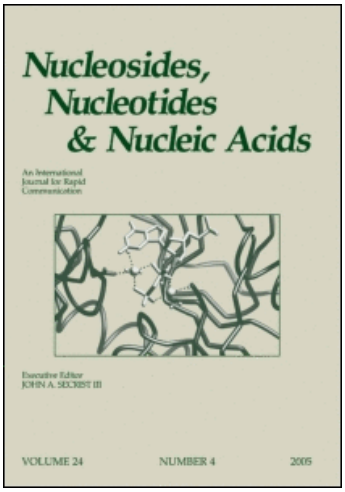

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Nucleosides 5[15]: Synthesis of Novel 1,2,4-Triazolo[3,4-c]-1,2,4-Triazole Nucleosides

M. A. N. Mosselhi[a]; R. Neidlein[b]
[a] Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt [b] Pharmazeutisch-Chemisches Institut, Heidelberg, Germany

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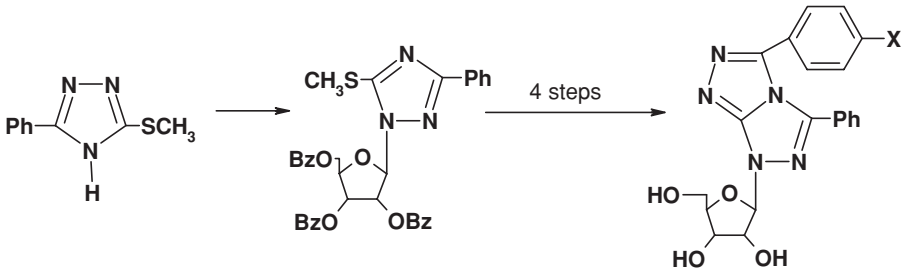
NUCLEOSIDES 5[15]: SYNTHESIS OF NOVEL 1,2,4-TRIAZOLO[3,4-c]-1,2,4-TRIAZOLE NUCLEOSIDES

M. A. N. Mosselhi[1] and R. Neidlein[2]

[1]*Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt*
[2]*Pharmazeutisch-Chemisches Institut, Heidelberg, Germany*



*Ribosylation of 3-methylthio-5-phenyl-1,2,4-triazole (**1**) with ribose derivative **2** gave the protected 1,2,4-triazole-nucleoside **3**, which reacted with hydrazine hydrate to afford the 3-hydrazino-1,2,4-triazole derivative **5**. Reaction of **5** with aromatic aldehydes yielded the corresponding hydrazones **6**, which cyclized under bromination in acetic acid to give **8**. Debenzoylation of **8** afforded novel 1,2,4-triazolo[3,4-c]-1,2,4-triazole nucleosides **9**.*

Keywords Ribosylation; 3-methylthio-5-phenyl-1,2,4-triazole; 1,2,4-triazole-nucleoside; 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose; 1,2,4-triazolo[3,4-c]-1,2,4-triazole nucleosides

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Present address for M.A.N.M.: Taif University, Faculty of Science, Department of Chemistry Taif, Saudi Arabia.

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Address correspondence to M.A.N. Mosselhi, Chemistry Department, Faculty of Science, Cairo University, Giza 12613, Egypt. E-mail: mosselhi2008@hotmail.com

