SHORT PAPER

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Synthesis and biological activity of new 1,2,3-triazole acyclonucleosides analogues of ACV†

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The synthesis of new 4,5-substituted 1-[(2-hydroxyethoxy)methyl]-1,2,3-triazole **3a–e** is described. The key step is the 1,3-dipolar cycloaddition between the azido group and an acetylenic group. Biological evaluation show significant activity.

Keywords: triazole, cycloaddition, azido, acetylenes, biological activity

The synthesis of acyclonucleosides as analogues of naturally occurring ribonucleosides has been the subject of major research investigations since the discovery of the chemotherapeutic agent acyclovir **1** (Zovirax), an acyclic analogue of guanosine[1] (Fig. 1). Derivatives with a 1,2,4-triazole in place of the guanine moiety in ACV such as 1-[(2-hydroxy ethoxy) methyl]-1,2,4-triazole-3-carboxamide **2**[2,3] (Fig. 1) were reported and these show interesting biological activities.

In continuation of our research programme on the chemistry of 1,2,3-triazole[4–7], we have examined the synthesis of a series of 1,2,3-triazole acyclonucleosides **3a–e** (Fig. 1) via a Diels–Alder reaction. These compounds were evaluated for their anti-HIV activity as analogues of ACV.

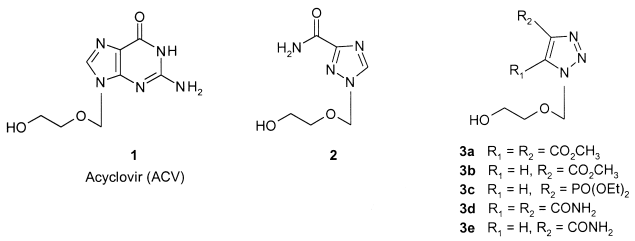
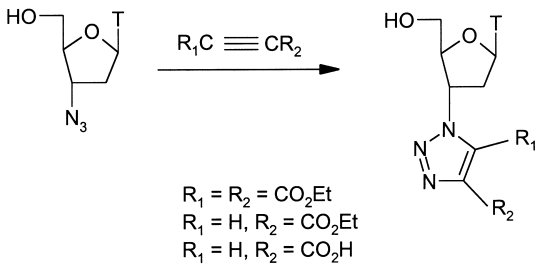


Figure 1



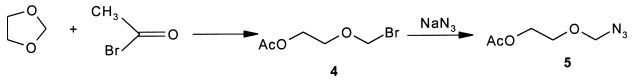
Scheme 1

Recently 1,3-dipolar cycloadditions were used to build the 1,2,3-triazole ring of branched nucleoside dimers.[8–11] Thus, Herdewijn *et al.*[12] have reported the synthesis of compounds in which the N_3 unit of AZT is transformed to a triazole ring (Scheme 1). Tittensor *et al.*[13] have used the cycloaddition of 5′-azido-5′deoxythymidine with carbonyl activated alkynes to synthesise 1,2,3-triazole as potential thymidylate kinase inhibitors.

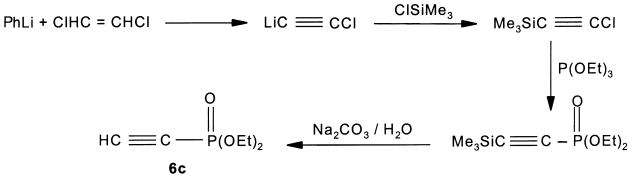
Results and discussion

In our study directed towards the synthesis of biologically active heterocycles, we employed the methodology of aglycon construction on the sugar moiety by using a 1,3-dipolar cycloaddition. Thus, compound **4** was reacted with sodium azide at 95°C for 4h to give the corresponding azido-compound **5**, acyclic portion of ACV, in high yield[14,15] (Scheme 2).

The second step of the synthesis was the condensation of azido-compound **5** as a diene with an acetylenic dienophile **6a–c** such as dimethyl acetylenedicarboxylate **6a**, methyl propiolate **6b** and the diethyl ethynylphosphonate **6c** which was synthesised in high yield[16] (Scheme 3). The cycloaddition reaction which was carried out in dry toluene under reflux, afforded **4a** and a mixture of two regioisomers **4b–c** and **4′b–c** (Scheme 4). The ratio of **4/4′** was determined from the ^{1}H NMR spectra. After separation on silica gel column chromatography, only the major isomers **4** were obtained as pure products. It has been reported that the addition of azides to unsymetrical acetylenes is determined by steric and electronic factors. In general, such addition tends to give mainly the isomers with electron-withdrawings groups at the 4-position and electron-releasing groups at the 5-position. The structure of the two isomers were established by comparaison of the chemical shift values for the triazole ring protons with those available from a known pair of 4- and 5-glycosyl-l,2,3-triazole derivatives.[12] In the case of the 4-substituted isomers **4b–c** the signal of H-5 proton appeared at lower field than the signal of H-4 proton in the 5-substituted derivatives **4′b–c**.



