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ALKYLGLYCOSIDE CARBONATES OF 3'-AZIDO-3'-DEOXYTHYMIDINE

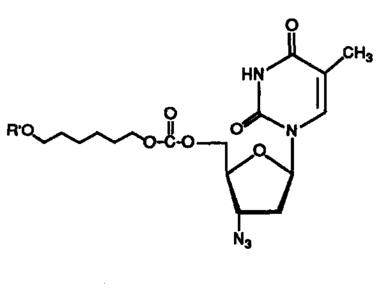
Sylvie Pochet[1], Vinod Kansal[1], Florence Destouesse[2] and Simon R. Sarfati[1]

Institut Pasteur, [1]Unité de Chimie Organique, [2] Unité d'Oncologie Virale,
associées au CNRS, 28, rue du Docteur Roux, 75724 Paris Cedex 15, France.

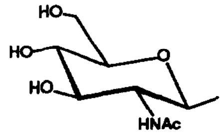
Abstract: Analogues of 3'-azido-3'-deoxythymidine (AZT) were synthesized by coupling glycosides and AZT through a carbonate bridge. The glycosides were prepared by treatment of 6-benzyloxy-1-hexanol (**1**) with 2-methyl-3,4,6-tri-O-acetyl-1,2-dideoxy-α-D-glucopyrano-[2,1-d]-2-oxazoline (**2**) and tetra-O-benzoyl-α-D-mannopyranosyl bromide (**3**), followed by O-deprotection, persilylation and catalytic hydrogenolysis to give the alcohols **10** and **11**, respectively. Condensation of **10** and **11** with AZT in the presence of 1,1'-carbonyldiimidazole, followed by removal of the silyl groups, afforded the title compounds.

The flow of molecules and ions between a cell and its environment is precisely regulated by specific transport systems through membranes, and glucose enters most cells by a specific carrier or active-transport system.

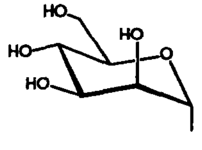
Recently, 6- and 1-substituted glycosyl phosphotriesters have been proposed as lipophilic carriers of antiviral nucleosides[1]. We propose as a new drug carrier a system which comprises as the hydrophilic part a glycoside with the 6-position free, and as the lipophilic part an alkyl chain; the molecule to be carried inside the cell is linked to the glycoside at position 1 via the alkyl chain with a carbonate group. The drug would be liberated inside the cell either by cellular enzymes, or by spontaneous hydrolysis of the carbonate. As an example, we describe the drug conjugates **14** and **15**, in which AZT, a potent anti AIDS agent[2], is linked to the glycoside by its 5' end.



(13) R'=

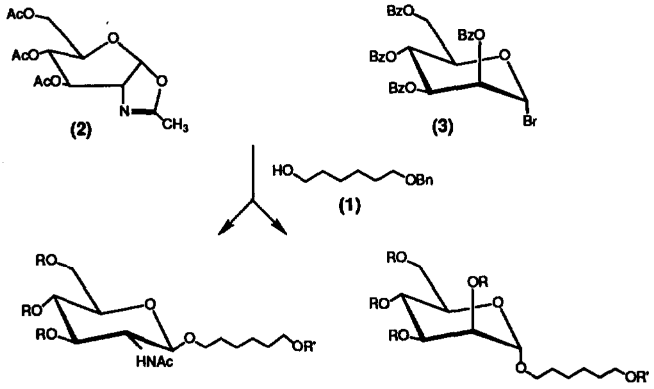


(14) R'=



The preparation of these AZT analogues required glycosides with a free hydroxyl group, which were synthesized according to Scheme 1. 6-Benzyloxy-1-hexanol **1**[3] was condensed with 2-methyl-3,4,6-tri-O-acetyl-1,2-dideoxy-α-D-glucopyrano-[2,1-d]-2-oxazoline **2**[4] and with tetra-O-benzoyl-α-D-mannopyranosyl bromide **3**[5], to afford the fully protected glycosides **4** (55% yld) and **5** (57% yld) respectively. Treatment of **4** and **5** with sodium methoxide afforded the corresponding deprotected glycosides **6** (88% yld) and **7** (81% yld). The osides were blocked as their tri- and tetra-*tert*-butyldimethylsilyl (TBDMS) ethers **8** (70% yld) and **9** (59% yld), respectively; these reactions were not complete even with a large excess of silylating agent. Catalytic hydrogenolysis of **8** and **9** over 10% palladium-on-charcoal in ethanol afforded syrupy **10**[6] and **11**[7], in 70% and 91% ylds.

