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Synthesis of 3′-1,2,4-Triazolo- and 3′-1,3,4-Thiadiazoliminothymidines

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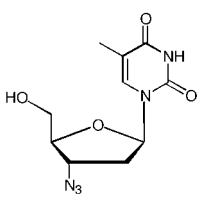
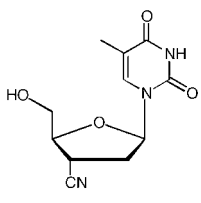
ABSTRACT: *New 5′-acetyl-3′-1,3,4-thiadiazoliminothymidines* **11, 14** *were prepared,* via *spontaneous rearrangments, by cycloaddition of 5′-acetyl-3′-deoxy-3′-isothiocyanatothymidine* **9** *with 1-aza-2-azoniaallene hexachloantimonates. Similary, 3′-cyano analogue* **19** *was reacted with the same cumulenes to furnish 3′-1,2,4-triazolo-thymidines* **22, 24**, *and* **26**. *Deblocking of the acylated products afforded the free nucleosides.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:298–303, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10146

INTRODUCTION

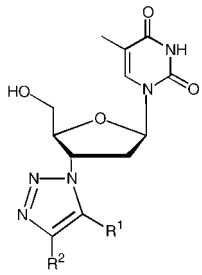
Intensive efforts are underway worldwide to develop chemotherapeutic agents effective against AIDS, since the attempts are continued to discover drugs which can interfere with a stage in the viral replicative cycle without damaging the normal processes of the host cell. Several 3′-modified 2′,3′dideoxynucleosides (AZT **1**, CNT **2**, ddI, ddC, ddT) [1–5] are approved as anti-AIDS drugs targeted as effective inhibitors of HIV reverse transcriptase (RT), the enzyme which catalyzes phosphodiester bond formation on route to the synthesis of a DNA copy of the viral RNA [6]. However, these compounds are quite toxic and not free of undesirable side effects [7] and for this reason different laboratories continue to search for new 3′-modified 2′,3′-dideoxynucleosides exhibiting anti-AIDS activity. The most promising agents of this class of drugs are 3'deoxy DNA nucleosides and 3′-azole derivatives [8–12], which might fulfill the need of this strategy. Herdewijin et al. [13] and Hirota et al. [14] have reported the synthesis of compounds, in which the azide group of AZT is transformed to a triazole ring **3**, but these compounds did not show appreciable activity against HIV. Our work here is concerned with the synthesis of new 3′-azole analogues from the cycloaddition of 5′-acetyl-3′-deoxy-3′-isothiocyanatothymidine **9** and 3′-cyano-analogue **19**, prepared from the antiviral nucleoside CNT [4,5], with some reactive cumulenes. In our recent work, these cumulenes have been used in the synthesis of new types of 1,2,4-triazole compounds such as *C*-ribonucleosides [15,16], acyclic *C*-nucleosides and homo-*C*-analogues [17], (D-*manno*-pentitol-1-yl)-anaslogues [18], as well as those 1,2,4-triazoles attached to thymine [19], phthalimide [20], indole [21], quinolone [21], and benzotriazole [22].



