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Synthesis of novel thymidine derivatives containing a polycyclic tetrazole linker

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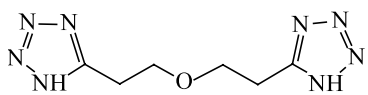
Abstract—The synthesis of mono- and bis-3′-substituted thymidine derivatives with a polycyclic tetrazole linker (1,5-bis(tetrazol-5-yl)-3-oxapentane) is described.

In the modern approach to the synthesis of various drugs, polyfunctional molecules are widely used. Due to its acid–base, complex-forming and non-biodegradable properties, the tetrazole ring is often used in the construction of potential antibiotic and antiviral agents.[1] Regioselective alkylation of tetrazoles has been investigated by several teams during the last 20 years.[2] However, this knowledge cannot be directly transferred onto polycyclic *NH*-tetrazoles. Our group has recently studied the interaction of bicyclic 1,5-bis(tetrazol-5-yl)-3-oxapentane (**1**) (Fig. 1) with various strong electrophiles in aprotic media to give bifunctional products of *N*-1 and *N*-2 substitution in both tetrazole rings, including novel tetrazole-containing crown-ethers.[3,4] Unusually high regioselectivity has been observed for the reaction of triethylammonium salts of 5-substituted mono *NH*-tetrazoles with 5′-*O*-benzoyl-2,3′-anhydrothymidine (**2**) (Fig. 1) to afford the corresponding 3′-(tetrazol-2-yl)-3′-deoxynucleosides.[2,5] The formation of *N*-2 isomers was explained by steric factors due to the bulky three-dimensional structure of the electrophile **2**. In this paper we describe the next step in the investigation of the reactivity of poly-*NH*-tetrazoles using ditetrazole **1**. As an electrophilic substrate, we chose nucleoside **2** having the potential to give promising antiviral agents having extra functional groups (hydrogen bonding in aqueous solutions, *NH*-acidity, etc).

It might be expected that the interaction of ditetrazole **1** with compound **2** would lead to both mono- and disubstituted tetrazole derivatives. However, when applying the modified procedure[5] with an excess of thymidine **2**, the reaction led to a mixture of unidentified products. Therefore, we carried out the synthesis of the target bisnucleoside **8** step by step through the corresponding monosubstituted tetrazole derivatives. When equimolar amounts of reagents **1** and **2** were used, 5′-*O*-benzoyl-3′-deoxy-3′-{5-[5-(tetrazol-5-yl)-3-oxapentyl]tetrazol-2-yl}thymidine (**3**) was isolated in 25% yield (Scheme 1).[6]

The removal of the 5′-*O*-protective benzoyl group of compound **3** using a 1 M solution of sodium methoxide in methanol for 30 min at room temperature led to 3′-deoxy-3′-{5-[5-(tetrazol-5-yl)-3-oxapentyl]tetrazol-2-yl}thymidine (**4**) in 80% yield.[7]



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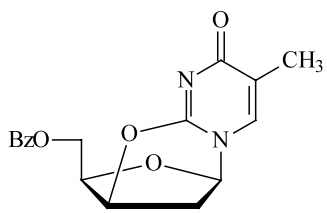

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Figure 1.

Keywords: tetrazole linker; electrophile; *N*-2 isomer; thymidine.
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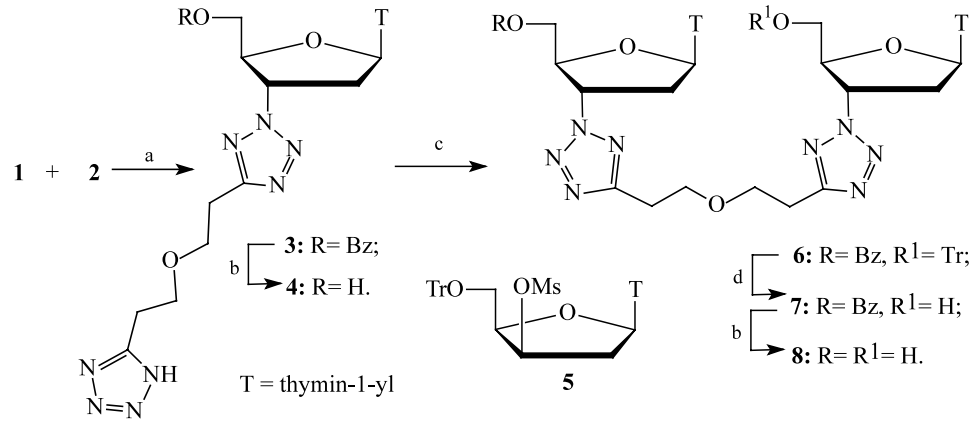

