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Synthesis and anti-HIV activity of some haloalkyl phosphoramidate derivatives of 3′-azido-3′-deoxythymidine (AZT): potent activity of the trichloroethyl methoxyalaninyl compound

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Summary

Phosphate triester derivatives of AZT have been prepared as membrane-soluble pro-drugs of the bio-active nucleotides, and have been evaluated against HIV-1 in vitro. In particular, the phosphorus centre carries a trichloro- or trifluoroethyl group and a carboxyl-protected, amino-linked amino acid. The compounds are prepared using phosphorochloridate chemistry, and are characterized by a range of techniques. They display potent anti-HIV activity and low host toxicity, but surprisingly this activity does not increase on the introduction of the haloalkyl moiety. The trichloroethyl methoxyalaninyl compound is exceptional: here the activity is enhanced 50-fold by the introduction of the trichloroethyl group.

Nucleoside analog; Nucleotide ester; Anti-HIV; Anti-AIDS; Phosphoramidate

Introduction

The nucleoside analogue AZT (1) is now established as a selective inhibitor of the proliferation of HIV, and is emerging as a useful drug in the treatment of AIDS (Wood, 1989; Yeo, 1989). As with other anti-viral nucleoside analogues AZT acts

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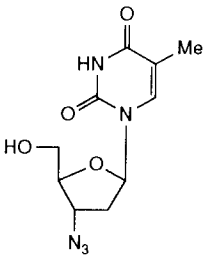

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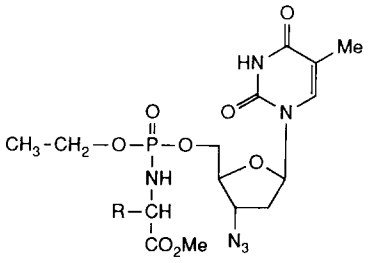

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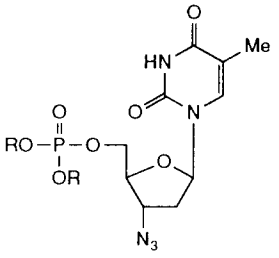
2b R iPr
2c R=H



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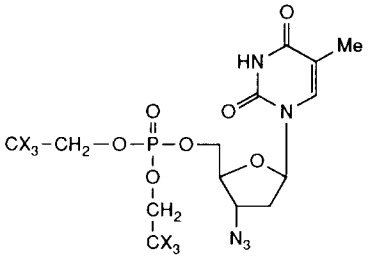
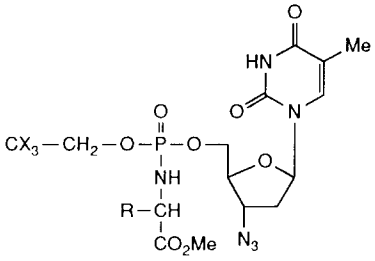
3b R=nPr
3c R=nBu



4a X=F
4b X=Cl



5a R=Me, X=F
5b R=iPr, X=F
5c R=H, X=F
5d R=Me, X=Cl
5e R=iPr, X=Cl
5f R=H, X=Cl

Fig. 1. AZT (1) and its derivatives.

only after intracellular conversion to its 5′-triphosphate (Furman et al., 1986). This dependence of nucleoside analogues on host kinases can be a major limitation (Furman et al., 1979) which cannot easily be overcome by the use of simple nucleotides, as their charge greatly impedes membrane penetration (Leibman and Heidelberger, 1955; Lichtenstein et al., 1960). Consequently, there has been much interest in the use of masked phosphate esters as membrane-soluble depot forms of the bio-active nucleotides of chemotherapeutic nucleoside analogues, including AZT (Farrow et al., 1990; Gouyette et al., 1989; Jones et al., 1989; McGuigan et al., 1989a,b; Schwartz et al., 1989). We have noted that certain phosphoramidate analogues (2a–c) are potent inhibitors of viral proliferation (McGuigan et al., 1990b). The initial rationale behind the synthesis of phosphoramidates was the idea that HIV aspartate proteinase (Dunn and Kay, 1990) might specifically hydrolyse these membrane-soluble pro-drugs. The resulting phosphate diesters would be trapped inside the (infected) cell, where phosphodiesterase action may yield either AZT or AZTMP or both. On the other hand, simple dialkyl phosphate derivatives (3a–c) of AZT are entirely inactive as anti-HIV agents (McGuigan et al., 1990a). However, more recently, we have noted that bis(trihaloethyl) phosphate derivatives (4a,b) are potent anti-HIV agents (McGuigan et al., 1990c). These data strongly suggest that the combination of a haloethyl and an amino acid moiety on the phosphorus of AZTMP may yield especially active materials. Here we report the synthesis and anti-HIV activity of these species, with trifluoro- or trichloroethyl groups, and (N-linked) amino acid methyl esters attached to phosphorus.