INTRODUCTION

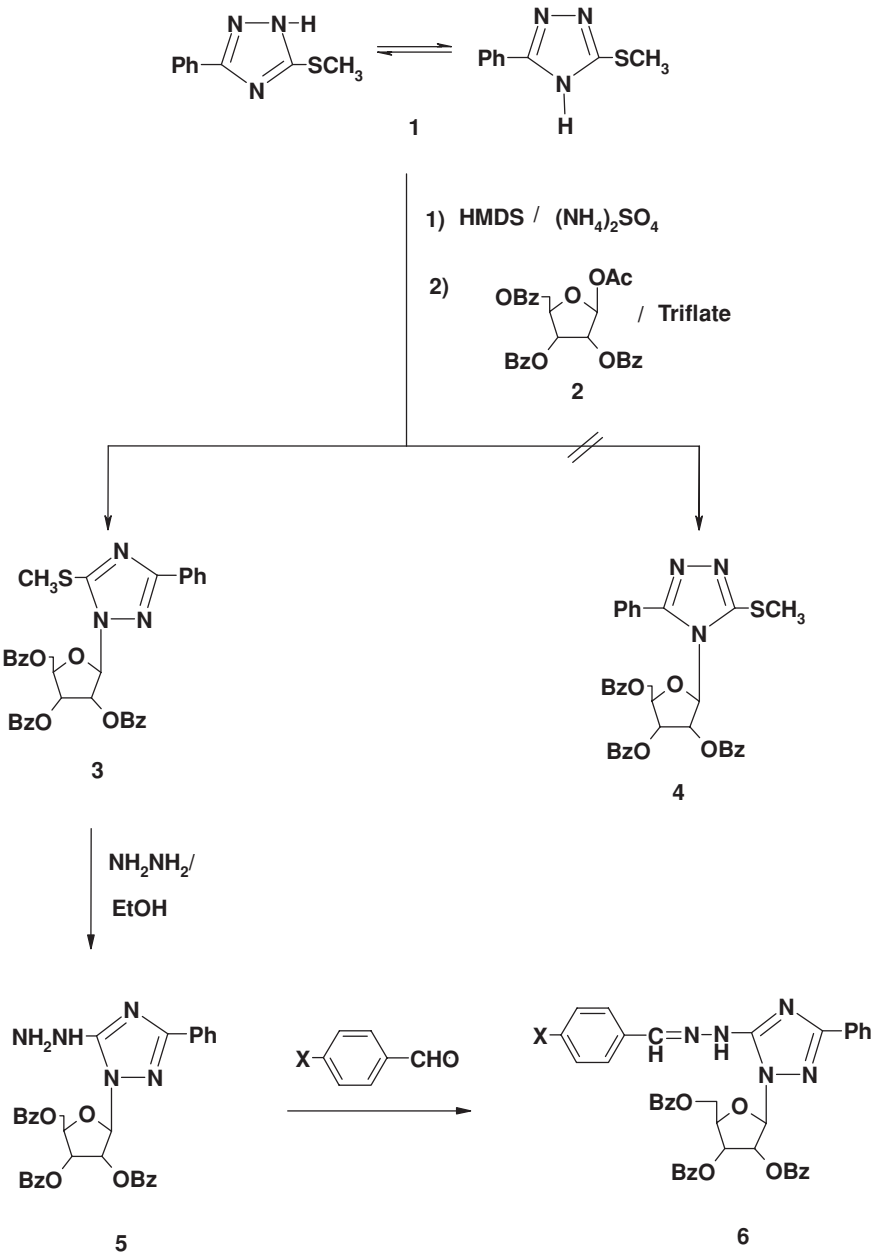
1,2,4-Triazoles represent a class of heterocyclic compounds of significant importance in agriculture and medicine.[1,2] Compounds with 1,2,4-triazole moiety also have received considerable attention among medicinal chemists because molecules with these structural features have been found to display a wide range of potent biological activities, such as antihypertensive,[2] antifungal,[3] and antibacterial[4] activities. Appropriately functionalized 1,2,4-triazoles, such as 4-[3,5-bis(2-hydroxyphenyl)-1,2,4-triazole-1-yl]benzoic acid, have been shown to selectively form a complex with iron (III), which is useful in iron overload therapy.[5]