Scheme 1. *Reagents and conditions*: (a) NEt_3, DMF, 50 h, 105–110°C; (b) 1 M MeONa in MeOH, 30 min, rt; (c) compound **5**, $NaN[Si(CH_3)_3]_2$, DMF, 20 h, 100°C; (d) 80% aq. HOAc.

The interaction of compound **3** with 5′-*O*-benzoyl-2,3′-anhydrothymidine (**2**) in the presence of triethylamine, analogous to the above mentioned interaction with an excess of nucleoside **2**, gave a complex mixture of products.

In place of **2**, we used 1-(2-deoxy-3-*O*-methanesulfonyl-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine (**5**) as the starting nucleoside.[8,9] The more reactive thymidine **5** permitted the reaction to proceed under milder conditions to afford a mixture of products among which compound **6** possessing two different protecting groups was present. The step-by-step deprotection of the mixture at different pH (TLC control) gave the intermediate **7**, isolated by silica gel column chromatography followed by treatment under basic conditions to afford the target bisnucleoside **8**.[10] The structures of the *N*-2 isomeric tetrazole-containing thymidine derivatives **3**, **4** and **8** were confirmed by the characteristic signals of the endocyclic carbon in their respective ^{13}C NMR spectra.[3–5] The ^1H and ^{13}C NMR spectra of 1,5-bis[2-(3′-deoxythymidine-3′-yl)tetrazol-5-yl]-3-oxapentane (**8**) were simpler than those of compounds **3** and **4** implying a symmetric structure for ether **8**.

Thus, as a part of an investigation of the reactivity of polynuclear tetrazoles with different electrophiles, we have synthesised new mono- and bis-3′-substituted thymidine derivatives containing 1,5-bis(tetrazol-5-yl)-3-oxapentane (**1**) as a linker. These compounds are of interest both as inhibitors of DNA chain elongation and as antisense agents. We also found that the interaction of 1-(2-deoxy-3-*O*-methanesulfonyl-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine (**5**) with *NH*-tetrazole **3** in the presence of a base gave only the corresponding *N*-2 isomer **6**.

We believe that this work will be useful in the synthesis of the nucleoside systems containing azole polycyclic moieties in the future.

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6. Separation of the reaction mixture was carried out by silica gel column chromatography [Kieselgel 100 (0.063–0.100), Fluka] using a gradient of $CHCl_3$ in CCl_4 (0–100%, v/v), then a gradient of MeOH in $CHCl_3$ (0–3.5%, v/v)]. TLC was performed on aluminium silica gel F_{254} sheets (Merck, Germany), products were visualised by UV light followed by developing with a 0.5% solution of $CuCl_2$ in MeOH, elution system $CHCl_3$–MeOH (9:1, v/v). NMR spectra were recorded on a Bruker DPX–300 spectrometer (with TMS as an internal standard) at 300.1 (^1H) and 75.5 MHz (^{13}C). Compound **3**, colourless crystals, yield 25%, mp 90–92°C (decomp.). R_f 0.35. ^1H NMR (DMSO-d_6) δ: 1.64 (3H, s, CH_3), 2.90 (2H, m, H-2′), 3.09 (4H, m, 2 tetrazole C-5–CH_2CH_2O), 3.79 (4H, m, 2 tetrazole C-5–CH$_2$CH_2O), 4.59 (3H, m, H-5′+H-4′), 5.94 (1H, m, H-3′), 6.46 (1H, t, *J* 6.3 Hz, H-1′), 7.55 (3H, m, C_6H_4), 7.68 (1H, s, H-6), 7.96 (2H, m, C_6H_5), 11.40 (1H, s, NH), 15.82 (1H, br.s, tetrazole NH). ^{13}C NMR (DMSO-d_6) δ: 165.5 (2,5-tetrazole C-5), 164.2 (Ph*C*O), 163.7 (C-4), 153.9 (*NH*-tetrazole C-5), 150.5 (C-2), 136.1 (C-6), 133.7, 129.4, 129.2, 128.9 (C_6H_5), 110.3 (C-5), 84.3 (C-1′), 80.3 (C-4′), 67.7, 67.2 (CH$_2$*C*H$_2$O*C*H$_2$CH$_2$), 63.8 (C-3′), 62.4 (C-5′), 35.8 (C-2′), 25.8 (2,5-tetrazole C-5–*C*H$_2$CH$_2$O), 23.9 (*NH*-tetrazole C-5–*C*H$_2$CH$_2$O), 11.9 (CH_3). Anal. calcd for $C_{23}H_{26}N_{10}O_6$: C, 51.30; H, 4.87; N, 26.01. Found: C, 51.44; H, 4.95; N, 26.07.
7. Compound **4** was purified by anion-exchange chromatography on cellulose DE-32 (Reanal, HCO_3^--form) column [elution with a gradient of NH_4HCO_3 in H_2O (0–0.3 M)].

