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3'-Deoxy-3'-(vinylsulphonyl)thymidine - A New Reactive Analogue of AZT: Its Synthesis and Reactivities Towards Various Nucleophiles[#]

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Abstract: A reactive triatomic analogue of AZT, 3'-deoxy-3'-(vinylsulphonyl)thymidine has been synthesised from easily accessible starting material. The vinyl-sulphone nucleoside was reacted with a variety of nucleophiles to generate new classes of modified nucleosides where the functional groups were attached to the C-3' of a nucleoside through flexible ethyl sulphone spacer.

INTRODUCTION

Since the discovery of the anti-HIV activity of AZT[1], enormous progress has been made in the synthesis of new 3'-deoxy-3'-substitutedthymidines[2,3] due to urgent need for better therapeautic agents. Although a plethora of 3'-deoxy-3'-substitutedthymidines have been synthesised and their biological properties studied, the number of compounds showing anti-HIV activities *via* viral DNA chain termination mechanism are still unfortunately very low. However, the spread of the dreaded disease AIDS, has made it imperative to synthesise new modified nucleosides.

In an attempt to mimic the triatomic structure of the azido functionality of AZT, several groups have reported the synthesis of 3'-deoxy-3'-substitutedthymidine analogues carrying three-atom functionalities[3a-k]. We envisaged that a modified nucleoside having a highly reactive triatomic[3l] functionality would show interesting biological properties in addition to the viral DNA-chain termination. Earlier attempts[3d] along this line was not successful as the functionalities attached to the 3'-end, namely thiocyanates or isothiocyanate were most probably not reactive enough to form a strong bonding with the biological nucleophiles. We decided, therefore, to incorporate, at the 3'-site, an electrophilic group such as vinyl-sulphone, a functionality known[4] for its efficiency for covalent bond formation with a wide variety of nucleophiles. It may be argued, therefore, that as a consequence of the high reactivity of vinyl-sulphones, 3'-deoxy-3'-(vinylsulphonyl)thymidine and related derivatives may interact more efficiently with natural or mutated enzymes. However, unlike nitrogen-mustards[5], the vinyl-sulphone group would react with only one nucleophile at a time.

The other reasons for introducing a vinyl-sulphone at the 3'-site of thymidine are as folllows: i) a limited number of modified nucleosides, having alkyl/aryl- sulphoxide or sulphone functionalities at the C-3' position were synthesised in the past and some of these were subjected to biological screening[3a,3k,4,6,7,8]. However, all these synthetic methodologies, except one[4] were not general in nature and produced only a handful of compounds. The 3'-deoxy-3'-(vinylsulphonyl)thymidine that we propose to synthesise, on the other hand, can be used for attaching various functionalities to generate new classes of modified nucleosides where a group will be attached to the C-3' of a nucleoside through a flexible ethyl sulphone spacer[8,9,10]; ii) several unnatural DNA/RNA fragments were synthesised where the phosphate backbones were replaced by sulphur[6] linkages; in quite a few of these reports, sulphur is present in its highest oxidation state[11]. However, in almost all of these cases no general synthetic methodology evolved which would generate a group of similar type of oligomers. The 3'-deoxy-3'-(vinylsulphonyl)thymidine may be reacted with various suitably 5'-functionalised nucleosides to generate a wide variety of sulphone linked dinucleotides.

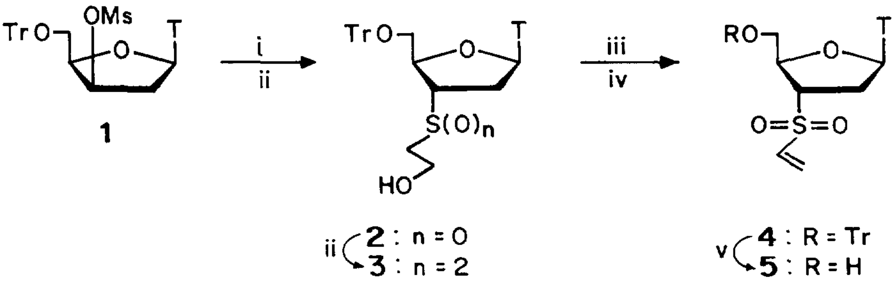
RESULTS AND DISCUSSION

Synthesis of 3'-deoxy-3'-(vinylsulphonyl)thymidine:

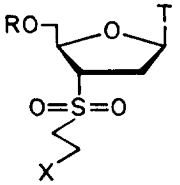
1-(5-O-Trityl-3-O-mesyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine **1** (ref. 3b) was treated with mercaptoethanol in the presence of an organic base. Although 1,1,3,3-tetramethylguanidine (TMG) produced the desired product in moderate yield, we observed that the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) furnished better yield (64% as opposed to 53%) of the desired product **2**. 1-(2,3-Dideoxy-5-O-trityl-β-D-*glycero*-pent-2-enofuranosyl)thymine was the other product formed in the reaction which could be removed from the mixture very easily by column chromatography. It should be mentioned that 5'-O-trityl-2,3'-O-anhydrothymidine as a substrate instead of compound **1** produced compound **2** in a much lower yield. Compound **2** was easily oxidised by magnesium monoperoxyphthalate (MMPP) in methanol at ambient temperature to the corresponding sulphone **3** in 75% yield. Compound **3** was converted to the mesylated derivative in pyridine at +4°C and the same pyridine solution was heated at 60°C for 0.5h to produce the desired vinylsulphone derivative **4** in 71% overall yield. It should be noted that prolonged heating of the pyridine solution of the mesylated derivative of compound **3** would result in the formation of compound **4** in reduced yield. Compound **4** could be detritylated, if necessary, to the free hydroxy derivative **5** in 85% yield by heating it in 80% aqueous acetic acid solution.