AZT, 1



CNT, 2



3

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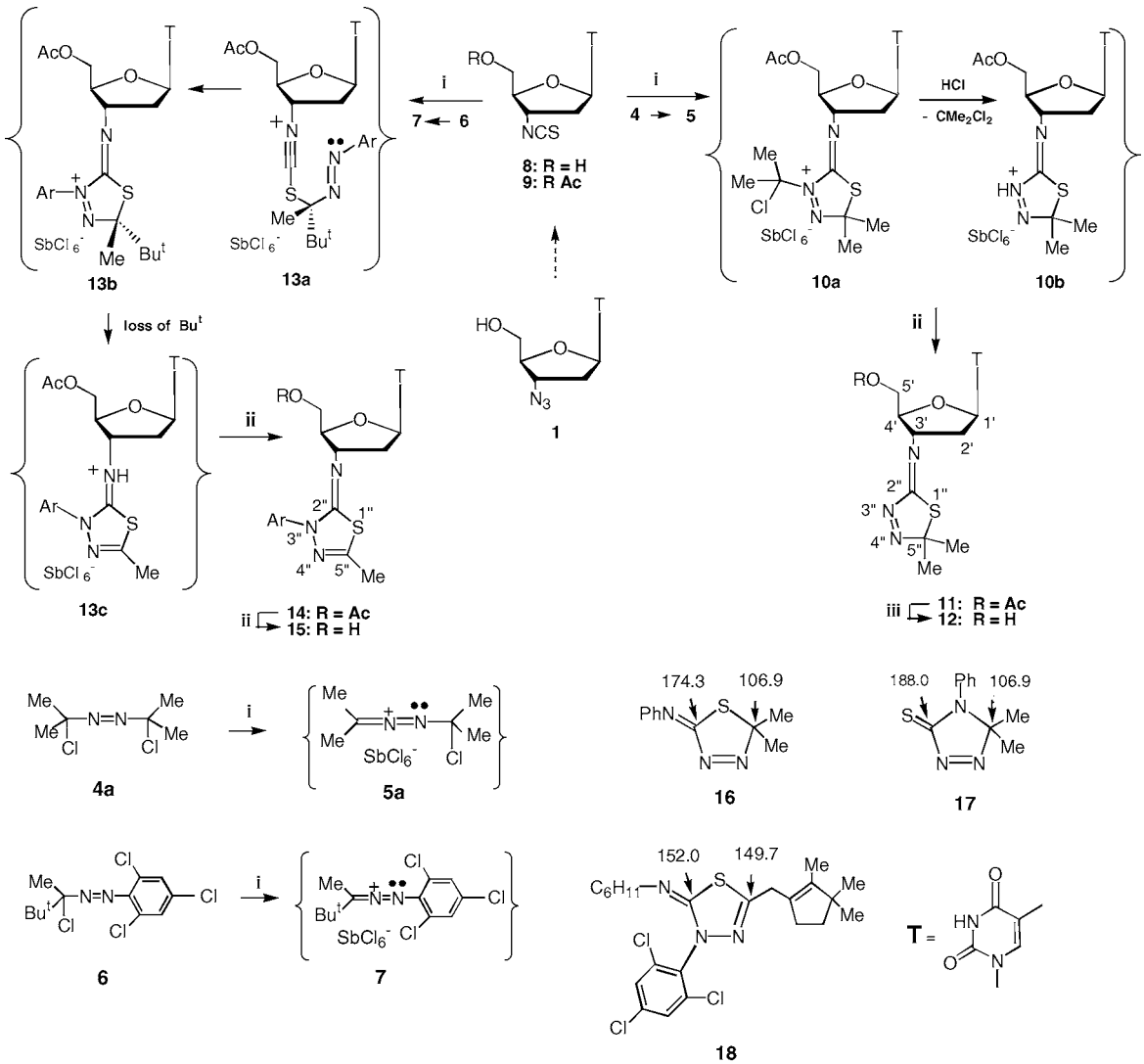
RESULTS AND DISCUSSION

3′-Isothiocyanatothymidine **8** was prepared according to the methods of Monila et al. [23] and Cech et al. [24], starting from the 3′-azido-3′-deoxythymidine **1** via two steps. Acetylation of **8** with acetic anhydride in dry pyridine afforded 5′-acetate **9** as a colorless foam in 73% yield. The α,α-dichloroazo compound **4a** [25] was obtained by chlorination of the bis-hydrazone, and the 1-aza-2-azoniaallene salt **5a** [26,27] by the treatment of **4a** at −60°C with $SbCl_5$. Addition of **9** to the reactive intermediate **5a**, by employing the methods of Jochims et al. [15,28], lead to a color change of the orange suspension of **5a** between −60°C and +23°C indicating a cycloaddition reaction. The resulting 1,3,4-thiadiazolium hexachloroantimonate **10a** lost its CMe_2Cl group and furnished the protonated salt **10b**. Deprotonation gave 1,3,4-thiadiazole **11** in 55% yield. Deblocking of **11** with NaOMe in MeOH at 23°C afforded the free nucleoside **12** in 75% yield. The *concerted* cycloadditions to isothiocyanates are known to occur both on the C=S and the C=N bond in a competitive manner [29]. The isothiocyanate group of compound **9** reacts as *S*-nucleophile resulting in 2,5-dihydro-1,3,4-thiadiazole **11** (cf. **16** [25]) and not as *N*-nucleophile, which would have resulted in an isomeric 4,5-dihydro-1*H*-1,3,4-triazole-5-thione (cf. **17** [28]) (Scheme 1). Compounds **11** and **12** were identified from the ^{1}H NMR and ^{13}C NMR spectra, which are in agreement with those of thiadiazole analogues obtained by Jochims et al. [15,28]. The ^{1}H NMR spectrum of **11** is characterized by the presence of two