Results

The synthetic route we employed to the target compounds was analogous to that we have previously used in the preparation of the un-halogenated analogues (2a–c). Thus, the reagents (MeOCOCHRNH) (CX_3CH_2O)POCl (R = Me, iPr, H; X = Cl, F) were prepared by the reaction of the appropriate amino acid methyl ester with the haloalkyl phosphorodichloridate (Curley et al., 1990). These phosphoramidates were then allowed to react with AZT in THF-containing *N*-methylimidazole (Van Boom et al., 1975).

Purification of the crude product by precipitation and column chromatography gave the pure materials (5a–f). The compounds were fully characterized by spectroscopic and analytical methods. For example, each compound displays ^{31}P-NMR signals at approximately 6 ppm, fully consistent with the proposed structures (Mark et al., 1969). Indeed, in all but the glycinyl compounds (5c,f) the signal is seen as two closely spaced resonances, corresponding to the presence of two diastereoisomers in the sample. This isomerism arises from mixed stereochemistry at the phosphate centre; with the ratio of isomers varying from 1:1 to 2:1. ^{13}C-NMR data (Table 1) confirm this, with many signals being split in the ratio of the isomers. In the case of the trifluoroethyl derivatives (5a–c) every signal is split in this way; excluding those for the methoxy carbon atoms. In the case of the trichloroethyl analogues (5d–f) rather more signals remain as singlets. For example the C2

TABLE 1

^{13}C-NMR data on compounds (5a–f) recorded at 100 MHz in $CDCl_3$

		5a	5b	5c	5d	5e	5f
Base	C2	163.8	163.8	163.8	163.9[e]	163.8[e]	163.9[e]
	C4	150.3	150.3	150.3	150.4	150.3	150.4
	C5	111.4	111.6	111.5	111.6	111.5	111.4
	C6	135.4	135.5	135.5	135.6	135.3	135.5
	Me	12.3	12.4	12.3	12.6[e]	12.5	12.4[e]
Sugar	C1′	84.8	85.4	85.3	85.4	85.7	85.2
	C2′	37.4	37.4	37.2	37.3[e]	37.1[e]	37.1
	C3′	60.2	60.3	60.1	60.5	60.4	60.3
	C4′	82.4[a]	82.2[f]	82.1[i]	82.2[m]	82.1[e,p]	82.1[u]
	C5′	65.7[b]	65.9[g]	65.8[j]	66.0[c]	66.0[q]	66.0[v]
Alkyl	$POCH_2$	62.5[c]	62.5[c]	62.5[k]	76.3[n]	76.2[e,r]	76.2[e,w]
	CX_3	121–124[c]	121–124[c]	121–124[i]	95.3	95.1	95.1
Amine	C*	50.1	58.9	42.5	50.1	59.8	42.6
	Me (1)	21.2[d]	19.2	–	20.9[o]	19.1	–
	Me (2)	–	17.3	–	–	17.1	–
	ValCH	–	31.9[h]	–	–	31.7[s]	–
	C=O	174.3	174.0	171.2	170.4	173.2[t]	171.2
	OMe	52.5[e]	52.6[e]	52.6[e]	52.8[e]	52.4	52.5[e]

All peaks display diastereomeric splitting unless otherwise noted; chemical shifts represent mean values. Superscripts refer to multiplicities as follows. Where coupling (to phosphorus unless otherwise noted) is resolved, the J value (in Hz) is given. For diastereomeric peaks separate J values are given: [a]7.2/6.7, [b]5.2/5.1, [c]multiplet, [d]5.0/5.2, [e]no diastereomeric splitting, [f]7.2/7.0, [g]6.0/6.3, [h]8.8/7.6, [i]7.6/7.7, [j]4.0/4.7, [k]multiplet/J_F=32, [l]multiplet/J_F=278, [m]7.6/7.4, [n] 3.4/3.2, [o]6.0/5.4, [p]7.2, [q]5.4/5.3, [r]3.5, [s]6.9/6.5, [t]3.6/3.0, [u]7.5/7.6, [v] 5.0/4.4, [w]3.0.

of the base is noted as a doublet for each of (5a–c) and a singlet for (5d–f). This may suggest some interaction between the halogenated chains and the base, at least in one series. The ^{13}C spectra are further complicated by phosphorus and fluorine coupling to carbon atoms within two bonds. In the case of (5a–c) one-bond fluorine coupling is especially noticeable (J approx. 280 Hz). Proton NMR spectra are also fully consistent with the proposed structures, and the purity of the products was confirmed in each case by microanalysis and analytical HPLC. The latter technique revealed the samples to be free of AZT in every case; this is crucial, given the high activity of the free nucleoside in the assay system employed.