Reactions of 3'-Deoxy-3'-(vinylsulphonyl)thymidine with nucleophiles:

It was shown that the 4'' amino group of the 3'-spiro moiety of the modified nucleoside TSAO[8], a HIV-1 specific inhibtor interacted[9] with the carboxylic group of Glu-138 of HIV-1 reverse transcriptase. It is interesting to note that unlike in case of AZT, the amino group of TSAO, which is not directly linked to the C-3' centre, interacts[9] with the enzyme through a spacer - in this case the spiro functionality. The unusual spiro group, namely, spiro-5''-(4''-amino-1'', 2''-oxathiole-2'', 2''-dioxide), incidentally carries a sulphur atom in its highest oxidised state[8]. On the basis of this observation we envisaged that the studies related to the reactivities of compounds **4** or **5** would not only prove the efficiency of interaction of the newly designed molecule with various nucleophiles but also lead to the generation of a series of new classes of modified nucleosides which themselves might act as DNA chain terminators.

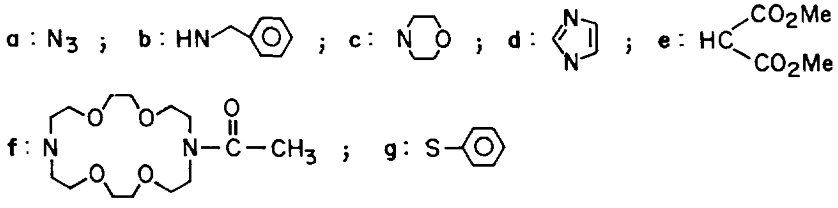


i) $HSCH_2CH_2OH$ / DBU / DMF / 60°C / 7h , 64% ; ii) MMPP / MeOH / r.t. / 6h, 75% ;
iii) Ms Cl / Py / + 4 °C / Overnight ; iv) 60 °C / 0·5 h , 71% (in two steps) ;
v) 80% HOAc / 100°C / 15m , 85%



6a : R = Tr ; X = a
7a : R = Bz ; X = a
8b : R = H ; X = b
9c : R = Tr ; X = c
10c : R = H ; X = c

11d : R = Bz ; X = d
12e : R = Tr ; X = e
13e : R = Bz ; X = e
14f : R = Tr ; X = f
15g : R = Tr ; X = g
16g : R = Bz ; X = g



Either the protected vinylsulphone **4** or the deprotected derivative **5** were reacted with various nucleophiles in Michael fashion (*see experimental*). In cases where the product of the Michael addition reactions were expected to be stable towards acidic detritylation conditions, compound **4** was used as the substrate. Nucleophiles, such as, hydrazoic acid[12], morpholine, sodium salt of dimethylmalonate, 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane and thiophenol reacted smoothly with compound **4** to furnish compounds **6a**, **9c**, **12e**, **14f** and **15g** respectively in excellent to moderate yields. Similarly compound **5** reacted with benzylamine and imidazole in protic solvent at ambient temperature to produce compounds **8b** and **11d** (after benzoylation in case of **11d**) respectively in high yields. The latter reactions with the deprotected compound **5** were performed to establish the point that the functional group that we have devised is indeed reactive enough in hydroxylic solvent at ambient temperature. Except for the benzylamino and morpholino derivatives **8b** and **10c** respectively, all other compounds were isolated and characterised as their 5'-O-benzoyl derivatives. The diaza crown ether product **14f** was, however, characterised as 5'-O-trityl-N-acetyl derivative. Compounds **6a**, **9c**, **12e** and **15g** were deprotected using 80% acetic acid at elevated temperature or using ion-exchange resins (IR 120H+). The deprotected products of **6a**, **12e** and **15g** were converted to the benzoyl derivatives **7a**, **13e** and **16g** respectively in high yields; compound **10c**, the deprotected derivative of **9c** was isolated as the 5'-free hydroxy compound.

The structures of all new compounds were assigned unambiguously by spectroscopic means. ^{1}H-NMR of all compounds are consistent with the structures assigned. The proton signals of compounds **3**, **4** and **11d** were assigned on the basis of COSY analysis. The additional unambiguous proof for the structures of new compounds were provided by exact mass measurement experiments.