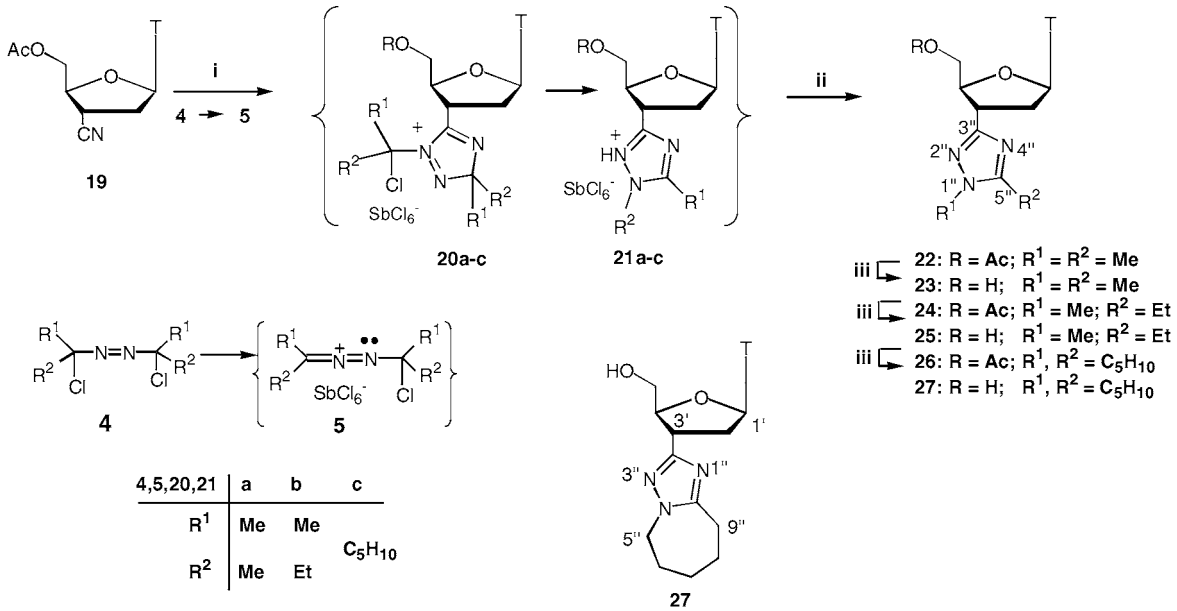


SCHEME 1 Reagents and conditions: (i) $SbCl_5$; CH_2Cl_2, −60°C to 23°C, 7 h, CH_2Cl_2, 23°C; (ii) aq. $NaHCO_3$, 2 h, 23°C; (iii) NaOMe, MeOH, 10 h, 23°C.

singlets at δ_H 1.91 and 1.88, which were attributed to the two 2″-methyl groups. The ^{13}C NMR shifts 106.7 and 177.5 (DMSO-d_6) observed for **12** are assigned to C-2″ and C-5″ of the thiadiazole ring, and δ_C 28.2 and 28.0 attributed to the methyl on C-2″.

Analogously, the heteroallene **7** carrying a *tert*-butyl group were used to synthesize neutral 2-substituted 1,2,4-triazoles [30,31]. Compounds **7**, which formed at low temperature from **6** [15,18] and $SbCl_5$, reacted with the isothiocyanate **9** via C=S cycloaddition to give the nitrilium ion **13a** as an intermediate. The latter is cyclized to the thiadiazolium salt **13b** affording, after the loss of the *tert*-butyl group (as isobutene [18]), the unseparable iminium salt **13c**. The *tert*-butyl group was probably lost during and not after the rearrangment. In situ deprotonation of **13c** with saturated aqueous solution of $NaHCO_3$ afforded the thiadiazole **14**. Removal of the acetate group at C-5′ by NaOMe in MeOH gave **15** in 79% yield (Scheme 1). The structure of **14** was identified from the ^{1}HNMR and mass spectra. The H-1′ appeared as a doublet of doublets at δ_H 6.34 ($J_{1',2'a}$ = 6.0 Hz, $J_{1',2'b}$ = 4.1 Hz), whereas the multiplets at δ_H 2.68, 3.79, 4.19, and 4.55 were attributed to H-2′a,b–H-5′a,b, respectively. The aromatic protons appeared at δ_H 7.90 and 7.88 as from an AB system. The structure of **15** was proven by homo- and heteronuclear NMR spectroscopy methods and by mass spectra. The $^3J_{C,H}$ correlation in the HMQC [32] spectrum of C-5″ at δ_C 156.2 and H-3′ at δ_H 4.50 is an additional proof for the C=S cycloaddition. Furthermore, L'abbé et al. reported values in the range of δ_C 151–164 ppm for C-2 and of δ_C 149–155 ppm for C-5 for several thiadiazoles of type **18** [18,33], which are in agreement with the data shown by compound **15** (δ_C 147.7 for C-2″ and δ_C 156.2 for C-5″).