Scheme 1

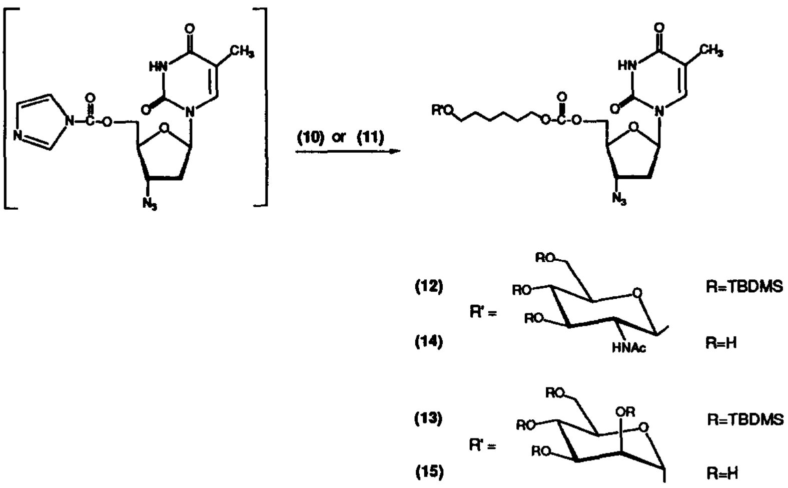


(4) R=Ac, R'=Bn
(6) R=H, R'=Bn
(8) R=TBDMS, R'=Bn
(10) R=TBDMS, R'=H

(5) R=Bz, R'=Bn
(7) R=H, R'=Bn
(9) R=TBDMS, R'=Bn
(11) R=TBDMS, R'=H

The free primary hydroxyl of the glycosides was condensed with the 5' hydroxyl of AZT in a one-flask procedure (Scheme 2). AZT was first treated with 1.1 equiv. of 1,1'-carbonyldiimidazole in acetonitrile for 1/2 h at room temperature. After addition of the glycosides **10** or **11** (0.9-1 equiv.), the reaction mixture was refluxed overnight, affording **12**[8] (70% yld) or **13**[9] (53% yld). Subsequent desilylation with 1M TBAF in THF afforded the 5'-(1-alkyl glycoside) carbonates of AZT **14**[10] and **15**[11]. The purity of the compounds **14** and **15** was checked by analytical reverse-phase HPLC on a Nucleosil 5-C18 by using a gradient of acetonitrile (A) in a 0.05M triethylammonium acetate buffer (B) (pH 7.5) during 20 min. at a flow rate of 0.5 ml/min..

Scheme 2



First, the stability of the carbonate bridge was checked in the buffer (RPMI 1640, Gibco OSI) and the medium (RPMI 1640, 1% glutamine, 5% foetal calf serum and 100 IU/ml penicillin, 100 µg/ml streptomycin) used in the activity tests. The preliminary activity of these compounds was measured on CEM-CI13 cell lines[12]. Two parameters were studied to evaluate the antiviral activity of the compounds (at doses 2 to 20 µg/ml final): inhibition of HIV-1 induced cytopathic effect using the MTT cell viability assay, and the inhibition of the reverse transcriptase (RT) production in culture supernatant, at day 6 and day 10. The reference compound AZT (obtained from SIGMA) was included in this assay. The two compounds were devoided of toxicity at day 6, or displayed a toxicity equivalent to AZT at day 10 for CEM-CI13 cells. The compound **15** was unable to inhibit the HIV-1 induced cytopathic effect (CPE) in cells and the RT production after day 10 post infection. The compound **14** totally (day 6) and partially (day 10) inhibited the CPE in CEM-CI13 cells. This antiviral activity was correlated with decreasing of the reverse transcriptase activity (RTA).

These preliminary results revealed that the compound **15** showed any significant activity, at a concentration up to 20 mg/ml. The compound **14** was clearly active on HIV-1 induced CPE cells, and decreased RT activity by 90% as compared to control virus (untreated cells).

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6. **10:** ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.04, 0.08 and 0.10 (6s, 18H, CH_3Si); 0.90 and 0.94 (3s, 27H, tBuSi); 1.38 (m, 4H, CH_2); 1.56 (m, 4H, CH_2); 1.74 (m, 1H, OH); 1.94 (s, 3H, CH_3CO); 3.32 (td, 1H, CH-O, J = 6.5 Hz, J = 9.5 Hz); 3.63 (t, 2H, CH_2OH, J = 6.5 Hz); 3.65-3.80 (m, 4H, CH-O, H-3, H-5 and H-6); 3.94 (m, 1H, H-6); 4.07 (broad d, 1H, H-2, $J_{2,NH}$ = 9 Hz); 4.31 (t, 1H, H-4, $J_{3,4} = J_{4,5}$ = 9.5 Hz); 4.59 (s, 1H, H-1); 6.83 (d, 1H, NH-$COCH_3$, $J_{2,NH}$ = 9.5 Hz); M.S. (C.I., NH_3): 664 (M+H), 546; TLC 0.50 (hexane/ethylacetate, 1:10).

