Y} = 20.5) Hz)</td>
<td>4.54 (m, 1H)</td>
<td>4.68 (m, 2H)</td>
<td>7.54–7.32</td>
<td>(m, 10H, benzoyl), 7.90–7.30</td>
</tr>
<tr>
<td>6b*</td>
<td>5.57 (dt, 1H, (J_{1',F} = 16.3) Hz)</td>
<td>5.12 (dt, 1H, (J_{2',F} = 50.8) Hz)</td>
<td>5.21 (dd, 1H, (J_{2',Y} = 12.2) Hz)</td>
<td>4.32 (m, 1H)</td>
<td>4.57 (m, 2H)</td>
<td>8.26–7.46</td>
<td>(m, 10H, benzoyl), 1.59 (t, 3H, OCH(_2)CH(_3))</td>
</tr>
<tr>
<td>7a*</td>
<td>7.42 (d, 1H, (J_{1',F} = 15.7) Hz)</td>
<td>6.20 (bd, 1H, (J_{2',F} = 49.9) Hz)</td>
<td>6.16 (dd, 1H, (J_{2',Y} = 23.2) Hz)</td>
<td>5.14 (m, 1H)</td>
<td>4.91 (m, 2H), 4.64 (q, 2H, OCH(_2)CH(_3))</td>
<td>8.28 (s, 1H, H-4)</td>
<td>8.18–7.45 (m, 10H, benzoyl), 1.50 (t, 3H, OCH(_2)CH(_3))</td>
</tr>
<tr>
<td>7b*</td>
<td>7.44 (d, 1H, (J_{1',F} = 8.0) Hz)</td>
<td>5.88 (dt, 1H, (J_{2',F} = 51.8) Hz)</td>
<td>6.48 (m, 1H, (J_{2',Y} = 16.1) Hz)</td>
<td>4.80 (m, 1H)</td>
<td>5.02 (m, 2H), 4.50 (q, 2H, OCH(_2)CH(_3))</td>
<td>8.29 (s, 1H, H-4)</td>
<td>8.36 and 7.99 (2s, 2H, NH(_2), D(_2)O exc.)</td>
</tr>
<tr>
<td>8a**</td>
<td>7.06 (d, 1H, (J_{1',F} = 6.1) Hz)</td>
<td>5.75 (d, 1H, (J_{2',F} = 53.5) Hz)</td>
<td>5.94 (d, 1H, 3'-OH, D(_2)O exc.)</td>
<td>4.30 (m, 1H, (J_{2',Y} = 26.7) Hz)</td>
<td>4.11 (bs, 1H)</td>
<td>8.86 (t, 1H, 5'-OH, D(_2)O exc.), 3.56 (m, 2H)</td>
<td>8.27 (s, 1H, H-4)</td>
</tr>
<tr>
<td>8b**</td>
<td>7.24 (d, 1H, (J_{1',F} = 6.1) Hz)</td>
<td>5.43 (dt, 1H, (J_{2',F} = 53.0) Hz)</td>
<td>5.60 (d, 1H, 3'-OH, D(_2)O exc.)</td>
<td>4.53 (m, 1H, (J_{2',F} = 18.1) Hz)</td>
<td>3.89 (m, 1H)</td>
<td>4.86 (t, 1H, 5'-OH, D(_2)O exc.), 3.66 (m, 2H)</td>
<td>8.37 (s, 1H, H-5)</td>
</tr>
<tr>
<td>9a*</td>
<td>6.54 (bd, 1H, (J_{1',F} = 13.2) Hz)</td>
<td>6.12 (bd, 1H, (J_{2',F} = 48.2) Hz)</td>
<td>5.76 (dd, 1H, (J_{2',Y} = 18.6) Hz)</td>
<td>4.82 (m, 1H)</td>
<td>4.42 (m, 2H), 4.68 (m, 2H, OCH(_2)CH(_3))</td>
<td>8.37 (s, 1H, H-5)</td>
<td>8.11–7.39 (m, 10H, benzoyl), 1.39 (t, 3H, OCH(_2)CH(_3))</td>
</tr>
<tr>
<td>9b*</td>
<td>6.73 (ddd, 1H, (J_{1',F} = 2.7) Hz)</td>
<td>5.39 (dd, 1H, (J_{2',F} = 49.9) Hz)</td>
<td>5.76 (bd, 1H, (J_{2',Y} = 14.8) Hz)</td>
<td>4.65 (m, 1H)</td>
<td>4.79 (m, 2H), 4.42 (q, 2H, OCH(_2)CH(_3))</td>
<td>8.40 (s, 1H, H-5, (J = 2.5) Hz)</td>
<td>8.11 and 7.70 (2s, 2H, NH(_2), D(_2)O exc.)</td>
</tr>
<tr>
<td>10a**</td>
<td>6.64 (dd, 1H, (J_{1',F} = 2.2) Hz)</td>
<td>5.73 (dt, 1H, (J_{2',F} = 51.6) Hz)</td>
<td>6.15 (d, 1H, 3'-OH, D(_2)O exc.)</td>
<td>4.48 (m, 1H, (J_{2',F} = 22.2) Hz)</td>
<td>4.31 (m, 1H)</td>
<td>5.16 (t, 1H, 5'-OH, D(_2)O exc.), 3.72 (m, 2H)</td>
<td>8.86 (s, 1H, H-5)</td>
</tr>
<tr>
<td>10b**</td>
<td>6.58 (dd, 1H, (J_{1',F} = 5.8) Hz)</td>
<td>5.36 (dt, 1H, (J_{2',F} = 52.6) Hz)</td>
<td>6.02 (d, 1H, 3'-OH, D(_2)O exc.)</td>
<td>4.47 (m, 1H, (J_{2',F} = 19.0) Hz)</td>
<td>3.89 (m, 1H)</td>
<td>5.20 (t, 1H, 5'-OH, D(_2)O exc.), 3.68 (m, 2H)</td>
<td>8.74 (s, 1H, H-5)</td>
</tr>
<tr>
<td>11a**</td>
<td>6.28 (dd, 1H, (J_{1',F} = 3.1) Hz)</td>
<td>5.80 (ddd, 1H, (J_{2',F} = 54.1) Hz)</td>
<td>5.98 (d, 1H, 3'-OH, D(_2)O exc.)</td>
<td>4.01 (m, 1H)</td>
<td>4.95 (bs, 1H, 5'-OH, D(_2)O exc.), 3.57 (m, 2H)</td>
<td>7.53 and 7.17 (2s, 2H, NH(_2), D(_2)O exc.), 6.66 (s, 2H, CONH(_2), D(_2)O exc.)</td>
<td></td>
</tr>
<tr>
<td>11b**</td>
<td>6.28 (dd, 1H, (J_{1',F} = 3.1) Hz)</td>
<td>5.80 (ddd, 1H, (J_{2',F} = 54.2) Hz)</td>
<td>5.97 (d, 1H, 3'-OH, D(_2)O exc.)</td>
<td>4.02 (m, 1H)</td>
<td>4.94 (bs, 1H, 5'-OH, D(_2)O exc.), 3.60 (m, 2H)</td>
<td>7.53 and 7.17 (2s, 2H, NH(_2), D(_2)O exc.), 6.67 (s, 2H, CONH(_2), D(_2)O exc.)</td>
<td></td>
</tr>
</tbody>
</table>