Our attempt to modify the 3′-position of the thymidine by introducing a disubstituted 1,2,4-triazole via cycloaddition reaction of the reactive 1-aza-2-azoniaallene salts **5a–c** with the sugar nitrile **19** was successful. In a similar manner as for the preparation of **5a**, the intermediates **5b,c** were prepared from the α,α-dichloroazo compounds **4b,c** by treatment with $SbCl_5$ at −60°C. At approximately −30°C the color changed from orange to brown, indicating that **5a–c** underwent cycloaddition reactions with the sugar nitrile **19** to give the unseparable 3′-(3*H*-1,2,4-triazolium-5-yl)thymidine hexachloroantimonates **20a–c**. After the increase of the temperature above −30°C, **20a–c** rearranged spontaneously by migration of the alkyl group at C-3″, via [1,2-shift] [30,34] to N-2″ accompanied by the elimination of the $CClR^1R^2$ group at N-1″, leading to the protonated 1,2,4-triazolium salts **21a–c**. In situ deprotonation with aqueous $NaHCO_3$ [30,31] afforded, after chromatographic purification, the 3′-(1,5-disubstituted-1,2,4-triazole) analogues **22, 24**, and **26**, as foam, in 72, 75, and 78% yield, respectively. Treatment of **22, 24**, and **26** with NaOMe in MeOH afforded the free nucleosides **23, 25**, and **27** respectively in 86, 81, and 78% yield (Scheme 2). The structures of **22–27** were identified by their ^{1}H NMR, ^{13}C NMR, and mass



SCHEME 2 Reagents and conditions: (i) $SbCl_5$; CH_2Cl_2, −60°C to 23°C, 7 h, CH_2Cl_2, 23°C; (ii) aq. $NaHCO_3$, 2 h, 23°C; (iii) NaOMe, MeOH, 10 h, 23°C.

spectra. The ^{1}H NMR spectra of **22–25** showed similar patterns. H-1′ appeared as triplet or doublet of doublets at δ_H 6.21, 6.31, 6.23, and 6.32, respectively. The singlets at δ_H 2.38, 2.35, 2.34, and 2.33 were attributed to the methyl groups at C-5″ of the triazole ring. The methyl and ethyl groups at N-1″ were identified. Compound **27** was selected for homo- and heteronuclear NMR study. Gradient selected HMBC [35] spectrum allowed via $^2J_{C,H}$ and $^3J_{C,H}$ couplings the assignment of most of the carbon atoms. C-2″ at δ_C 159.9 was identified from its $^2J_{C,H}$ correlation to H-3′ at δ_H 3.52. CH_2-9″ at δ_C 49.7 was identified from its $^2J_{C,H}$ correlation to C-10″ at δ_C 156.5, since CH_2-5″ at δ_H 1.55 was identified from its $^3J_{C,H}$ correlation to C-10″ as well. The rest azepine and sugar protons were fully analyzed using the same method.

EXPERIMENTAL

General Procedure [15–22] for the Preparation of the Acylated 3′-(Disubstituted 1,2,4-triazolo)- and 3′-(Disubstituted-1,3,4-thiadiazolimino)-2′,3′dideoxythymidines **11, 14, 22, 24***, and* **26**

A solution of $SbCl_5$ (0.90 g, 3.0 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a stirred, cooled (−60°C) solution of compound **9** (0.27 g, 1.0 mmol) or **19** (0.29 g, 1.0 mmol) and **4a–c** or **6** (3.0 mmol) in CH_2Cl_2 (15 ml). After stirring the mixture at −60°C for 1 h, then at 0°C for 1 h, and finally at 23°C for 10 min, the solvent was evaporated to dryness. The brown residue was dissolved in MeCN (15 ml). After cooling the mixture to 0°C, an aqueous solution of $NaHCO_3$ [2.52 g (30 mmol) in H_2O (10 ml)] was added slowly. The mixture was stirred at 23°C for 30 min and filtered. The organic solvent was removed in vacuo, and the aqueous phase was extracted with $CHCl_3$ (3 × 20 ml). The combined organic extracts were washed with water (3 × 10 ml), dried (Na_2SO_4), filtered, and evaporated to dryness. The amorphous residue was purified on a column of SiO_2 (15 g) using first $CHCl_3$ and then $CHCl_3$—MeOH (99:1) as eluents.