Considering the important biological properties of 1, 2, 4-triazole compounds, several efficient triazole syntheses have been reported.[6,7,8] According to these interesting biological activities, and as a part of our research program on the nucleoside chemistry, we report here a synthesis of two novel fused 1,2,4-triazole nucleosides. So far in the literature the few examples of 1,2,4-triazolo-[1,2,4]triazole, include 1,2,4-triazolo[1,2-a],[9] 1,2,4-triazolo[3,4-c],[10–12] and 1,2,4-triazolo[3,4-b] [1,2,4]triazoles.[13]

RESULTS AND DISCUSSION

The starting material, 3-methylthio-5-phenyl-1(2H)[1,2,4]triazole (**1**), was prepared according to the literature reported method.[14] The ribosylation of **1** with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (**2**) was carried out in two different methods to give the benzoylated nucleoside; 3-methylthio-5-phenyl-2-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-(*2H*)-1,2,4-triazole **3** or 3-methylthio-5-phenyl-4-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-(*4H*)-1,2,4-triazole **4** (see Scheme 1). The first method was silylation of **1** by reflux in hexamethyl disilazane (HMDS) with ammonium sulfate as a catalyst and then stirring of the silylated product with ribose derivative **2** in dry acetonitrite and TMS-triflate ($CF_3SO_2OSiMe_3$) at room temperature for 48 hours. This method afforded a product in 60% yield.

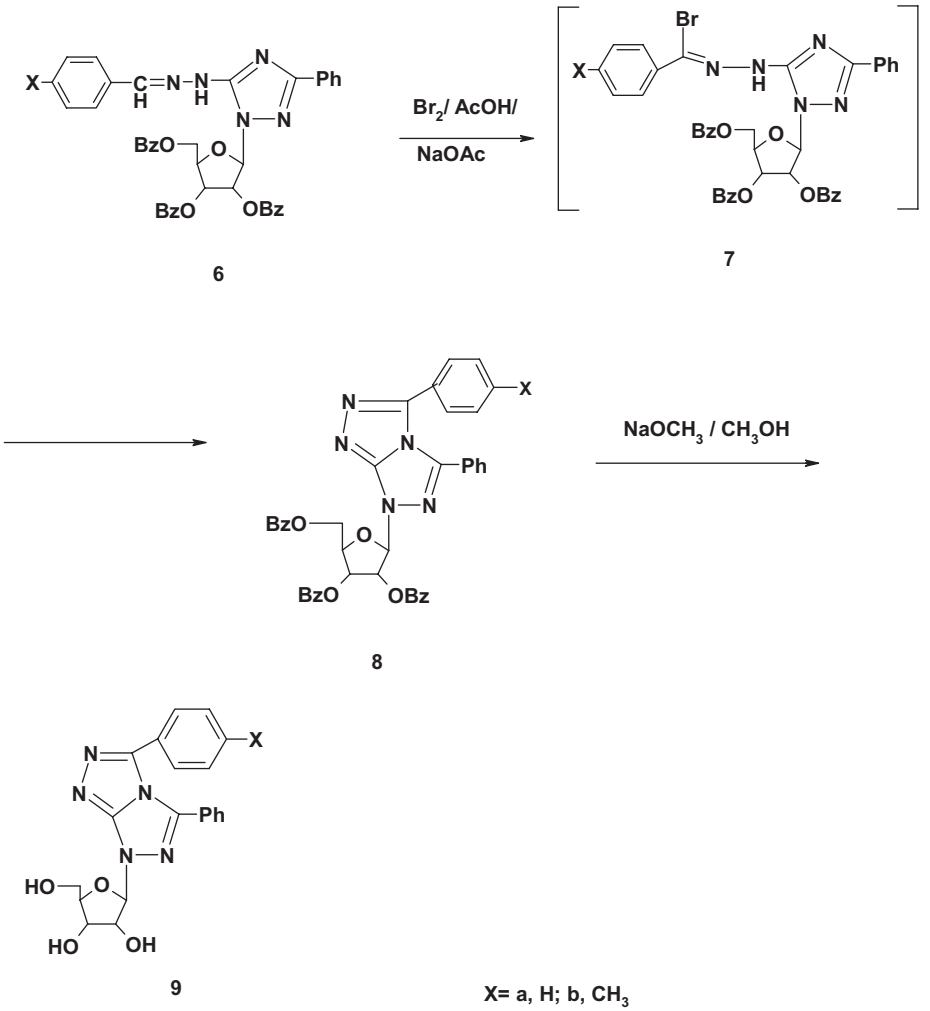
The second method was stirring of the lithium salt of compound **1** with **2** in tetrahydrofurane and TMS-triflate at $-78°C$ for 5 hours and followed by stirring at room temperature for 24 hours. This method yielded a product in 90%. The structure of the latter product was established and confirmed on the bases of its elemental analyses and spectral data. Thus, the analytical data for it revealed a molecular formula $C_{35}H_{29}N_3O_7S$ (m/z 635). Its ^1H NMR spectrum showed a doublet at δ 6.1 assigned to the anomeric proton of the ribose moiety with a spin-spin coupling constant equal to 4.1 Hz, which corresponds to a diaxial orientation for the 1′- and 2′- H protons; that is, the β-configuration.[15–19] The ultraviolet (UV) spectra of the above product revealed λmax (ethanol) at 249 nm, which is similar to that of 5-methyl-4-phenyl-3-(tri-O-acetyl-β-D-xylopyranosylmercapto)-1,2,4-