In conclusion, we have synthesised a reactive triatomic analogue of AZT, 3'-deoxy-3'-(vinylsulphonyl)thymidine **5** (and **4**) from easily accessible starting material. We have also established that these vinyl-sulphone nucleosides do indeed react very efficiently with a variety of nucleophiles; these experiments established further that compounds **4** or **5** may also be used to generate new classes of modified nucleosides where the functional groups are attached to the C-3' of a nucleoside through flexible ethyl sulphone spacer[13].

EXPERIMENTAL

Melting points were uncorrected. Thymidine was purchased from Pharma Waldhof GmbH, Germany and used as received. Thin Layer Chromatography was performed on Merk precoated 60 F_{254} plates. Compounds were visualised on TLC plate under UV light. Column chromatographic separations were done using silica gel (Silica gel 60, 230-400 mesh, E. Merck) or basic alumina (Brockmann Grade I for Chromatography, S.D. Fine Chem. Ltd., India). ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) spectra were recorded on Bruker ACF200 NMR spectrometer (δ scale) using TMS or solvent chloroform-d as internal standards. All mass spectrometric experiments were carried out on a VG Analytical 70-250-SE normal geometry double focussing mass spectrometer. Accurate mass measurements were carried out at 10 000 resolution using mixtures of polyethylene glycols as mass calibrants.

3'-Deoxy-3'-S-(2-hydroxyethylthio)-5'-O-tritylthymidine 2: A mixture of marcaptoethanol (30mmol) and DBU (12.5mmol) in DMF (20ml) was heated at 60°C for 10m. Compound **1** (5mmol) was then added at a time. The mixture was heated at 60°C for 7h. The reaction mixture was cooled and poured into saturated aqueous sodium bicarbonate solution. The white residue was filtered and was washed with water.

The residue was then dissolved in ethyl acetate and the solution was dried over sodium sulphate. The solution was filtered and the filtrate was evaporated to dryness under reduced pressure. The solid material thus obtained was purified by chromatography on a silica gel column. Yield: 64%; m.p. 56-8°C; ^{1}H-NMR ($CDCl_3$): δ 7.76 (d, 1.1 Hz, 1H) H-6; 7.45-7.24 (m, 15H) trityl; 6.14 (dd, 1H) H-1'; 3.96 (m, 1H) H-4'; 3.66 (m, 4H) CH_2O, H-5'or H-5'' and H-3'; 3.36 (m, 1H) H-5'or H-5''; 2.54 (m, 4H) H-2', H-2'', CH_2S; 1.46 (d, 3H) CH_3. ^{13}C-NMR ($CDCl_3$): δ 164.4, C-4; 150.7, C-2; 143.4, trityl; 135.8, C-6; 128.8, 128.2, 127.6, trityl; 110.9, C-5; 87.4, trityl; 85.8/85.1, C-1'/C-4'; 62.4/61.5, CH_2O/C-5'; 41.0, CH_2S/C-3'; 34.6, C-2'; 12.1, CH_3. MS (FAB^+): $(M+H)^+$ calc. for $C_{31}H_{32}N_2O_5S$: 545.2112, found 545.2198.

3'-Deoxy-3'-S-(2-hydroxyethylsulphonyl)-5'-O-tritylthymidine 3: To a solution of compound **2** (6.6mmol) in methanol (100ml) was added MMPP (80%, 21mmol). The mixture was stirred at room temperature for 6h (the reaction was complete within 0.5h as was evident from tlc; however, it was nesessary to continue the stirring for the precpitation of the reagents to occur). The mixture was filtered and the residue was washed with methanol. The methanol solution was evaporated to dryness. The oily material thus obtained was dissolved in ethyl acetate, and the organic layer was washed with saturated aqueous sodium bicarbonate solution (2x50ml) followed by water (2x50ml). The ethyl acetate solution was dried over sodium sulphate. The solution was filtered and the filtrate was evaporated to dryness under reduced pressure. The solid material thus obtained was purified by chromatography on a silica gel column. Yield: 75%; m.p. 110-1°C; ^{1}H-NMR ($CDCl_3$): δ 7.59 (d, 1.0 Hz, 1H) H-6; 7.45-7.24 (m, 15H) trityl; 6.23 (t, 1H) H-1'; 4.66 (m, 1H) H-4'; 4.23 (m, 1H) H-3'; 4.05 (t, 2H) CH_2O; 3.70 (dd, 1H) and 3.45 (dd, 1H) H-5' and H-5''; 3.10 (m, 3H) CH_2SO_2, H-2' or H-2''; 2.58 (m, 1H) H-2' or H-2''; 1.47 (d, 3H) CH_3. ^{13}C-NMR ($CDCl_3$): δ 164.5, C-4; 150.7, C-2; 143.3, trityl; 135.9, C-6; 128.8, 128.2, 127.7, trityl; 111.5, C-5; 87.7, trityl; 85.5, C-1'; 77.2, C-4'; 64.3, C-5'; 62.1, C-3'; 56.3, CH_2O; 55.0, CH_2SO_2; 34.1, C-2'; 11.9, CH_3. MS (FAB^+): $(M+H)^+$ calc. for $C_{31}H_{32}N_2O_7S$: 577.2010, found 577.1987.