*5′-Acetyl-2′,3′-dideoxy-3′-(2,3-dihydro-5,5-dimethyl-[1,3,4]thiadiazolimino)thymidine (***11***).* From **4a** (0.55 g). Yield: 0.23 g (58%). ^{1}H NMR ($CDCl_3$): δ 11.28 (br s, 1H, NH); 7.68 (d, 1H, $J_{6,Me}$ = 1.0 Hz, H-6); 6.55 (t, 1H, $J_{1',2'a} = J_{1',2'b}$ = 6.3 Hz, H-1′); 5.15 (m, 1H, H-3′); 4.48 (m, 1H, H-4′); 4.12 (d, 2H, H-5′a, H-5′b); 2.71 (m, 2H, H-2′a, H-2′b); 2.08 (s, 3H, OAc); 1.91, 1.88 (2s, 6H, 2 × $C_{5''}$-Me); 1.85 (d, 3H, J = 1.0 Hz, C_5-Me). Anal. calc. for $C_{16}H_{21}N_5O_5S$ (395.44): C, 48.60; H, 5.35; N, 17.71. Found: C, 48.41; H, 5.34; N, 17.39. MS: *m/z* (FAB) 396 (MH^+).

*5′-Acetyl-2′,3′-dideoxy-3′-(2,3-dihydro-5-methyl-3-(2,4,6-trichlorophenyl)-[1,3,4]thia-diazolimino)thymidine (***14***).* From **6** (0.98 g). Yield: 0.36 g (64%). ^{1}H NMR ($CDCl_3$): δ 11.29 (br s, 1H, NH); 7.90, 7.88 (AB, 2H, J_{AB} = 2.5 Hz ,ArH); 7.72 (d, 1H, $J_{6,Me}$ = 1.0 Hz, H-6); 6.34 (dd, 1H, $J_{1',2'a}$ = 6.0 Hz, $J_{1',2'b}$ = 4.1 Hz, H-1′); 4.55 (m, 1H, H-3′); 4.19 (m, 1H, H-4′); 3.79 (m, 2H, H-5′a, H-5′b); 2.68 (m, 2H, H-2′a, H-2′b); 2.11 (s, 3H, OAc); 1.91 (s, 3H, $C_{2''}$-Me); 1.86 (d, 3H, J = 1.0 Hz, C_5-Me). Anal. calc. for $C_{21}H_{19}Cl_3N_5O_5S$ (559.83): C, 45.05; H, 3.42; N, 12.51. Found: C, 44.83; H, 3.40; N, 12.27. MS: *m/z* (FAB) 560/562 (MH^+).

*5′-Acetyl-2′,3′-dideoxy-3′-(1,5-dimethyl-1*H*-[1,2,4]-triazol-3-yl)thymidine (***22***).* From **4a** (0.55 g). Yield: 0.26 g (72%). ^{1}H NMR ($CDCl_3$): ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.75 (d, 1H, $J_{6,Me}$ = 1.2 Hz, H-6); 6.21 (t, 1H, $J_{1',2'a} = J_{1',2'b}$ = 6.0 Hz, H-1′); 4.10 (m, 1H, H-4′); 3.64 (s, 3H, $N^{2''}$-Me); 3.61 (dd, 1H, $J_{4',5'a}$ = 5.5 Hz, $J_{5'a,5'b}$ = 11.0 Hz, H-5′a); 3.52 (dd, 1H, $J_{4',5'b}$ = 3.5, 11.0 Hz, H-5′b); 3.50 (m, 1H, H-3′); 2.63 (m, 1H, H-2′a); 2.48 (m, 1H, H-2′b); 2.38 (s, 3H, $C_{5''}$-Me); 1.85 (d, 3H, J = 1.2 Hz, C_5-Me). Anal. calc. for $C_{16}H_{21}N_5O_5$ (363.37): C, 52.89; H, 5.82; N, 19.27. Found: C, 52.62; H, 5.68; N, 19.01. MS: *m/z* (FAB) 364 (MH^+).