SCHEME 1 X = a, H, b, CH_3.

triazole [λmax (ethanol) 245 nm].[19] Furthermore, the irradiation of the anomeric proton of **3** gave a clear nuclear Overhauser effect (NOE) response from the *ortho* protons of the 5-phenyl group due to spatial neighborhood. These findings confirmed the structure of **3** and the structure **4** was discarded.

The reaction of compound **3** with hydrazine hydrate under reflux in ethanol afforded 3-hydrazino-2-(2′,3′,5′-tri-O-benzoyl)-*β*-D-ribo-furanozyl-5-phenyl-(*2H*)-1,2,4-triazole (**5**). Furthermore compound **5** reacted with aromatic aldehydes in presence of acetic acid to give the corresponding hydrazones (**6**) in good yields. Next, we examined the bromination of **6** in acetic acid and anhydrous sodium acetate at room temperature. Thus, it afforded directly the triazolotriazole nucleosides (**8**) via in situ formed hydrazonoyl halide derivatives (**7**) that were not isolated (see Scheme 2). However, the debenzoylation of compounds **8** in methanol containing sodium methoxide was succeeful and gave the free 1,2,4-triazolo[3,4-c]-1,2,4-triazole nucleosides (**9**) (Scheme 2). Structural assignments of the



SCHEME 2

products **8** and **9** isolated were made on the basis of their mass spectrometry (MS), ^{1}H NMR, ^{13}C NMR, infrared (IR) spectra, and elemental analyses (see Experimental section). For example, the absence of the methine and nitrogen protons of hydrazones **6** in the ^{1}H NMR spectra of **8** or **9** confirmed the structure.

EXPERIMENTAL

All chemicals were supplied by Sigma-Aldrich and Merck (Germany).

IR spectra were recorded for KBr discs on Testscan Shimadzu FTIR 8000 Series and Bruker IFS 113V spectrophotometers (Germany), ^{1}H-NMR and ^{13}C-spectra were recorded on a Bruker Ac 250 MHz and on a Varian Gemini 200 MHz NMR spectrometer (Germany) using trimethylsilane (TMS) as an internal standard; NOE-diffraction was recorded on a Bruker AM 400 MHz spectrometer (Germany); UV spectra were recorded on a Perkin Elmer spectrophotometer Lambda 5 (USA); MS spectra were recorded on Varian Mat 711 spectrometer (electron ion [EI] and fast atom bambardment [FAB] in nitrobenzyl alcohol [NBA]). Thin layer chromatography (TLC) was performed on silica gel sheets F 1550 LS 254 of Schleicher & Schull and column chromatography on Merck silica gel 60 (particle size 0.063–0.20 mm). Melting points were measured on Gallenkamp melting point apparatus (UK) and are uncorrected. Elemental analyses were carried out at Pharmazeutisch-Chemisches Institut (Heidelberg, Germany) and at Microanalytical Centre (Cairo University, Egypt). 3-Methylthio-5-phenyl-1,2,4-triazole[10] was prepared as previously described.