3'-Deoxy-3'-S-(1-vinylsulphonyl)-5'-O-tritylthymidine 4: A solution of methanesulphonyl chloride (16mmol) in pyridine (10ml) was added dropwise to an ice-cold solution of compound **3** (5.2mmol) in pyridine (25ml). The mixture was left overnight at +4°C. The mixture was then heated at 60°C for 0.5h. The reaction mixture was then cooled and carefully added to saturated aqueous sodium bicarbonate solution. The bicarbonate mixture was extracted with ethyl acetate (3x25ml). The organic layer was separated and was evaporated to dryness under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column. Yield: 71%; m.p. 102-4°C ; ^{1}H-NMR ($CDCl_3$): δ 7.60 (d, 1.2 Hz, 1H) H-6; 7.43-7.27 (m, 15H) trityl; 6.45 (m, 2H) $=CH_2$; 6.26 (t, 1H) H-1'; 6.13 (t, 1H) $CHSO_2$; 4.56 (m, 1H) H-4'; 3.90 (m, 1H) H-3'; 3.73 (dd, 1H) and 3.37 (dd, 1H) H-5' and H-5''; 2.90 (m, 1H) and 2.50 (m, 1H) H-2' and H-2''; 1.51 (s, 3H) CH_3. ^{13}C-NMR ($CDCl_3$): δ 164.1, C-4; 150.4, C-2; 143.2, trityl; 135.3/134.4, C-6/$CHSO_2$; 132.9, $=CH_2$; 128.8, 128.2, 127.7, trityl; 111.7, C-5; 87.7, trityl; 85.1, C-1'; 78.3, C-4'; 63.8, C-5'; 61.5, C-3'; 33.6, C-2'; 12.0, CH_3. MS (FAB^+): $(M+H)^+$ calc. for $C_{31}H_{30}N_2O_6S$: 559.1904, found 559.1943.

3'-Deoxy-3'-S-(1-vinylsulphonyl)-thymidine 5: A mixture of compound **4** (3mmol) and aqueous acetic acid (80%, 20ml) was heated at 100°C for 15m. Acetic acid was removed under reduced pressure. The residual acetic acid and water were coevaporated with ethanol (2x15ml) and toluene (20ml). The residue was triturated with ether, filtered and the residue was purified by chromatography on a silica gel column. Yield: 85%; m.p. 205-6°C; ^{1}H-NMR ($CDCl_3$+DMSO-d_6): δ 7.68 (s, 1H) H-6; 6.97 (q, 1H) $CHSO_2$; 6.33 (t, 2H) $=CH_2$; 6.12 (t, 1H) H-1'; 4.35 (m, 1H) H-4'; 3.98 (m, 1H) H-3'; 3.78 (m, 1H) and 3.57 (m, 1H) H-5' and H-5''; 2.60 (m, 1H) and 2.29 (m, 1H) H-2' and H-2''; 1.77 (s, 3H) CH_3. ^{13}C-NMR ($CDCl_3$): δ ($CDCl_3$+DMSO-d_6) 164.2, C-4; 150.7, C-2; 136.1/135.3, C-6/$CHSO_2$; 132.3, $=CH_2$; 110.3, C-5; 84.5, C-1'; 78.9, C-4'; 62.6, C-5'; 61.2, C-3'; 32.7, C-2'; 12.6, CH_3. MS (FAB^+): $(M+H)^+$ calc. for $C_{12}H_{16}N_2O_6S$: 317.0808, found 317.0827.

3'-Deoxy-3'-S-(2-azidoethylsulphonyl)-5'-O-tritylthymidine 6a: To a suspension of sodium azide (0.9g) in methanol (20ml), a solution of conc. sulphuric acid (0.3mg) in methanol (5ml) was added dropwise at 0°C. After 10m. at the same temperature, the turbid solution was added to a methanolic (10ml) solution of compound **4** (0.62mmol). The mixture was stirred overnight at ambient temperature. Methanol was removed and the residue was dissolved in ethyl acetate and the organic layer was washed with saturated aqueous sodium bicarbonate solution followed by water. The ethyl acetate solution was dried over sodium sulphate. The solution was filtered and the filtrate was evaporated to dryness under reduced pressure. The solid material thus obtained was purified by chromatography on a silica gel column. Yield: 83%; m.p. 92-3°C; IR: 2090cm^{-1}; ^1H-NMR ($CDCl_3$): δ 7.59 (d, 1.0 Hz, 1H) H-6; 7.45-7.25 (m, 15H) trityl; 6.27 (t, 1H) H-1'; 4.64 (m, 1H) H-4'; 4.17 (m, 1H) H-3'; 3.77 (m, 3H) CH_2N_3 and H-5' or H-5''; 3.42 (m, 1H) H-5' or H-5''; 3.07 (m, 3H) CH_2SO_2 and H-2' or H-2''; 2.53 (m, 1H) H-2' or H-2''; 1.49 (s, 3H) CH_3. ^{13}C-NMR ($CDCl_3$): δ 164.2, C-4; 150.5, C-2; 143.2, trityl; 135.5, C-6; 128.7, 128.2, 127.7, trityl; 111.6, C-5; 87.7, trityl; 85.3, C-1'; 77.5, C-4'; 64.2, C-5'; 62.0, C-3'; 51.4, CH_2SO_2; 44.8, CH_2N_3; 33.8, C-2'; 12.0, CH_3. MS (FAB^+): $(M+H)^+$ calc. for $C_{31}H_{31}N_5O_6S$: 602.2074, found 602.2055.