* In CDCl\(_3\); ** In DMSO.
rimeter. TLC were performed on Uniplates (silica gel) purchased from Analtech Co. Column chromatography was performed using either Silica Gel-60 (220–440 mesh) for flash chromatography or Silica Gel G (TLC grade > 440 mesh) for vacuum flash column chromatography. UV Spectra were obtained on a Beckman DU 650 spectrophotometer. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

1,3,5-Tri-O-benzoyl-2-O-(2-imidazolylsulfonyl)-α-L-ribofuranose (2)

To a stirred solution of 1 (22.5 g, 48.6 mmol) in anhydrous CH2Cl2 (225 ml) and DMF (60 ml) at \(-40^\circ\text{C}\) was added sulfuryl chloride (15.9 ml, 136.5 mmol) through a syringe. The resulting solution was stirred at \(-40^\circ\text{C}\) for 30 min and then gradually warmed up to rt. After 3 h, imidazole (48 g, 703.5 mmol) was added at 0 °C, and the mixture was stirred at rt for 15 h. The hazy solution was diluted with CH2Cl2 (450 ml) and washed with ice-water, and the aqueous layer was extracted again with CH2Cl2. The combined organic layer was dried over MgSO4. Removal of solvent and purification by silica gel column chromatography (5:1-1:1 hexanes-EtOAc) gave compound 2 as a white solid (21.0 g, 73%).