7. **11:** ^{1}H-NMR (300MHz, $CDCl_3$) δ 0.04 (s, 24 H, CH_3Si); 0.83 (s, 36H, tBuSi); 1.33 (m, 4H, CH_2); 1.52 (m, 4H, CH_2); 1.63 (m, 1H, OH); 3.33 (m, 1H, CH-O); 3.51 (t, 2H, CH_2OBn, J = 8 Hz); 3.61-3.80 (m, 7H, H-2, H-3, H-4, H-5, H-6', H-6" and CH-O); 4.68 (d, 1H, H-1, $J_{1,2}$ = 1 Hz); M.S. (C.I., NH_3): 754 (M + 18), 737 (M + H), 636, 619; TLC 0.20 (hexane/ethylacetate, 5:100)..

8. **12:** ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.05-0.10 (m, 6H, CH_3Si); 0.88 and 0.93 (2s, 27 H, tBuSi); 1.37 (m, 4H, CH_2); 1.53 (m, 2H, CH_2-CH_2O); 1.67 (t, 2H, CH_2-CH_2-OCO); 1.93 and 1.94 (2s, 6H, CH_3-C5 and CH_3-CONH); 2.37 (m, 1H, H-2'); 2.45 (m, 1H, H-2"); 3.30 (dt, 1H, CH-O); 3.65-3.80 (m, 3H, CH-O, H-5' and H-5"); 3.70 (s, 1H, H-4'); 4.18 (m, 2H, CH_2OCO); 4.29 (m, 1H, H-3'); 4.57 (s, H, H-1); 6.24 (t, 1H, H-1', $J_{1',2'}$ = 6.25 Hz); 6.84 (d, 1H, *NH*$COCH_3$, $J_{2,NH}$ = 9.43 Hz); 7.39 (s, 1H, H-C6); 9.14 (d, 1H, NH-C3, J = 9.14 Hz). M.S. (FAB+): 957.55 (MH+); TLC 0.49 (hexane/ethylacetate, 1:3).

9. **13:** ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.05-0.10 (m, 6H, CH_3Si); 0.90 (s, 27H, tBuSi); 1.30 (m, 4H, CH_2); 1.52 (m, 2H, CH_2O); 1.65 (m, 2H, CH_2-CH_2O); 1.93 (s, 3H, CH_3-C5); 2.30 (m, 1H, H-2'); 2.40 (m, 1H, H-2"); 3.50 (m, 2H, H-5' and H-5"); 3.70 (m, 1H, H-4'); 4.15 (m, 1H, H-3'); 4.52 (d, 1H, H-1, $J_{1,2}$ = 0.5 Hz); 6.16 (t, 1H, H-1', J = 6.2 Hz); 7.26 (s, 1H, H-C6); 8.61 (broad s, 1H, NH-C3). M.S. (FAB-): 1028 (MH-); TLC 0.67 (hexane/ethylacetate, 1:3).

10. **14:** ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.35 (m, 4H, CH_2); 1.54 (m, 2H, CH_2-CH_2O); 1.66 (m, 2H, CH_2OCO); 1.92 (d, 3H, CH_3-C5); 2.03 (s, 3H, NHCOCH_3); 2.57 (t, 2H, H-2' and H-2", $J_{1',2'}$ = 6.50 Hz); 4.50 (d, 1H, H-1, $J_{1,2}$ = 7.5 Hz); 6.23 (t, 1H, H-1', $J_{1',2'}$ = 6.25 Hz); 7.56 (d, 1H, H-C6, J = 1.5 Hz). M.S. (FAB$^+$): 637 (MNa$^+$); RT 13.1 min. (5-70% of A in B).

11. **15:** ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.29 (m, 4H, 2 x CH_2); 1.55 (m, 4H, 2 x CH_2); 1.78 (s, 3H, CH_3-C5); 2.32 (m, 1H, H-2'); 2.42 (m, 1H, H-2"); 4.05 (m, 3H, H-4', H-5' and H-5"); 4.32 (t, 2H, CH_2OCO); 4.50 (t, 1H, H-3'), 4.58 (s, 1H, H-1); 6.13 (t, 1H, H-1'); 7.50 (s, 1H, H-C6); M.S. (FAB$^-$): 572 (MH$^-$); RT 13.2 min. (5-70% of A in B).

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