*5′-Acetyl-2′,3′-dideoxy-3′-(1-Ethyl-5-methyl-1*H*-[1,2,4]triazol-3-yl)thymidine (***24***).* From **4b** (0.63 g). Yield: 0.28 g (75%), foam. ^{1}H NMR ($CDCl_3$): 11.37 (br s, 1H, NH); 7.72 (d, 1H, $J_{6,Me}$ = 1.0 Hz, H-6); 6.23 (dd, 1H, $J_{1',2'a}$ = 6.5 Hz, $J_{1',2'b}$ = 3.7 Hz, H-1′); 4.13 (m, 1H, H-4′); 3.80 (q, 2H, J 7.0 Hz, CH_2CH_3); 3.71 (s, 3H, $N^{2''}$-Me); 3.70 (dd, 1H, $J_{4',5'a}$ = 3.5 Hz, $J_{5'a,5'b}$ = 11.5 Hz, H-5′a); 3.60 (dd, 1H, $J_{4',5'b}$ = 3.0 Hz, H-5′b); 3.56 (m, 1H, H-3′); 2.65 (m, 1H, H-2′a); 2.46 (m, 1H, H-2′b); 2.34 (s, 3H, $C_{5''}$-Me); 2.10 (s, 3H, OAc); 1.86 (d, 3H, J = 1.0 Hz, C_5-Me); 1.08 (t, 3H, CH_2CH_3). Anal. calc. for $C_{17}H_{23}N_5O_5$ (377.40): C, 54.10; H, 6.11; N, 18.56. Found: C, 53.86; H, 6.00; N, 18.32. MS: *m/z* (FAB) 378 (MH^+).

*5′-Acetyl-2′,3′-dideoxy-3′-(6,7,8,9-tetrahydro-5*H*-[1,2,4]-triazolo[1,5-a]azepin-2-yl)-thymidine (***26***).* From **4c** (0.71 g). Yield: 0.29 g (78%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 11.22 (br s, 1H, NH); 7.70 (d, 1H, $J_{6,Me}$ = 1.0 Hz, H-6); 6.24 (dd, 1H, $J_{1',2'a}$ = 7.3 Hz, $J_{1',2b}$ = 4.0 Hz, H-1′); 4.18 (ddd, 1H, $J_{4',5'b}$ = 3.2 Hz, H-4′); 4.00 (m, 2H, CH_2-5″); 3.81 (m, 1H, H-3′); 3.77 (dd, 1H, $J_{4',5'a}$ = 5.2 Hz, $J_{5'a,5'b}$ = 11.0 Hz, H-5′a); 3.71 (dd, 1H, $J_{4',5'b}$ = 3.0 Hz, H-5′b); 2.75 (m, 1H, H-2′a); 2.72 (m, 2H, CH_2-6″); 2.54 (m, 1H, H-2′b); 2.13 (s, 3H, OAc); 1.77 (m, 2H, CH_2-8″); 1.81 (d, 3H, J = 1.0 Hz, C_5-Me); 1.59 (m, 2H, CH_2-9″); 1.48 (m, 2H, CH_2-7″). Anal. calc. for $C_{17}H_{23}N_5O_5$ (377.4): C,

54.10; H, 6.11; N, 18.56. Found: C, 53.86; H, 6.00; N, 18.32. MS: *m/z* (FAB) 378 (MH^+).

General Procedure for Preparation of the Free Nucleosides **12, 15, 23, 25***, and* **27**

A solution of the acylated nucleosides (0.75 mmol) in dry MeOH (10 ml) was stirred in 0.3 M NaOMe (7 ml) at 23°C for 7 h. The solution was neutralized with 0.1 M HCl and filtered. The filtrate was evaporated to dryness and the residue was poured onto a column of SiO_2 (10 g). Elution with MeOH, in gradient, (0–10%) and $CHCl_3$ afforded the pure nucleoside.