3'-Deoxy-3'-S-(2-azidoethylsulphonyl)-5'-O-benzoylthymidine 7a: A solution of compound **6a** (0.5mmol) in aqueous acetic acid (80%, 15ml) was heated at 100°C. After 0.5h, acetic acid was removed under reduced pressure. Residual acetic acid was coevaporated with ethanol followed by toluene. The white residue, thus obtained was triturated with ether and filtered to remove tritanol. The residue was dissolved in pyridine (10ml) and benzoyl chloride (2mmol) in pyridine (5ml) was added dropwise at 0°C. The reaction mixture was stirred at the same temperature for 2h. Saturated aqueous sodium bicarbonate solution was added to the reaction mixture and the mixture was evaporated to dryness. The residue was dissolved in ethyl acetate and the solution was washed thoroughly with saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried over sodium sulphate and filtered. The filtrate was evaporated to dryness under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column. Yield: 73%; m.p. 69-71°C; IR: 2090cm^{-1}; ^1H-NMR ($CDCl_3$): δ 8.04-7.19 (m, 6H) H-6 and phenyl; 6.06 (t, 1H) H-1'; 4.87 (m, 2H) and 4.64 (m, 1H) H-4', H-5' and H-5''; 4.23 (m, 1H) H-3'; 3.90 (m, 3H) CH_2N_3; 3.31 (m, 2H) CH_2SO_2; 3.02 (m, 1H) and 2.57 (m, 1H) H-2' and H-2''; 1.69 (s, 3H) CH_3. ^{13}C-NMR ($CDCl_3$): δ 166.2, benzoyl CO; 164.2, C-4; 150.6, C-2; 135.7, C-6; 133.8, 129.7, 129.3, 128.8 phenyl; 111.4, C-5; 86.7, C-1'; 76.3, C-4'; 65.1, C-5'; 62.1, C-3'; 51.7, CH_2SO_2; 44.7, CH_2N_3; 33.6, C-2'; 12.3, CH_3. MS (FAB^+): $(M+H)^+$ calc. for $C_{19}H_{21}N_5O_7S$: 464.1241, found 464.1281.

3'-Deoxy-3'-S-(2-N-benzylaminoethylsulphonyl)-thymidine 8b: A mixture of compound **5** (0.5mmol) and benzylamine (2.5mmol) in methanol (10ml) was stirred at ambient temperature for 0.5h. After removing methanol under reduced pressure, excess benzylamine was removed by trituration with ether. The residue was purified by chromatography on a basic alumina column. Yield: 71%; m.p. 132-4°C. ^1H-NMR ($CDCl_3$+DMSO-d_6): δ 7.71 (s, 1H) H-6; 7.26 (m, 5H) phenyl; 6.18 (t, 1H) H-1'; 4.50 (m, 1H) H-4'; 4.25 (m, 1H) H-3'; 3.82 (m, 4H) H-5', H-5''and benzyl CH_2; 3.27 (m, 2H) CH_2N; 3.10 (m, 2H) CH_2SO_2; 2.76 (m, 1H) and 2.40 (m, 1H) H-2' and H-2''; 1.86 (s, 3H) CH_3. ^{13}C-NMR ($CDCl_3$+DMSO-d_6): δ 163.5, C-4; 149.8, C-2; 138.1, phenyl; 135.3, C-6; 127.6, 127.4, 126.4, phenyl; 109.7, C-5; 84.1, C-1'; 77.9, C-4'; 61.6, C-5'; 59.9, C-3'; 52.2, SO_2CH_2; 50.9, benzyl CH_2; 40.8, CH_2N; 32.4, C-2'; 11.6, CH_3. MS (FAB^+): $(M+H)^+$ calc. for

$C_{19}H_{25}N_3O_6S$: 424.1543, found 424.1601.