To a stirred solution of 2 (20.9 g, 35.2 mmol) and KHF2 (11.1 g, 141.6 mmol) in 2,3-butanediol (180 ml) was stirred under N2 at 160 °C. To this was added HF–H2O (48%, 5.1 ml, 141.6 mmol), and the mixture was stirred at 160 °C for 1 h. It was quenched by brine-ice and then extracted with CH2Cl2 (4 x 75 ml). The combined extract was washed with brine, water and saturated NaHCO3 respectively. The organic layer was dried over MgSO4 and treated with charcoal. It was put on a silica gel pad (5 cm x 5 cm), eluted with CH2Cl2 to give a syrup which was recrystallized from 95% EtOH to give compound 3 (10.5 g, 64%).

3,5-Di-O-benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl azide (5b) and 3,5-di-O-benzoyl-2-deoxy-2-fluoro-α-L-arabinofuranosyl azide (5a)

To a solution of 3 (7.5 g, 15.0 mmol) in CH2Cl2 (50 ml) was added HBr/AcOH (7 ml, 45% w/v), and the mixture was stirred at rt overnight. After usual work-up, 4 was obtained as a syrup which was used directly for the next reaction without further purification.

To a stirred solution of 4 in anhydrous DMF (50 ml) was added NaN3 (10.7 g, 165 mmol), and the mixture was stirred at rt for 5 h. The solvent was evaporated and the residue was extracted with EtOAc (50 ml x 2), washed with water, and dried over MgSO4. Removal of solvent gave a syrup which was separated by silica gel column chromatography (10:1 hexanes-EtOAc). The fast moving spot was collected to give 5b as an oil (1.3 g, 20%), which upon standing became a wax-like solid. The slow moving spot was collected and crystallized from MeOH to give 5a as a white solid of (3.6 g, 57%).

1,3,5-Tri-O-benzoyl-2-deoxy-2-fluoro-α-L-arabinofuranose (3)

A suspension of 2 (20.9 g, 35.2 mmol) and KHF2 (11.1 g, 141.6 mmol) in 2,3-butanediol (180 ml) was stirred under N2 at 160 °C. To this was added HF–H2O (48%, 5.1 ml, 141.6 mmol), and the mixture was stirred at 160 °C for 1 h. It was quenched by brine-ice and then extracted with CH2Cl2 (4 x 75 ml). The combined extract was washed with brine, water and saturated NaHCO3 respectively. The organic layer was dried over MgSO4 and treated with charcoal. It was put on a silica gel pad (5 cm x 5 cm), eluted with CH2Cl2 to give a syrup which was recrystallized from 95% EtOH to give compound 3 (10.5 g, 64%).

Ethyl triphenylphosphorylidenepyruvate (6)

To a stirred solution of triphenylphosphine (19.0 g, 72 mmol) in THF (150 ml) was added ethyl bromopyruvate (5.0 ml, 36 mmol), and the mixture was stirred at rt for 30 min and then refluxed under argon for 2 h. The solvent was removed under reduced pressure and the residue was triturated with Et2O (50 ml x 3), redissolved in water (200 ml) and extracted with Et2O (50 ml x 2). The pH of the aqueous layer was adjusted with saturated NaHCO3 to ca. 8 when no more precipitate formed. It was filtered and the filter
cake was washed thoroughly with water. After crystallization from EtOH, 6 was obtained as a yellow solid (6.0 g, 44%).

M.p. 186–187 °C. – IR (film): ν = 1705, 1578, 1559 cm⁻¹. – ¹H NMR (CDCl₃): δ = 7.70–7.46 (m, 15H, phenyl), 4.84 (d, 1H, Ph₃P=CHCO, J = 23.3 Hz), 4.26 (q, 2H, CO₂CH₂CH₃), 1.35 (t, 3H, CO₂CH₂CH₃).