*2′,3′-Dideoxy-3′-(2,5-dihydro-5,5-dimethyl-[1,3,4]-thiadiazolimino)thymidine (***12***).* From **11** (0.30 g) Yield: 0.20 g (75%), as foam. ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.30 (br s, 1H, NH); 7.73 (d, 1H, $J_{6,Me}$ = 1.0 Hz, H-6); 6.45 (t, 1H, $J_{1',2'a} = J_{1',2'b}$ = 6.5 Hz, H-1′); 5.22 (t, 1H, $J_{5'a,5'b',OH}$ = 5.0 Hz, $C_{5'}$-OH); 4.89 (m, 1H, H-3′); 4.15 (m, 1H, H-4′), 3.63 (br s, 2H, H-5′a, H-5′b); 2.65–2.59 (m, 2H, H-2′a, H-2′b); 1.87, 1.86 (2s, 6H, 2 × Me); 1.80 (d, 3H, J = 1.0 Hz, C_5-Me). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 177.5 (C-5″); 163.5 (C-4); 150.1 (C-2); 136.5 (C-6); 109.6 (C-5); 106.7 (C-2″); 85.0 (C-4′); 84.2 (C-1′); 66.9 (C-3′), 61.0 (C-5′); 38.1 (C-2′); 28.2, 28.0 ($C_{2''}$-Me_2); 12.5 (C_5-Me). Anal. calc. for $C_{14}H_{19}N_5O_4S$ (353.4): C, 47.58; H, 5.42; N, 19.82. Found: C, 47.35; H, 5.31; N, 19.59. MS: *m/z* (FAB) 354 (MH^+).

*2′,3′-Dideoxy-3′-(2,3-dihydro-5-methyl-3-(2,4,6-trichlorophenyl)-[1,3,4]thiadiazolimino)-thymidine (***15***).* From **14** (0.42 g). Yield: 0.29 g (79%), mp 201–204°C. ^{1}H NMR for (600 MHz, DMSO-d_6): δ 11.21 (br s, 1H, NH); 7.85 (s, 2H, ArH); 7.69 (d, 1H, $J_{6,Me}$ = 1.0 Hz, H-6); 6.20 (dd, 1H, $J_{1',2'a}$ = 6.5 Hz, $J_{1',2'b}$ = 4.2 Hz, H-1′); 5.25 (t, 1H, $J_{5'a,5'b,OH}$ = 5.3 Hz, $C_{5'}$-OH); 4.50 (m, 1H, H-3′); 4.15 (m, 1H, H-4′); 3.72-3.61 (m, 2H, H-5′a, H-5′b); 2.65-2.49 (m, 2H, H-2′a, H-2′b); 1.90 ($C_{2''}$-Me); 1.86 (d, 3H, J = 1.0 Hz, C_5-Me). ^{13}C NMR (62.9 MHz, DMSO-d_6): 163.7 (C-4); 156.2 (C-5″); 150.3 (C-2); 147.7 (C-2″); 135.7, 135.6, 133.4, 128.7, 128.6, 128.4 (Aryl); 136.5 (C-6); 109.6 (C-5); 85.1 (C-4′); 84.5 (C-1′); 68.1 (C-3′), 61.5 (C-5′); 37.5 (C-2′); 17.3 ($C_{2''}$-Me); 12.6 (C_5-Me). Anal. calc. for $C_{19}H_{17}Cl_3N_5O_4S$ (517.8): C, 44.07; H, 3.31; N, 13.53. Found: C, 43.85; H, 3.20; N, 13.21. MS: *m/z* (FAB) 540/542 (MNa^+).

*2′,3′-Dideoxy-3′-(1,5-dimethyl-1*H*-1,2,4-triazol-3-yl)thymidine (***23***).* From **22** (0.27 g). Yield: 0.21 g (86%), as foam. ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.40 (br s, 1H, NH); 7.78 (d, 1H, $J_{6,Me}$ = 1.1 Hz, H-6); 6.15 (dd, 1H, $J_{1',2'a}$ = 7.5 Hz, $J_{1',2'b}$ = 3.9 Hz, H-1′); 5.30 (br s, 1H, $C_{5'}$-OH); 4.13 (dt, 1H, $J_{3',4'}$ = 8.8 Hz, H-4′); 3.71 (s, 3H, $N^{2''}$-Me); 3.70 (dd, 1H, $J_{4',5'a}$ = 3.1 Hz, H-5′a); 3.60 (dd, 1H, $J_{4',5'b}$ = 2.9 Hz, H-5′b); 3.56 (m, 1H, H-3′); 2.65 (m, 1H, H-2′a); 2.46 (m, 1H, H-2′b); 2.35 (s, 3H, $C_{5''}$-Me); 1.86 (d, 3H, J = 1.1 Hz, C_5-Me). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 163.9 (C-4); 161.0 (C-3″); 152.1 (C-5″); 150.0 (C-2); 137.1 (C-6); 110.2 (C-5); 87.1 (C-4′); 85.1 (C-1′); 61.7 (C-5′); 37.9 (C-2′); 34.5 ($N^{2''}$-Me); 29.1 (C-3′); 12.4 (C_5-Me); 11.30 ($C_{2''}$-Me). Anal. calc. for $C_{14}H_{19}N_5O_4$ (321.33): C, 52.33; H, 5.96; N, 21.79. Found: C, 52.01; H, 5.88; N, 21.58. MS: *m/z* (FAB) 344 (MNa^+).