3-Methylthio-5-phenyl-2-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-(*2H*)-1,2,4-triazole 3

Method A. A mixture of **1** (20 mmol) and dry hexamethyldisilazane (100 ml) was heated under reflux for 10 hours with a catalytic amount of ammonium sulfate (100 mg). After the clear solution was cooled, it was evaporated to dryness under anhydrous condition to give the silylated derivative, which directly was dissolved in 50 ml of dry 1,2-dichloroethane. To this a solution of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose **(2)** (9.6 g, 19.6 mmol) in dry 1,2-dichloroethane (50 ml) was added. The mixture was cooled in ice bath and a solution of trimethylsilyl trifluoromethanesulfonate (4 ml, 20 mmol) in dry 1,2-dichloroethane (20 ml), which was added dropwise. It was stirred at room temperature for 24 hours, diluted with chloroform (500 ml), washed with a saturated solution of aqueous sodium bicarbonate (200 ml) and water (3 × 150 ml), and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the residue was chromatographed on silica gel with chloroform as eluent to afford white

solid, which was crystallized from ethanol to yield colorless crystals of the corresponding nucleoside derivative **3**.

Method B. A mixture of **1** (20 mmol) and sodium hydride (20 mmol) was dissolved in dry tetrahydrofurane (100 ml) at −70°C and stirred for 1 hour. To this mixture a solution of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose **(2)** (9.6 g, 19.6 mmol) in dry tetrahydrofurane (40 ml) was then added and the mixture was stirred at −70°C for 5 hours. The excess solvent was evaporated and the residue was extracted from chloroform and purified by chromatography as in the above method to give **3**, which is identical in all physical constants with that obtained from the above method.

Compound **3**: Yield (60%, method A and 90% method B); m.p. 158–159°C; ν (cm^{-1}) (KBr) 1750 (CO); λ_{max} (EtOH) (249 nm); δ_H ($CDCl_3$): 2.61 (s, 3H, SCH_3), 4.6–4.9 (m, 3H, 2 H-5′, H-4′), 6.1 (d, 1H, H-1′, $J_{1',2'}$ = 4.1 Hz), 6.25–6.35 (pt, 1H, H-3′), 6.4–6.5 (pt, 1H, H-2′), 7.3–8.1 (m, 20H, Ar-H); δ_C ($CDCl_3$): 18, 60, 71, 78, 84, 93, 121, 125–140, 151, 159, 168 (CO); m/z (M^+): 635, 445, 323, 201, 105, 77; Anal. Found: C, 65.70; H, 4.60; N, 6.72; S, 4.88% $C_{34}H_{26}N_2O_8S$ requires; C,66.14; H, 4.57; N, 6.61; S, 5.04%.

3-Hydrazino-5-phenyl-2-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-(*2H*)-1,2,4-triazole 5

A mixture of the protected nucleoside **3** (15 mmol), absolute ethanol (50 ml), and hydrazine hydrate (20 ml) was heated under reflux for 2 hours. Evaporation of the solvent under vacuum gave a colorless solid, which was crystallized from ethanol/dioxane to give **5** as colorless crystals.