Scheme 2



Scheme 3

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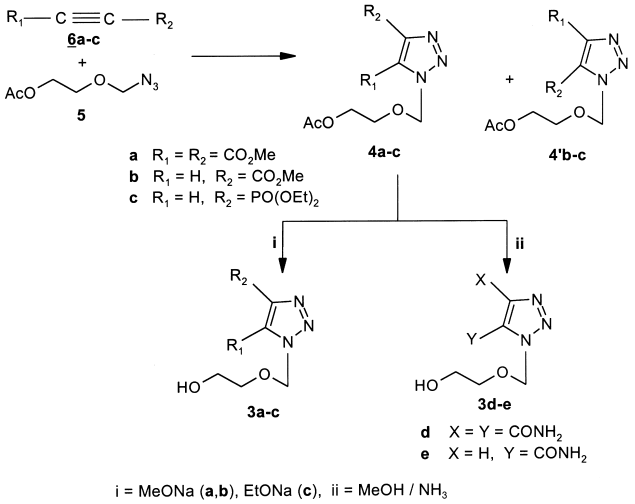
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 4

Table 1 1,3-dipolar cycloaddition of acetylenic derivatives with azidoacyclic **5**

Substrate	Equiv. of azide	Reaction time/h	Yield/% of **4**	Ratio[a] **4/4′**
6a	16	72	73	-
6b	1.1	72	63	92/8
6c	1.1	72	70	94/6

[a]The ratio were determined from ^{1}H NMR spectra.

The anti-HIV reverse transcriptase compounds should have the 5′-OH free to be converted by cellular enzymes to its triphosphate and incorporated in the terminal position of DNA. Thus, the acetyl groups in C-5′ of the newly compounds **4a–c** was removed from each with sodium methylate (for **a, b**) / ethylate (for **c**) and ammonia in methanol (for **a, b**) to give respectively **3a–b / 3c** and **3d–e** after treatment with Dowex H^+ 50x8 and flash column chromatography (Scheme 4).

Antiviral activity

Compounds **3a–e** were evaluated for cytoxicity and inhibition of HIV replication in CEM-SS (10^{-4}M). Only **3c** and **3e** were significantly active giving 20% and 43% inhibition HIV multiplication without toxicity.

In conclusion, 1,3-dipolar cycloaddition has been used successfully to provide an easy entry into the biologically active 1,2,3-triazole acyclonucleoside analogues of ACV. Extension of this methodology to the synthesis of other novel acyclonucleosides analogues of DHPG and iso-NDG will be reported in due course.

Experimental

General procedure of cycloaddition: To a stirred solution of the azido synthon **5** (1 mmole) in anhydrous toluene (10 ml) was added the dimethyl acetylenedicarboxylate **6a** (16 mmole) or methyl propiolate **6b** (1.1 mmole) or diethyl ethynyl phosphonate **6c** (1.1 mmole). The reaction mixture was refluxed for 72 hours and the solvent and excess of acetylenic dienophil were evaporated under reduced pressure. The residue thus obtained was chromatographed on a silica gel column using a mixed solvent of chloroform and hexane (95:5) as eluent.

General procedure of deacetylation with RONa: To a solution of anhydrous methanol (5 ml) was added metallic sodium (0.9 mmole) and the mixture was stirred for 20 minutes. Compound **4a–b** (0,6 mmole) was then added and the reaction mixture was stirred continuously until TLC showed only one product present. The mixture was then neutralised with Dowex H^+ 50 × 8, evaporated to dryness and chromatographed on a silica gel column using a mixed solvent of chloroform and methanol (20:1) as eluent to give the **3a–b** respectively. The same reaction sequence was adopted to prepare **3c** from **4c** in anhydrous ethanol.

General procedure of deacetylation with MeOH/NH$_3$: A solution of **4a–b** (2 mmole) in methanolic ammonia (20 ml) was stirred at room temperature for 24 hours. The solvent from the reaction mixture was then removed by evaporation, and the resulting gum was chromatographed on a silica gel column using a mixed solvent of chloroform and methanol (20:1) as eluent to give the **3d–e** respectively.