**Ethyl 1-(3,5-di-O-benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl)-1,2,3-triazole-5-carboxylate (7b)**

Compound 5b (162 mg, 0.4 mmol) and 6 (189 mg, 0.5 mmol) were stirred in refluxing toluene (20 ml) for 18 h. After removal of the solvent in vacuo, the residue was purified by silica gel column chromatography (5:1 hexanes–EtOAc) to give a white solid (115 mg, 60%).


1-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)-1,2,3-triazole-5-carboxylate (8b)

Compound 7b (107.5 mg, 0.2 mmol) was stirred in sat. NH₃/CH₃OH at rt for 12 h. Removal of solvent followed by silica gel column chromatography (10:1 CHCl₃–CH₃OH) gave a white solid (53 mg, 90%).

M.p. 174–175 °C. – UV/vis (H₂O): λ_max (lg ε) = 214.5 nm (4.03) (pH 2), 226.0 nm (3.85) (pH 7), 215.0 nm (4.03) (pH 11). – [α]_D²⁵ = 17.58° (c 0.18, MeOH). – MS (FAB): m/z = 247 (M+1)+. – C₈H₁₁FN₄O₄ (246.20): calcd. C 39.03, H 4.50, N 8.72; found C 38.69, H 4.46, N 22.41.

Ethyl 1-(3,5-di-O-benzoyl-2-deoxy-2-fluoro-α-L-arabinofuranosyl)-1,2,3-triazole-5-carboxylate (7a)

The α-azide 5a (175 mg, 0.5 mmol) and 6 (301 mg, 0.9 mmol) were stirred in refluxing toluene under nitrogen for 18 h. Removal of solvent followed by silica gel column chromatography (5:1–2:1 hexanes–EtOAc) gave a white solid (124 mg, 61%).

M.p. 94–95 °C. – UV/vis (MeOH): λ_max = 233.0, 273.0 nm. – [α]_D²⁵ = -60.33° (c 0.4, CHCl₃). – MS (FAB): m/z = 484 (M+1)+. – C₂₃H₂₂FN₃O₇ (483.45): calcd. C 59.63, H 4.59, N 8.69; found C 59.24, H 4.49, N 8.49.

1-(2-Deoxy-2-fluoro-α-L-arabinofuranosyl)-1,2,3-triazole-5-carboxamide (8a)

Compound 7a (93 mg, 0.2 mmol) was stirred in sat. NH₃/CH₃OH at rt for 12 h. Removal of solvent followed by silica gel column chromatography (10:1 CHCl₃–CH₃OH) gave 8a as an oil (37 mg, 72%).

M.p. 140–141 °C. – UV/vis (H₂O): λ_max (lg ε) = 212.5 nm (3.89) (pH 2), 218.5 nm (3.71) (pH 7), 225.5 nm (3.92) (pH 11). – [α]_D²⁵ = -142.13° (c 0.13, MeOH). – MS (FAB): m/z = 247 (M+1)+. – C₂₃H₁₁FN₄O₄ (246.20): calcd. C 39.03, H 4.50, N 22.76; found C 38.81, H 4.49, N 22.36.

Ethyl 1-(3,5-di-O-benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl)-1,2,3-triazole-4-carboxylate (9b)

The β-azide 5b (464 mg, 1.2 mmol) and ethyl propiolate (0.5 ml) were stirred in toluene (5 ml) at 100 °C for 14 h. After cooling to rt, a white precipitate formed. It was filtered and washed with toluene to give 9b as a white solid of 397 mg. The mother liquor was evaporated to dryness and the residue was separated by silica gel column chromatography (2:1 hexanes–EtOAc) to give 7b (115 mg, 24%) and 9b (416 mg, 73%).


1-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)-1,2,3-triazole-4-carboxamide (10b)

Compound 9b (355 mg, 0.8 mmol) was treated with sat. NH₃/CH₃OH at rt for 16 h. After purification by silica gel column chromatography (100:1 CHCl₃–CH₃OH), 10b was obtained as an oil which upon standing, became a white solid (154 mg, 79%).