3’-Deoxy-3’-S-(2-N-morpholinoethylsulphonyl)-5’-O-tritylthymidine 9c: A mixture of compound **4** (1mmol) and morpholine (5mmol) in dichloromethane (20ml) was stirred at ambient temperature for 10m. After removing dichloromethane under reduced pressure the oily residue was dissolved in ethylacetate and washed with water. The organic layer was separated, dried over sodium sulphate and filtered. The filtrate was evaporated to dryness under reduced pressure. The residue thus obtained was purified by chromatography on a basic alumina column. Yield: 85%; m.p. 98-9°C. ^{1}H-NMR ($CDCl_3$): δ 7.65 (d, 1H) H-6; 7.41-7.22 (m, 15H) trityl; 6.27 (t, 1H) H-1’; 4.74 (m, 1H) H-4’; 4.25 (m, 1H) H-3’; 3.77 (m, 1H) and 3.45 (m, 1H) H-5’and H-5’’; 3.60 (t, 4H) CH_2OCH_2; 3.29 (m, 1H) and 2.95 (m, 3H) $SO_2CH_2CH_2N$; 2.77 (m, 1H) H-2’or H-2’’; 2.45 (m, 5H) H-2’or H-2’’and CH_2NCH_2; 1.50 (s, 3H) CH_3. ^{13}C-NMR ($CDCl_3$): δ 164.4, C-4; 150.5, C-2; 143.4, trityl; 135.5, C-6; 128.7, 128.3, 127.8, trityl; 111.5, C-5; 87.7, trityl; 85.3, C-1’; 76.9, C-4’; 66.7, CH_2OCH_2; 64.6, C-5’; 61.8, C-3’; 53.6, CH_2NCH_2; 51.8, CH_2SO_2; 49.3, CH_2N; 34.3, C-2’; 12.1, CH_3. MS (FAB$^+$): $(M+H)^+$ calc. for $C_{35}H_{39}N_3O_7S$: 646.2589, found 646.2640.

3’-Deoxy-3’-S-(2-N-morpholinoethylsulphonyl)thymidine 10c: Compound **9c** (0.39mmol) was dissolved in a mixture of water and methanol (8ml+2ml) and was applied on an ion-exchange column (IR 120H$^+$, 15ml settled volume). The column was first eluted with methanol to remove tritanol followed by 3% aqueous ammonia solution. The fractions containing the title compound were pooled together and evaporated to dryness. Yield: 74%; hygroscopic; ^{1}H-NMR (D_2O): δ 7.67 (s, 1H) H-6; 6.17 (t, 1H) H-1’; 4.61 (m, 1H) H-4’; 4.26 (m, 1H) H-3’; 3.90 (m, 2H) H-5’and H-5’’; 3.73 (m, 4H) CH_2OCH_2; 3.52 (m, 2H) CH_2N; 3.16 (m, 1H) H-2’or H-2’’; 2.91 (m, 3H) CH_2SO_2, H-2’or H-2’’; 2.60 (m, 4H) CH_2NCH_2; 1.86 (s, 3H) CH_3. ^{13}C-NMR (D_2O): δ 167.1, C-4; 152.2, C-2; 138.1, C-6; 112.2, C-5; 86.3, C-1’; 79.1, C-4’; 67.0, CH_2OCH_2; 62.9, C-5’; 61.5, C-3’; 53.1, CH_2NCH_2; 50.3, CH_2SO_2; 49.1, CH_2N; 33.1, C-2’; 12.4, CH_3.

3’-Deoxy-3’-S-(2-N-imidazolylethylsulphonyl)-5’-O-benzoylthymidine 11d: A mixture of compound **5** (0.5mmol) and imidazole (5mmol) in methanol (10ml) was stirred at ambient temperature. After 20h methanol was removed under reduced pressure and the product mixture was triturated with ether to remove excess imidazole. The residue was dissolved in pyridine (10ml) and benzoyl chloride (2mmol) in pyridine (5ml) was added dropwise at 0°C. The reaction mixture was stirred at the same temperature for 2.5h. Saturated aqueous sodium bicarbonate solution was added to the reaction mixture and the mixture was partitioned with ethyl acetate. The organic layer was separated and evaporated to dryness under reduced pressure. The brown residue was purified by chromatography on a silica gel column. Yield: 65%; m.p. 104-7°C. ^{1}H-NMR ($CDCl_3$): δ 8.01-6.99 (m, 9H) H-6, phenyl and imidazole; 5.98 (t, 1H) H-1’; 4.62 (m, 5H) H-4’, H-5’, H-5’’and CH_2N; 3.60 (m, 3H) H-3’ and CH_2SO_2; 2.88 (m, 1H) and 2.39 (m, 1H) H-2’ and H-2’’; 1.63 (s, 3H) CH_3. ^{13}C-NMR ($CDCl_3$+DMSO-d_6): δ 165.7, benzoyl CO; 163.9, C-4; 150.3, C-2; 137.4, C-6; 135.0, 133.4, 129.3, 128.9, 128.4, 119.1, phenyl and imidazole; 110.9, C-5; 85.6, C-1’; 75.4, C-4’; 64.8, C-5’; 61.4, C-3’; 52.5, CH_2SO_2; 40.1 CH_2N; 32.9 C-2’; 11.9, CH_3. MS (FAB$^+$): $(M+H)^+$ calc. for $C_{22}H_{24}N_4O_7S$: 489.1445, found 489.1475.

