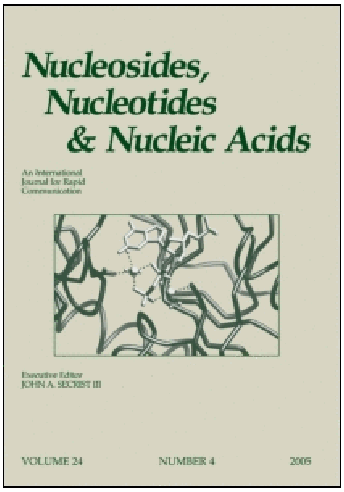

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Synthesis of Extended Carbamate and Urea Linked Thymidine Dimers

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SYNTHESIS OF EXTENDED CARBAMATE AND UREA LINKED THYMIDINE DIMERS[1]

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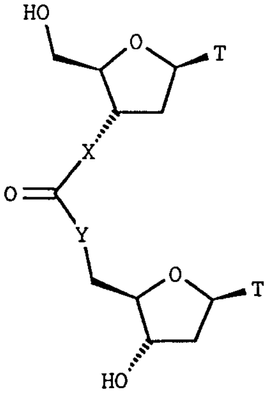
Abstract: Thymidine dimers with extended carbamate and urea linkages were synthesized. The length of the linker is expected to increase flexibility and improve duplex formation after incorporation into oligomer.

INTRODUCTION

The use of modified oligodeoxynucleotides for modulation of gene expression and viral replication has gained increasing attention in the past few years[2-4]. The use of unmodified oligomers is limited due to their instability towards exo and endo nucleases and their inability to penetrate through the cell membrane. Oligomers with modified internucleoside linkages are designed to circumvent the stability and cellular uptake problems. Several reviews of the subject have appeared recently[4-6].



1 X= O, Y= NH

2 X= NH, Y= NH

3 X= O, Y= $NH(CH_2)_2NH$

4 X= NH, Y= $NH(CH_2)_2NH$

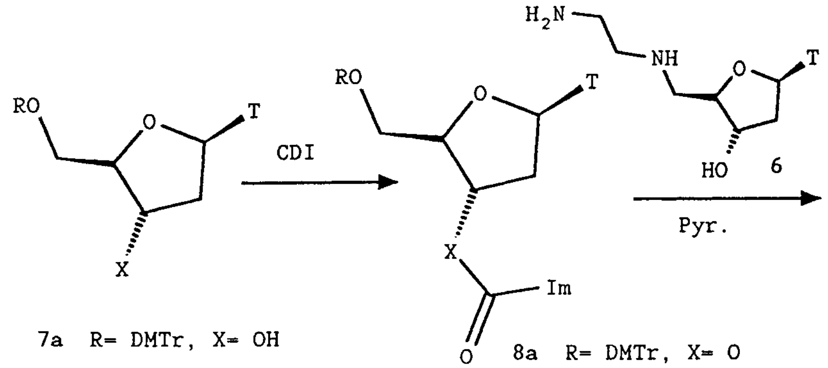
5 X= $O(CH_2)_2NH$, Y=NH

Several modifications in which a carbonyl group replaces the phosphoryl group have been introduced. Carbamate analogs (**1**)[7a,b] have been shown to be stable towards enzymatic degradation but display poor binding. The simple carbamate linkage is calculated[8] to be shorter than a phosphodiester linkage by 0.032 nm, possibly resulting in restricted rotation of the linkage compared to the phosphodiester linkage. Recently Just et al.[9] and De Mesmaeker et al.[10] independently reported the synthesis of simple urea linked thymidine dimers (**2**) and their incorporation into antisense sequences. Similar poor binding behaviour was observed.

We report here the synthesis of thymidine dimers (**3** - **5**) with extended carbamate and urea linkages. An increase in the length of the linkage should give more conformational freedom for binding to complimentary base sequences. Dimer **5** contains a neutral backbone whereas dimers **3** and **4** contain a weakly basic secondary amino group. There are several reports in the literature[11,12] showing that oligomers with cationic groups in the backbone form duplexes with their complimentary oligonucleotides which exhibit unusually high melting temperatures (Tms). Higher Tms were also observed in peptide nucleic acid (PNA) analogs[13,14] containing lysine. Therefore, we anticipate that the presence of a secondary amino group in the linkage, which may carry a positive charge under physiological conditions, should not only enhance cellular uptake but may also improve hybridization to negatively charged oligonucleotides.

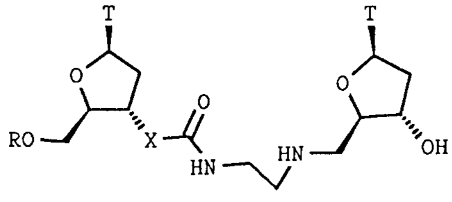
CHEMISTRY

Synthesis of dimer 1 requires the 3' modified synthon **8a** and the 5' modified synthon **6**, both of which have been reported recently[7c,15]. Imidazolide **8a** was dissolved in dry pyridine, amine **6** was added, and the solution was stirred at room temperature for 36 hours. After evaporation