M.p. 136–138 °C. – UV/vis (H₂O): λ_max (lg ε) = 208.5 nm (4.05) (pH 2), 208.5 nm (3.63) (pH 7), 220.5 nm (3.99) (pH 11). – [α]_D²⁵ = -6.18° (c 0.8, MeOH). – MS (FAB): m/z = 247 (M+1)+. – C₂₃H₁₁FN₄O₄ (246.20): calcd. C 39.03, H 4.50, N 22.76; found C 38.68, H 4.45, N 22.38.

Ethyl 1-(3,5-di-O-benzoyl-2-deoxy-2-fluoro-α-L-arabinofuranosyl)-1,2,3-triazole-4-carboxylate (9a)

The title compound was obtained by stirring the α-azide 5a (359 mg, 0.9 mmol) with ethyl propiolate (0.4 ml) in toluene (5 ml) at 100 °C for 12 h. Separation by silica gel column chromatography
(5:1–1:1 hexanes–EtOAc) gave 7a as a white solid (124 mg, 30%) and 9a as a syrup (284 mg, 68%).

UV/vis (MeOH): \( \lambda_{\text{max}} = 232.0, 273.5 \text{ nm} \) – [\( \alpha \)]\text{D} = -72.23° (c 0.25, CHCl\(_3\)). – MS (FAB): \( m/z \) 484 (M+1)+. – C\(_{24}\)H\(_{22}\)FN\(_3\)O\(_7\)/H\(_2\)O (483.45): calcd. C 58.54, H 4.71, N 8.53; found C 58.20, H 4.55, N 8.59.

1-(2-Deoxy-2-fluoro-\( \alpha \)-L-arabinofuranosyl)-1,2,3-triazole-4-carboxamide (10a)

Compound 9a (230 mg, 0.5 mmol) was treated with sat. NH\(_3\)/CH\(_3\)OH at rt for 12 h. Removal of solvent gave a syrup which was triturated with Et\(_2\)O at 0 °C to give 10a as a white solid (88 mg, 70%).

M.p. 146–149 °C. – UV/vis (H\(_2\)O): \( \lambda_{\text{max}} \) (lg \( \varepsilon \) = 210.5 nm (4.05) (pH 2), 222.0 nm (3.69) (pH 7), 218.0 nm (4.01) (pH 11) – [\( \alpha \)]\text{D} = -92.78° (c 0.19, MeOH). – MS (FAB): \( m/z \) 247 (M+1)+. – C\(_8\)H\(_{11}\)FN\(_2\)O\(_4\) (246.20): calcd. C 38.47, H 4.40, N 22.43; found C 38.60, H 4.48, N 22.17.

1-(2-Deoxy-2-fluoro-\( \beta \)-L-arabinofuranosyl)-1,2,3-triazole-5-amino-4-carboxamide (11b)

The \( \beta \)-azide 5b (332 mg, 0.9 mmol) in DMF (5 ml) was added to a stirred solution of KOH (681 mg, 1.2 mmol), water (1 ml), Cyanoacetamide (110 mg, 1.3 mmol) in DMF (5 ml) at 0 °C. After 5 min, it was warmed up and stirred at rt for 5 h. The solvent was removed in vacuo and the residue was co-evaporated with EtOH (10 ml x 3), then treated with NaOCH\(_3\) in MeOH at rt for 12 h. It was evaporated to dryness and purified by silica gel column chromatography (7:1 CHCl\(_3\)–CH\(_3\)OH) to give a syrup which was crystallized from MeOH-ether to give a white solid (114 mg, 51%).

M.p. 115 °C. – UV/vis (H\(_2\)O): \( \lambda_{\text{max}} \) (lg \( \varepsilon \) = 234.0 nm (3.99), 260.5 nm (3.94) (pH 2), 234.5 nm (3.90), 260.5 nm (3.86) (pH 7), 234.5 nm (3.96), 260.5 nm (3.92) (pH 11). – [\( \alpha \)]\text{D} = -151.15° (c 0.29, MeOH). – MS (FAB): \( m/z \) 262 (M+1)+. – C\(_8\)H\(_{12}\)FN\(_3\)O\(_4\) (261.21): calcd. C 36.79, H 4.63, N 26.81; found C 37.00, H 4.44, N 26.53.

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