3’-Deoxy-3’-S-(2-dimethylmalonateylethylsulphonyl)-5’-O-tritylthymidine 12e: Dimethyl malonate (12mmol) was added dropwise to a stirred suspension of sodium hydride (5mmol) in THF (15ml) at 0°C. After the addition the reaction mixture was allowed to warm up to ambient temperature and the mixture was stirred for 0.5h. A solution of compound **4** (0.57mmol) in THF (10ml) was added dropwise and the mixture was stirred at the ambient temperature for 20h. THF was removed under reduced pressure. The oily material was dissolved in ethyl acetate and the ethyl acetate layer was washed thoroughly with saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried over sodium sulphate and filtered. The filtrate was evaporated to dryness under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column. Yield: 66%; m.p. 79-80°C. ^{1}H-NMR ($CDCl_3$): δ 7.59 (d, 1.2 Hz, 1H) H-6; 7.44-7.24 (m, 15H) trityl; 6.25 (t, 1H) H-1’; 4.62 (m, 1H) H-4’; 3.96 (m, 1H) H-3’; 3.76 (s, 3H) and 3.74 (s, 3H) 2xOCH_3; 3.75 (m, 1H), 3.60 (m, 2H) and 3.40 (m, 1H) H-5’, H-5’’ and malonate CH; 3.07 (t, 2H) CH_2SO_2; 2.98 (m, 1H) and 2.55 (m, 1H) H-2’ and H-2’’; 2.35 (m, 2H) CH_2CH; 1.56 (s, 3H) CH_3. ^{13}C-NMR ($CDCl_3$): δ 168.7, 2xmalonate CO; 164.2, C-4; 150.4, C-2; 143.3, trityl; 135.5, C-6; 128.7, 128.2, 127.7, trityl; 111.5, C-5; 87.7, trityl; 85.4, C-1’; 77.6, C-4’; 64.1, C-5’; 60.2, C-3’; 53.1, 2xOCH_3; 49.4, CH_2SO_2 and malonate CH; 33.8, C-2’; 21.1, CH_2CH; 12.1, CH_3. MS (FAB$^+$): (M+H)$^+$ calc. for $C_{36}H_{38}N_2O_{10}S$: 691.2327, found 691.2295.

3’-Deoxy-3’-S-(2-dimethylmalonateylethylsulphonyl)-5’-O-benzoylthymidine 13e: A solution of compound **12e** (0.3mmol) in aqueous acetic acid (80%, 10ml) was heated at 65°C. After 2h, acetic acid was removed under reduced pressure. Residual acetic acid was coevaporated with ethanol. The white residue, thus obtained was triturated with ether and filtered to remove tritanol. The residue was dissolved in pyridine (10ml) and a solution of benzoyl chloride (1.2mmol) in pyridine (5ml) was added dropwise at 0°C. The reaction mixture was stirred at the same temperature for 2h. Saturated aqueous sodium bicarbonate solution was added to the reaction mixture and the mixture was partitioned with ethyl acetate. The organic layer were pooled together and evaporated to dryness. Residual pyridine was coevaporated with toluene. The solid residue thus obtained was purified by chromatography on a silica gel column. Yield: 82%, m.p. 71-3°C. ^{1}H-NMR ($CDCl_3$): δ 8.05-7.18 (m, 6H) H-6 and phenyl; 6.06 (t, 1H) H-1’; 4.85 (m, 2H) and 4.61 (m, 1H) H-4’, H-5’ and H-5”; 4.10 (m, 1H) H-3’; 3.76 (s, 3H) and 3.75 (s, 3H) 2xOCH_3; 3.64 (t, 1H) malonate CH; 3.25 (m, 2H) CH_2SO_2; 2.98 (m, 1H) and 2.59 (m, 1H) H-2’ and H-2’’; 2.44 (m, 2H) CH_2CH; 1.68 (s, 3H) CH_3. ^{13}C-NMR ($CDCl_3$): δ 168.8, malonate CO; 166.1, benzoyl CO; 164.2, C-4; 150.4, C-2; 135.9, C-6; 133.7, 129.7, 129.4, 128.7 phenyl; 111.3, C-5; 86.9, C-1’; 76.5, C-4’; 65.1, C-5’; 60.4, C-3’; 53.0, 2xOCH_3; 49.7, CH_2SO_2; 49.4, malonate CH; 33.6, C-2’; 21.1, CH_2CH; 12.1, CH_3. MS (FAB$^+$): (M+H)$^+$ calc. for $C_{24}H_{27}N_2O_{11}S$: 553.1493, found 553.1499.

3’-Deoxy-3’-S-(2-N-N’-acetyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecanylethylsulphonyl)-5’-O-tritylthymidine 14f: A solution of compound **4** (0.5mmol) and 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (2mmol) in dichloromethane (15ml) was stirred at room temperature. After 2days, dichloromethane was removed under reduced pressure and the solid residue was purified on a silica gel column to remove excess crown ether. The product was dissolved in pyridine (15ml) and acetic anhydride (2mmol) was added dropwise. The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was poured into saturated aqueous sodium bicarbonate solution and the mixture was partitioned with ethylacetate (3x20ml). The organic layers were pooled together and evaporated to dryness under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column. Yield: 35%; m.p. 78-80°C. ^{1}H-NMR ($CDCl_3$): δ 7.59 (d, 1H) H-6; 7.43-7.29 (m, 15H) trityl; 6.27 (t, 1H) H-1’; 4.69 (m, 1H) H-4’; 4.06 (m, 1H) H-3’; 3.75-2.40 (m, 32H) crown ether, $SO_2CH_2CH_2N$, H-5’, H-5’’, H-2’, H-2’’; 2.09 (s, 3H) acetyl CH_3; 1.47 (s, 3H) CH_3. ^{13}C-NMR ($CDCl_3$+DMSO-d_6): δ 170.6 acetyl CO; 163.9, C-4; 150.2, C-2; 143.0, trityl; 134.9, C-6; 128.4, 127.8, 127.3, trityl; 111.0, C-5; 87.2, trityl; 84.9, C-1’; 76.6, C-4’; 70.6, 70.2, 69.6, 69.4, crown ether CH_2; 64.4, C-5’; 61.3, C-3’; 53.7, 49.9, 49.5, 47.8, 46.6 crown ether CH_2 and $SO_2CH_2CH_2N$; 33.5, C-2’; 21.3, acetyl CH_3; 11.7, CH_3. MS (FAB$^+$): (M+H)$^+$ calc. for $C_{45}H_{58}N_4O_{11}S$: 863.3903, found 863.3947.