*2′,3′-Dideoxy-3′-(1-ethyl-5-methyl-1*H*-[1,2,4]triazol-3-yl)thymidine (***25***).* From **24** (0.28 g). Yield: 0.20 g (81%), as foam. ^{1}H NMR (DMSO-d_6): δ 11.19 (br s, 1H, NH); 7.70 (d, 1H, $J_{6,Me}$ = 1.0 Hz, H-6); 6.32 (dd, 1H, $J_{1',2'a}$ = 6.5 Hz, $J_{1',2'b}$ = 3.6 Hz, H-1′); 5.80 (t, 1H, $J_{5'a,5'b,OH}$ = 4.8 Hz, $C_{5'}$-OH); 3.98 (m, 1H, H-4′); 3.78 (q, 2H, J 7.0 Hz, CH_2CH_3); 3.75 (m, 1H, H-3′); 3.70 (s, 3H, $N^{2''}$-Me); 3.67 (m, 1H, H-5′a); 3.61 (m, 1H, H-5′b); 3.52 (m, 1H, H-3′); 2.60-2.51 (m, 2H, H-2′a, H-2′b); 2.33 (s, 3H, $C_{5''}$-Me); 1.86 (d, 3H, J 1.0 Hz, C_5-Me); 1.11 (t, 3H, CH_2CH_3). ^{13}C NMR (DMSO-d_6) 163.0 (C-4); 155.4 (C-3″); 150.1 (C-5″); 1484 (C-2); 136.7 (C-6); 109.6 (C-5); 87.0 (C-4′); 85.2 (C-1′); 61.5 (C-5′); 45.0 (CH_2CH_3); 37.4 (C-2′); 29.0 (C-3′); 13.1, 12.2, 10.2 (3 × Me). Anal. calc. for $C_{15}H_{21}N_5O_4$ (355.56): C, 53.72; H, 6.31; N, 20.88. Found: C, 53.51; H, 6.19; N, 20.53. MS: *m/z* (FAB) 378 (MNa^+).

*2′,3′-Dideoxy-3′-(6,7,8,9-tetrahydro-5*H*-1,2,4-triazolo[1,5-a]azepin-2-yl)thymidine (***27***).* From **26** (0.30 g). Yield: 0.21 g (78%), mp 129–132°C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.20 (br s, 1H, NH); 7.71 (d, 1H, $J_{6,Me}$ = 1.0 Hz, H-6); 6.19 (dd, 1H, $J_{1',2'}$ = 7.5 Hz, $J_{1',2'b}$ = 4.0 Hz, H-1′); 5.30 (br t, 1H, $C_{5'}$-OH); 4.15 (m, 1H, H-4′); 3.92 (m, 2H, CH_2-9″); 3.72 (m, 1H, H-5′a); 3.69 (m, 1H, H-5′b); 3.52 (m, 1H, H-3′); 2.71 (m, 1H, H-2′a); 2.68 (m, 2H, CH_2-8″); 2.45 (m, 1H, H-2′b); 1.71 (m, 2H, CH_2-6″); 1.80 (d, 3H, J = 1.0 Hz, C_5-Me); 1.55 (m, 2H, CH_2-5″); 1.45 (m, 2H, CH_2-7″). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 163.9 (C-4); 159.9 (C-2″); 156.5 (C-10″); 151.2 (C-2); 137.8 (C-6); 110.5 (C-5); 87.8 (C-4′); 85.0 (C-1′); 60.8 (C-5′); 49.7 (C-9″); 37.0 (C-2′); 29.3 (C-6″); 28.5 (C-3′); 27.8 (C-5″); 26.1 (C-8″); 24.4 (C-7″); 12.4 (C_5-Me). Anal. calc. for $C_{19}H_{25}N_5O_4$ (361.4): C, 56.40; H, 6.41; N, 19.38. Found: C, 56.20; H, 6.33; N, 19.08. MS: *m/z* (FAB) 384 (MNa^+).

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