Discussion

AZT (1), alkyl phosphoramidate derivatives (2a–c) and haloalkyl compounds (5a–f) were evaluated, by methods previously described, for their ability to inhibit the proliferation of HIV-1 in vitro (Kinchington et al., 1989); the results are pre-

TABLE 2

ED_{50} values of phosphoramidates (2a–c) and (5a–f), evaluated as inhibitors of HIV-1

Compound	ED_{50} (μM)
1	0.004
2a	3
2b	10
2c	10
5a	3
5b	5
5c	3
5d	0.08
5e	5
5f	10

These are the minimum concentrations of drug in μM which will reduce HIV antigen production by 50%. Each result is the average of three independent assays.

sented in Table 2. All of the compounds tested were active in this assay, and none were toxic to uninfected cells at the maximum concentration studied (100 μM).

We have previously noted that replacement of the alkyl groups in dialkyl phosphate triesters of AZT by trihaloalkyl (particularly trifluoroethyl) groups converted inactive compounds into compounds with notable anti-HIV activity (McGuigan et al., 1990a,c). It is therefore striking that we note no similar enhancement of activity for the phosphoramidates (2a–c) on introduction of the trifluoroethyl moiety (5a–c). This difference may represent different mechanisms by which the phosphate and phosphoramidate compounds are activated inside the cell.

The same lack of enhancement was noted for the trichloroethyl group, in the valinyl (5e) and glycinyl (5f) cases. However, most surprising of all was the remarkable activating effect of the trichloroethyl group on the alaninyl compound (5d). As noted in Table 2, this compound is 50 times more active than its ethyl (2a) or trifluoroethyl (5a) analogues. The reason for this anomaly is entirely unknown, but is the subject of our current investigations.

In conclusion, phosphate triester derivatives of AZT bearing amino acid moieties and trihaloethyl groups do have anti-HIV activity. The introduction of the halogenated alkyl chain does not have a beneficial effect in terms of anti-viral activity in most cases, this being in contrast to the situation in analogous phosphate compounds. However, the case of the trichloroethyl methoxyalaninyl compound is exceptional; here is a very marked enhancement of activity on the introduction of the haloalkyl moiety. The origins of this most promising result are unclear.

Materials and Methods

Chemistry

All reactions were carried out under scrupulously dry conditions. Reagents were dried as follows before use: THF was distilled from Na/benzophenone under nitro-

gen. *N*-Methylimidazole was heated to 100°C over CaH_2 for 4 h, and then distilled at 15 mm Hg. Nucleosides were dried at approx. 50°C/0.1 mm Hg for several hours before use. For TLC, Merck 60 F_{254} pre-coated silica plates were employed. For flash column chromatography Woelm 32-63 silica was used. Proton spectra were recorded on a Varian XL200 spectrometer operating at 200 MHz or a Varian VXR400 operating at 400 MHz; peaks displaying diastereomeric splitting are indicated by asterisks in the following text. ^{31}P-NMR spectra were obtained on these instruments, operating at 81 MHz and 162 MHz respectively. ^{13}C spectra were recorded on the latter instrument at 100 MHz. Proton spectra were referenced to TMS, phosphorus spectra to 85% phosphoric acid, and carbon spectra to $CDCl_3$; positive shifts are downfield of the reference. All NMR spectra were recorded in $CDCl_3$ unless otherwise stated.

Microanalyses were performed at UCL, in the laboratory of Mr. A. Stones; the phosphate triesters were noted to be hygroscopic, and analytical data are presented appropriately. The triesters were analysed by HPLC prior to biological evaluation (ACS system, 5% water in MeCN on a 50 + 250 mm × 4.6 mm Spherisorb CN 5 μM column, with flow rate of 2 ml/min and detection by UV at 265 nm) and were free of AZT.

A standard procedure was used for all nucleotide derivatives; a typical procedure is listed in full, and then simply departures from this, for proceeding compounds.