3’-Deoxy-3’-S-(2-S-thiophenylethylsulphonyl)-5’-O-tritylthymidine 15g: To a stirred solution of thiophenol (2.5mmol) and tetramethylguanidine (2mmol) in dichloromethane (10ml) compound **4** (0.5mmol) was added. After 0.5h at ambient temperature, the mixture was poured into water. The organic material from the aqueous mixture was extracted with dichloromethane. The dichloromethane solution was dried over sodium sulphate. The solution was filtered and the filtrate was evaporated to dryness under reduced pressure. The solid material thus obtained was purified by chromatography on a silica gel column. Yield: 82%; m.p. 95-6°C. ^{1}H-NMR ($CDCl_3$): δ 7.58 (d, 1.0 Hz, 1H) H-6; 7.44-7.22 (m, 20H) trityl and phenyl; 6.22 (t, 1H) H-1'; 4.60 (m, 1H) H-4'; 3.96 (m, 1H) H-3'; 3.74 (m, 1H) H-5' 3.40-3.07 and 3.11 (m, 5H) H-5' or H-5'' and $SCH_2CH_2SO_2$; 2.86 (m, 1H) and 2.38 (m, 1H) H-2' and H-2''; 1.55 (s, 3H) CH_3. ^{13}C-NMR ($CDCl_3$): δ 164.1, C-4; 150.4, C-2; 143.3, trityl; 135.5, C-6; 133.5, 130.5, 129.6, 128.7, 128.3, 127.7, 127.6, trityl and phenyl; 111.6, C-5; 87.8, trityl; 85.5, C-1'; 77.7, C-4'; 64.1, C-5'; 61.0, C-3'; 51.9, CH_2SO_2; 33.9, C-2'; 25.9, CH_2S; 12.1, CH_3. MS (FAB^+): $(M+H)^+$ calc. for $C_{37}H_{36}N_2O_6S_2$: 669.2095, found 669.2129.

3'-Deoxy-3'-S-(2-S-thiophenylethylsulphonyl)-5'-O-benzoylthymidine 16g: A solution of compound **15g** (0.4mmol) in aqueous acetic acid (80%, 15ml) was heated at 100°C. After 15m, acetic acid was removed under reduced pressure. Residual acetic acid was coevaporated with ethanol. The white residue, thus obtained was triturated with ether and filtered to remove tritanol. The residue was dissolved in pyridine (15ml) and benzoyl chloride (1.6mmol) was added dropwise at 0°C. The reaction mixture was stirred at the same temperature for 2h. Saturated aqueous sodium bicarbonate solution was added to the reaction mixture and the mixture was evaporated to dryness. The residue was dissolved in ethyl acetate and the solution was washed thoroughly with saturated aqueous sodium bicarbonate solution. The organic layer was separeted, dried over sodium sulphate and filtered. The filtrate was evaporated to dryness under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column. Yield: 82%; m.p. 73-5°C. ^{1}H-NMR ($CDCl_3$): δ 8.03 and 7.66-7.15 (m, 11H) H-6 and 2xphenyl; 6.02 (t, 1H) H-1'; 4.83 (m, 2H) and 4.58 (m, 1H) H-4', H-5' and H-5''; 4.10 (m, 1H) H-3'; 3.32 (m, 4H) $SO_2CH_2CH_2S$; 2.91 (m, 1H) and 2.49 (m, 1H) H-2' and H-2''; 1.69 (s, 3H) CH_3. ^{13}C-NMR ($CDCl_3$): δ 166.1, benzoyl CO; 164.2, C-4; 150.4, C-2; 135.9, C-6; 133.7, 133.5, 130.4, 129.7, 129.5, 129.3, 128.8, 127.5, 2xphenyl; 111.2, C-5; 87.1, C-1'; 76.6, C-4'; 65.1, C-5'; 61.1, C-3'; 52.3, CH_2SO_2; 33.8, C-2'; 25.8, CH_2S; 12.3, CH_3. MS (FAB^+): $(M+H)^+$ calc. for $C_{25}H_{26}N_2O_7S_2$: 531.1261, found 531.1298.

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