Compound **4**, viscous oil, yield 80%. R_f 0.18. ^{1}H NMR (DMSO-d_6) δ: 1.82 (3H, s, CH_3), 2.70 (2H, m, H-2′), 3.09 (4H, m, 2 tetrazole C-5–CH_2CH_2O), 3.79 (4H, m, 2 tetrazole C-5–CH$_2$CH_2O), 3.69 (2H, m, H-5′), 4.23 (1H, m, H-4′), 4.75 (2H, br s, tetrazole NH+OH), 5.64 (1H, m, H-3′), 6.42 (1H, t, *J* 6.3 Hz, H-1′), 7.79 (1H, s, H-6), 11.30 (1H, br s, NH). ^{13}C NMR (DMSO-d_6) δ: 164.1 (2,5-tetrazole C-5), 163.8 (C-4), 153.9 (*NH*-tetrazole C-5), 150.6 (C-2), 136.2 (C-6), 109.9 (C-5), 84.1 (C-1′), 82.5 (C-4′), 67.7, 67.2 (CH$_2$*C*H$_2$O*C*H$_2$CH$_2$), 63.0 (C-3′), 61.1 (C-5′), 36.3 (C-2′), 25.8 (2,5-tetrazole C-5-*C*H$_2$CH$_2$O), 23.9 (*NH*-tetrazole C-5–*C*H$_2$CH$_2$O), 12.3 (CH_3). Anal. calcd for $C_{16}H_{22}N_{10}O_5$: C, 44.24; H, 5.10; N, 32.24. Found: C, 44.35; H, 5.15; N, 32.28.

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10. Compound **8**, colourless crystals, mp 176°C (H_2O), yield 15%. R_f 0.22. ^{1}H NMR (DMSO-d_6) δ: 1.81 (6H, s, CH_3), 2.72 (4H, m, H-2′), 3.09 (4H, t, *J* 6.7 Hz, 2 tetrazole C-5–CH_2CH$_2$O), 3.83 (4H, t, *J* 6.7 Hz, 2 tetrazole C-5–CH$_2$CH_2O), 3.72 (4H, m, H-5′), 4.25 (2H, q, *J* 4.5 Hz, H-4′), 5.34 (2H, t, *J* 4.9 Hz, OH), 5.64 (2H, m, H-3′), 6.44 (2H, t, *J* 6.3 Hz, H-1′), 7.80 (2H, s, H-6), 11.37 (2H, s, NH). ^{13}C NMR (DMSO-d_6) δ: 165.0 (2,5-tetrazole C-5), 164.5 (C-4), 151.3 (C-2), 136.9 (C-6), 110.7 (C-5), 84.9 (C-1′), 84.7 (C-4′), 68.5 (CH$_2$*C*H$_2$O*C*H$_2$CH$_2$), 63.5 (C-3′), 61.9 (C-5′), 37.0 (C-2′), 26.6 (2,5-tetrazole C-5–*C*H$_2$CH$_2$O), 13.1 (CH_3). Anal. calcd for $C_{26}H_{34}N_{12}O_9$: C, 47.41; H, 5.20; N, 25.52. Found: C, 47.40; H, 5.23; N, 25.53.