3′-Azidothymidine-5′-(trifluoroethyl methoxyalaninyl)phosphate (5a)

Compound (1) (0.20 g, 0.75 mmol) and trifluoroethyl methoxyalaninyl phosphorochloridate (0.64 g, 2.24 mmol) were stirred together in anhydrous tetrahydrofuran (THF) (5 ml) containing *N*-methylimidazole (0.36 ml, 4.49 mmol) at ambient temperature for 24 h. The solvent was removed under reduced pressure and the gummy residue dissolved in chloroform (30 ml) and extracted with saturated sodium bicarbonate solution (15 ml), and water (2 × 15 ml). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. This was dissolved in chloroform (10 ml) and precipitated with petroleum ether (400 ml; b.p. 30–40°C). The precipitate was further purified by flash chromatography on silica (30 g), with elution by 5% methanol in chloroform. Pooling and evaporation of appropriate fractions gave the product as a white solid (0.35 g, 91%). δ_P 5.84, 5.72 (3:2); δ_H 8.30* (1H,bs,NH), 7.30* (1H,s,H-6), 6.15* (1H,t,H-1′), 4.20–4.40 (5H,m,H-4′,H-5′,CH_2OP), 4.00 (1H,m,H-3′), 3.90 (1H,m,ala-CH), 3.70 (3H,s,OMe), 3.60 (1H,m,ala-NH), 2.40 (1H,m,H-2′), 2.30 (1H,m,H-2′), 1.90 (3H,s,5-Me), 1.40 (3H,d,ala-Me); found C 36.97%, H 4.27, N 16.11, P 5.96; $C_{16}H_{22}F_3N_6O_8P$ requires C 37.36%, H 4.31. N 16.34, P 6.02.

3′-Azidothymidine-5′-(trifluoroethyl methoxyvalinyl)phosphate (5b)

This was prepared from compound (1) using a method entirely analogous to that for compound (5a) above. Thus, from 0.20 g of (1) was isolated 0.33 g (81%) of (5b). δ_P 7.04, 6.80 (2:1); δ_H 8.25* (1H,bs,NH), 7.25* (1H,s,H-6), 6.15* (1H,t,H-1′), 4.20–4.45 (5H,m,H-4′,H-5′,CH_2OP), 4.00 (1H,m,H-3′), 3.70 (4H,m,OMe,val-CH), 3.40 (1H,m,val-NH), 2.40 (1H,m,H-2′), 2.30 (1H,m,H-2′), 2.10 (1H,m,iPrCH);

1.90 (3H,s,5-Me), 1.00 (3H,t,val-Me), 0.85 (3H,t,val-Me); found C 39.57%, H 4.37, N 15.85, P 6.04; $C_{18}H_{26}F_3N_6O_8P$ requires C 39.86%, H 4.83, N 15.49, P 5.71.

3′-Azidothymidine-5′-(trifluoroethyl methoxyglycinyl)phosphate (5c)

This was prepared from compound (1) using a method entirely analogous to that for compound (5a) above. Thus, from 0.20 g of (1) was isolated 0.28 g (75%) of (5c). δ_P 6.90; δ_H 9.45* (1H,bs,NH), 7.30 (1H,s,H-6), 6.15* (1H,t,H-1′), 4.20–4.40 (5H,m,H-4′,H-5′,CH_2OP), 4.00 (2H,m,gly-CH_2), 3.80 (5H,m,H-3′,OMe,gly-NH), 2.35 (2H,m,H-2′), 1.90 (3H,s,5-Me); found C 34.75%, H 4.07, P 6.51; $C_{15}H_{20}F_3N_6O_8P$ requires C 34.76%, H 4.28, P 6.81.

3′-Azidothymidine-5′-(trichloroethyl methoxyalaninyl)phosphate (5d)

This was prepared from compound (1) using a method entirely analogous to that for compound (5a) above, except that 4% methanol in chloroform was used as the column eluant. Thus, from 0.10 g of (1) was isolated 0.17 g (90%) of (5d). δ_P 4.73, 4.56; δ_H 9.00* (1H,bs,NH), 7.25* (1H,s,H-6), 6.13* (1H,t,H-1′), 4.50 (2H,m,CH_2OP), 4.35 (1H,m,H-4′), 4.25 (2H,m,H-5′), 3.9–4.0 (2H,m,H-3′,ala-CH), 3.80 (1H,sb,ala-NH), 3.60 (3H,s,OMe), 2.40 (1H,m,H-2′), 2.30 (1H,m,H-2′), 1.90 (3H,s,5-Me), 1.40 (3H,d,ala-Me); found C 33.69%, H 3.96, N 14.63, P 5.54; $C_{16}H_{22}Cl_3N_6O_8P$ requires C 34.09%, H 3.93, N 14.91, P 5.49.