Compound **5:** Yield (75%); m.p. 222–224°C; υ (cm^{-1}) (KBr) 3310, 3190 (NH_2, NH), 1750 (CO); δ_H (DMSO-d_6): 4.65–4.90 (m,3H, 2 H-5′, H-4′), 5.9 (s, 2H, NH_2), 6.2 (d, 1H, H-1′, $J_{1',2'}$ = 4.1 Hz), 6.30–6.35 (pt, 1H, H-3′), 6.45–6.50 (pt, 1H, H-2′), 7.25–8.3 (m, 20H, Ar-H), 9.2 (s, 1H, NH); m/z (M^+): 603, Anal. Found: C, 69.5; H, 4.8; N, 6.6%. $C_{35}H_{29}N_3O_7$ requires; C, 69.64; H, 4.84; N, 6.96%.

Benzaldehyde and p-Methylbenzaldehyde-[(5-phenyl-2-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-(*2H*)-1,2,4-triazol-3-yl] Hydrazones 6

General method. A mixture of **5** (0.01 mol) and benzaldehyde or p-methylbenzaldehyde (5 ml each) in ethanol (50 ml) and acetic acid (0.5 ml) was heated under reflux for 1 hour. The mixture was evaporated to half and then cooled. The solid formed was filtered and crystallized from ethanol to give **6** as colorless crystals.

Compound **6a:** Yield (48%); m.p. 192–193°C, υ (cm^{-1}) (KBr) 3311 (NH), 1755 (CO); δ_H (DMSO-d_6): 4.6–4.7 (m, 1H, 4′-H), 4.85–4.95 (m, 2H, 5′,5″-H; 6.0 (d, 1H, $J_{1',2'}$ = 4.0 Hz, 1′-H), 6.2–6.25 (m, 1H, 3′-H); 6.35–6.45

(m, 1H, 2′-H); 7.2–8.5 (m, 26H, Ar-H & = CH), 9.3 (s, 1H, NH); m/z (M^+): 707; Anal. Found: C, 69.2; H, 4.7; N, 10.1%. $C_{41}H_{33}N_5O_7$ requires; C,69.58; H,4.70; N, 9.90%.

Compound **6b:** Yield (50%); m.p. 180–182°C, υ (cm^{-1}) (KBr) 3315 (NH), 1755 (CO); δ_H (DMSO-d_6): 2.2 (s, 3H, CH_3), 4.5–4.6 (m, 1H, 4′-H); 4.75–4.8 (m, 2H, 5′,5″- H); 5.95 (d,1H,$J_{1',2'} = 4.0$ Hz, 1′-H), 6.1–6.2 (m, 1H, 3′-H); 6.3–4.4 (m, 1H, 2′-H); 7.3–8.2 (m, 25H, Ar-H & = CH), 9.1 (s, 1H, NH); m/z (M^+): 721; Anal. Found: C, 69.5; H, 4.5; N, 10.0%. $C_{42}H_{35}N_5O_7$ requires; C,69.89; H,4.89; N, 9.70%.

1-(2′,3′,5′-Tri-O-benzoyl-β-D-ribofuranosyl)-5-aryl-3-phenyl–1,2,4-triazolo[3,4-c]-1,2,4-triazole Nucleosides 8

General method. A suspension of **6** (5 mmol) in acetic acid (10 ml) was treated with bromine (5 ml) in acetic acid (2 ml) dropwise and the reaction mixture was stirred for 24 hours. It was then diluted with water and the product was filtered and crystallized from ethanol/dioxane to give **8**.

Compound **8a:** Yield (65%); m.p. 220–222°C, υ (cm^{-1}) (KBr) 1765 (CO); λ_{max} (EtOH) (253 nm); δ_H (DMSO-d_6) 4.6–4.7 (m, 1H, 4′-H); 4.8–4.85 (m, 2H, 5′,5″- H); 6.0 (d,1H, $J_{1',2'} = 2.0$ Hz, 1′-H), 6.1–6.2 (m, 1H, 3′-H); 6.3–4.4 (m, 1H, 2′-H); 7.2–8.3 (m, 25H, Ar-H); δ_C (DMSO-d_6): 65, 73, 75, 82, 90, 123, 128–135, 162, 170 (CO); m/z (M^+): 705; Anal. Found: C, 68.0; H, 4.5; N, 9.8%. $C_{41}H_{31}N_5O_7$ requires; C,69.78; H,4.43; N, 9.92%.