All melting points were determined with a Büchi apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded with a 250 MHz Bruker AC-250 spectrometer. Chemical shifts are reported in parts per million (δ) using internal TMS standard. Thin-layer chromatography was performed on silica gel 60F-254 plates. Column chromatography was performed on silica gel (0.0063–0.2 mm, Merck). The mass spectrum was optained on a Jeol JMX-DX 300. The compounds were analysed for C, H and N. The results were within 0.4 % of the calculated theoretical values.

1-[(2-acetoxyethoxy) methyl]-1,2,3-triazole-4,5-dimethyl carboxylate **4a**: Rdt = 73%. ^{1}H NMR ($CDCl_3$) δ: 2.03 (s,3); 3.60–3.95 (m,4); 3.98 (s,3); 4.00 (s,3); 6.00 (s,2). Anal. Calc. for $C_{11}H_{15}N_3O_7$: C 43.85, H 5.01, N 13.94, Found: C 43.80, H 4.95, N 13.88 *m/z*: 301 (M^+).

1-[(2-acetoxyethoxy) methyl]-1,2,3-triazole-4-methyl carboxylate **4b**: Rdt = 63%. m.p. = 85–87°C (EtOH). ^{1}H NMR (DMS0 d_6) δ: 1.95 (s,3); 3.75 (m,2); 3.85 (s,3); 4.10 (m,2); 5.80 (s,2); 9.00 (s,l). Anal. Calc. for $C_9H_{13}N_3O_5$: C 44.44, H 5.38, N 17.27, Found: C 44.00, H 4.95, N 17.09 *m/z*: 243 (M^+).

1-[(2-acetoxyethoxy) methyl]-1,2,3-triazole-4-diethylphosphonate **4c**: Rdt = 70%. ^{1}H NMR (DMSO d_6) δ:1.28 (t,6); 1.98 (s,3); 3.70 (m,2); 4.10 (m,6); 5.85 (s,2); 8.85 (s,l). Anal. CaIc. for $C_{11}H_{20}N_3O_6P$: C 43.85, H 5.01, N 13.94, Found: C 43.80, H 4.95, N 13.88 *m/z* (FAB >0): 322 $(M+H)^+$.

1-[(2-hydroxyethoxy) methyl]-1,2,3-triazole-4,5-dimethyl carboxylate **3a**: Rdt = 98%. ^{1}H NMR (DMSO d_6) δ: 3.75 (m,4); 3.98 (s,3); 4.00 (s,3); 4.70 (t,1); 6.00 (s,2). *m/z* (FAB >0): 260 $(M+H)^+$.

1-[(2-hydroxyethoxy) methyl]-1,2,3-triazole-4-methyl carboxylate **3b**: Rdt = 98%. M.p. = 61–63°C (EtOH). ^{1}H NMR (DMSO d_6) δ: 3.52 (m,4); 3.85 (s,3); 4.70 (t,1); 5.80 (s,2); 9.00 (s,1). Anal. Calc. for $C_7H_{11}N_3O_4$: C 41.79, H 5.51, N 20.88, Found: C 41.70, H 5.46, N 20.91 *m/z* (FAB >0): 202 $(M+H)^+$.

1-[(2-hydroxyethoxy) methyl]-1,2,3-triazole-4-diethylphosphonate **3c**: Rdt = 98%. ^{1}H NMR (DMSO d_6) δ:1.25 (t,6); 3.50 (m,4); 4.08 (q,4); 4.73 (t,1); 5.80 (s,2); 8.82 (s,l). *m/z* (FAB >0): 280 $(M+H)^+$.

1-[(2-hydroxyethoxy) methyl]-1,2,3-triazole-4, 5-dicarboxamide **3d**: Rdt = 98%. M.p. = l56–159°C (EtOH). ^{1}H NMR (DMSO d_6) δ: 3.40–3.60 (m,4); 4.70 (t,l); 6.15 (s,2); 8.20 (s,2); 8.55 (s,1); 10.20 (s,l). Anal. Calc. for $C_7H_{11}N_5O_4$: C 36.68, H 4.83, N 30.55, Found: C 37.19, H 4.89, N 30.09 *m/z* : 229 (M^+).

1-[2-hydroxyethoxy) methyl]-1,2,3-triazole-4-carboxamide **3e**: Rdt = 98%. M.p. = 125–126°C (EtOH). ^{1}H NMR (DMSO d_6) δ: 3.40–3.60 (m,4); 4.70 (t,1); 5.80 (s,2); 7.55 (s,l); 7.95(s,1); 8.70 (s,l). Anal. Calc. for $C_6H_{10}N_4O_3$: C 38.71, H 5.41, N 30.09, Found: C 38.70, H 5.40, N 30.05 *m/z*:186 (M^+).

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