3′-Azidothymidine-5′-(trichloroethyl methoxyvalinyl) phosphate (5e)

This was prepared from compound (1) using a method entirely analogous to that for compound (5a) above. Thus, from 0.2 g of (1) was isolated 0.35 g (85%) of (5e). δ_P 5.96, 5.72; δ_H 8.70* (1H,bs,NH), 7.25* (1H,s,H-6), 6.15* (1H,t,H-1′), 4.50 (2H,m,CH_2OP), 4.2–4.4 (3H,m,H-4′,H-5′), 4.00 (1H,m,H-3′), 3.80 (1H,m,val-CH), 3.70 (3H,s,OMe), 3.60 (1H,m,val-NH), 2.50 (1H,m,H-2′), 2.40 (1H,m,H-2′), 2.10 (1H,m,iPrCH), 1.90 (3H,s,5-Me), 1.00 (3H,t,val-Me), 0.80 (3H,t,val-Me); found C 36.24%, H 4.25, N 13.81, P 5.16; $C_{18}H_{26}Cl_3N_6O_8P$ requires C 36.53%, H 4.43, N 14.20, P 5.23.

3′-Azidothymidine-5′-(trichloroethyl methoxyglycinyl)phosphate (5f)

This was prepared from compound (1) using a method entirely analogous to that for compound (5a) above. Thus, from 0.15 g of (1) was isolated 0.18 g (66%) of (5f). δ_P 5.82; δ_H 9.60* (1H,bs,NH), 7.35 (1H,s,H-6), 6.15* (1H,t,H-1′), 4.60 (2H,m,CH_2OP), 4.3–4.4 (3H,m,H-4′,H-5′), 4.05 (2H,m,gly-CH_2), 3.7–3.8 (2H,m,H-3′,gly-NH), 3.65 (3H,s,OMe), 2.40 (1H,m,H-2′), 2.30 (1H,m,H-2′), 1.85 (3H,s,5-Me); found C 32.21%, H 3.30, N 14.89, P 5.90; $C_{15}H_{20}Cl_3N_6O_8P{\cdot}[H_2O]_{0.5}$ requires C 32.25%, H 3.79, N 15.04, P 5.54.

Biological evaluation

High titre virus stocks of the human immunodeficiency virus HIV-1 (RF strain of HTLV III) were grown in H9 cells with RPMI 1640 (Flow laboratories) supplemented with 10% fetal calf serum. Cell debris was removed by low speed cen-

trifugation, and the supernatant stored at −180°C until required. The target cell used in these assays was the C8166 CD4 + lymphoblastoid cell line. In a typical assay C8166 cells were incubated with 10 $TCID_{50}$ HIV-1 at 37°C for 90 min and then washed thoroughly with phosphate-buffered saline (PBS, Dulbecco A). Cell aliquots (2×10^5) were resuspended in 1.5 ml growth medium in 6-ml tubes, and compounds in half-log dilutions (100–0.01 μM) were added immediately. The nucleoside phosphate triesters were sparingly soluble in aqueous solution, and 10-mM stock solutions of each compound were made up in DMSO. The final DMSO concentration in the tissue culture medium was 1%. The cells were then incubated at 37°C in a 95% air/5% CO_2 incubator. At 72 h post-infection 200 μl of supernatant was taken from each culture and assayed for HIV (Kinchington, 1989) using an antigen-capture ELISA (Coulter, Luton, U.K.). The following controls were used: supernatants taken from uninfected, and infected cells (with and without 1% DMSO); infected cells treated with AZT (Roche Products U.K. Ltd.), and ddCyd (Roche Products U.K. Ltd.). The average ED_{50} values of AZT and ddCyd were approx. 0.004 and 0.2 μM respectively. The ELISA plates were read with a Biorad spectrophotometer. Compounds were tested in duplicate at each concentration, and each compound was tested on at least three different occasions. To test for compound toxicity, 2×10^5 aliquots of uninfected cells were cultured with the compounds in the same half-log dilutions for 72 h. The cells were then washed with PBS and resuspended in 200 μl of growth medium containing ^{14}C-protein hydrolysate. After 12 h the cells were harvested and the ^{14}C incorporation measured. Uninfected, untreated cells were used as controls. The compounds (2a–c) and (5a–f) showed a range of activities (Table 2), but none showed toxicity at 100 μM in this system.

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