Compound **8b:** Yield (70%); m.p. 212–213°C, υ (cm^{-1}) (KBr) 1760 (CO); λ_{max} (EtOH) (250 nm); δ_H (DMSO-d_6) 2.1 (s, 3H, CH_3), 4.5–4.6 (m, 1H, 4′-H); 4.75–4.8 (m, 2H, 5′,5″- H); 6.0 (d,1H, $J_{1',2'} = 2.0$ Hz, 1′-H), 6.15–6.25 (m, 1H, 3′-H); 6.3–4.4 (m, 1H, 2′-H); 7.2–8.3 (m, 24H, Ar-H); δ_C (DMSO-d_6) 24, 63, 71, 78, 84, 95, 121, 126–136, 160, 169 (CO); m/z (M^+): 719; Anal. Found: C, 69.6; H, 4.4; N, 9.5%. $C_{42}H_{33}N_5O_7$ requires; C,70.09; H,4.62; N, 9.73%.

1-(β-D-ribofuranosyl)-5-aryl-3-phenyl-1,2,4-triazolo[3,4-c]-1,2,4-triazole Nucleosides 9

General method. A mixture of the protected nucleoside **8** (1 mmol), absolute methanol (20 ml), and sodium methoxide (60 mg, 1.1 mol) was stirred at room temperature for 24 hours. Evaporation of the solvent under vacuum gave a colorless solid, which was dissolved in hot water and neutralized with acetic acid. The precipitate was filtered off and afforded upon crystallization from water, the nucleosides **9** as colorless crystals.

Compound **9a:** Yield (40%); m.p. 245–246°C, υ (cm^{-1}) (KBr) 3356 (OH); λ_{max} (EtOH) (265 nm); δ_H (DMSO-d_6) 3.5–3.6 (m, 2H, 5′,5″-H); 3.9–4.0 (m, 1H,4′-H); 4.15–4.2 (m, 1H, 3′-H); 4.35–4.45 (m, 1H, 2′-H); 4.7–4.8 (t, 1H, 5′-OH); 5.1–5.2 (d, 1H, 3′-OH); 5.4–5.5 (d, 1H, 2′-OH);

6.1–6.2 (d,1H,$J_{1',2'}$ = 2.0 Hz, 1′-H); 7.2–8.0 (m, 10H, Ar-H); m/z (M^+): 393; Anal. Found: C, 60.0; H, 4.5; N, 17.4%. $C_{20}H_{19}N_5O_4$ requires; C, 61.06; H, 4.87; N, 17.8%.

Compound **9b:** Yield (45%); m.p. 233–234°C, υ (cm^{-1}) (KBr) 3360 (OH); λ_{max} (EtOH) (260nm); δ_H (DMSO-d_6) 2.0 (s, 3H, CH_3), 3.45–3.55 (m, 2H, 5′,5″-H); 3.7–3.9 (m, 1H,4′-H); 4.15–4.25 (m, 1H, 3′-H); 4.3–4.4 (m, 1H, 2′-H); 4.65–4.75 (t, 1H, 5′-OH); 5.1–5.2 (d, 1H, 3′-OH); 5.4–5.5 (d, 1H, 2′-OH); 6.1–6.2 (d,1H,$J_{1',2'}$ = 2.0 Hz, 1′-H); 7.2–7.8 (m, 9 H, Ar-H); m/z (M^+): 407; Anal. Found: C, 62.0; H, 5.4; N, 16.8%. $C_{21}H_{21}N_5O_4$ requires; C, 61.91; H, 5.2; N, 17.19%.

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