7a R= DMTr, X= OH
7b R= anisoyl, X= N_3
7c R= anisoyl, X= NH_2

8a R= DMTr, X= O
8b R= anisoyl, X= NH



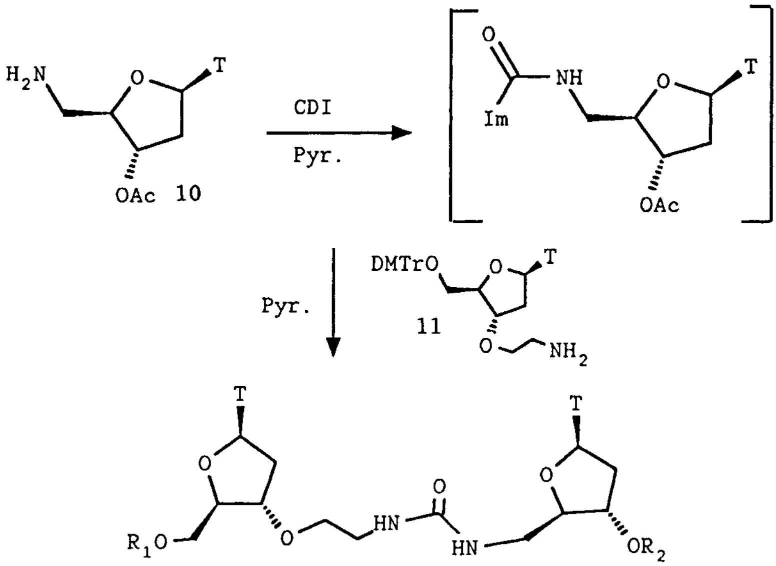
9a R= DMTr, X= O
3 R= H, X= O

9b R= anisoyl, X= NH
4 R= H, X= NH

of the solvent, the resulting residue was purified by column chromatography, and compound **9a** was isolated in 42% yield. The dimethoxytrityl group was removed by treatment with 80% aqueous acetic acid at room temperature. Purification by column chromatography gave the deprotected dimer **3** in 70% yield. The proton nmr spectrum of **3** showed a triplet at 7.33 ppm (1H) for the carbamate NH and overlapping broad peaks between 5.20 and 5.23 ppm (2H) corresponding to 5'OH and 3'OH. A peak at 163.2 ppm corresponding to the carbamate carbon was observed in the ^{13}C spectrum.

The synthesis of dimer **4** requires a different 3' modified building block **8b**, which should be prepared from a 5'-protected 3'-amino-3'-deoxythymidine **(7c)**. Preparation of this latter compound was accomplished using a variation on a published sequence of reactions[16]. Thymidine was converted to 3'-anhydro-5'-O-(4-methoxybenzoyl)thymidine by a one pot reaction with p-methoxybenzoic acid, triphenylphosphine and DEAD. Ring opening with sodium azide gave 5'-O-anisoyl-3'-azidothymidine **(7b)**. Attempts to reduce the azido group by hydrogenation in ethanol resulted in poor yields due to the poor solubility of **7b** in ethanol. Therefore the reaction was carried out in ethyl acetate, over a 10% palladium on carbon catalyst at room temperature, and the amine **(7c)** was obtained in 82% yield. Compound **7c** was dissolved in dry pyridine and 1,1'-carbonyldiimidazole was added. Excess CDI was used to avoid the possibility of the formation of a symmetrical urea. The reaction was quenched with water and the solvents were removed. The intermediate **8b** was not purified, but instead, after coevaporating several times with pyridine, compound **6** was added in dry pyridine and the solution was stirred overnight. The product **(9b)** was isolated and the 5'-O-protecting group was removed with sodium methoxide in methanol. Compound **4** was purified by column chromatography. The proton spectrum of compound **4** showed a triplet at 6.63 ppm and a doublet at 7.08 ppm for $NHCON\underline{H}CH_2$ and $N\underline{H}CONHCH_2$ respectively.

The synthesis of dimer **5** requires 3'-protected 5'-amino-5'deoxythymidine (**10**) and 5'-protected 3'-O-(β-aminoethyl)thymidine (**11**). The 3'OH group of 5'azido-5'-deoxythymidine[17] was first protected with an acetyl group to avoid any potential competition during the later coupling step. Reduction of the azido group to amine **(10)** was performed using hydrogen in ethanol over 10% palladium on carbon at room temperature. Compound **11** was synthesized by the selective alkylation[18] of the 3' hydroxyl group using chloroethylamine hydrochloride as the alkylating agent and potassium hydroxide as the base. Coupling between **10** and **11** was done in the same fashion as for dimer **9b**. Compound **10** was first treated with CDI and later coupled with compound **11**. The fully protected dimer **(12)** was first shaken with ammonium hydroxide in methanol. After evaporation of



12 R_1=DMTr, R_2=Ac
13 R_1=DMTr, R_2=H
3 R_1=R_2=H

the solvent the residue **(13)** was stirred with 80% acetic acid. Purification was done by chromatography. The proton NMR of the fully deprotected dimer **5** exhibited a triplet at 6.01 ppm (1H) for $CH_2NHCON\underline{H}CH_2$-5' and overlapping peaks between 6.10-6.19 ppm (3H) corresponding to H1' and $CH_2N\underline{H}CONHCH_2$-5' respectively. A triplet at 5.10 ppm (1H) and a doublet at 5.28 ppm (1H) were also observed for 5'OH and 3'OH respectively. The chemical shifts for the sugar protons and carbons for deprotected dimers were assigned from COSY and HETCOR spectra.

EXPERIMENTAL SECTION

NMR data was recorded on a Varian VXR-300 spectrometer and the chemical shifts are reported in parts per million downfield from TMS. Column chromatography was carried out using silica gel (200-400 mesh) 60 A° (Aldrich). Thin layer chromatography (TLC) was performed on pre-coated sheets of silica gel 250 μM layer (Whatman), and the spots were visualized using short wavelength (254nm) UV light. Pyridine was distilled from calcium hydride and stored over 3 A° molecular sieves (Aldrich). 2-Chloroethylamine hydrochloride was purchased from Fluka. Other reagents including the starting material (thymidine) were purchased from Aldrich chemical company.

5'-O-Anisoyl-3'-azido-3'-deoxythymidine (7b)

2,3'-anhydro-5'-O-anisoylthymidine (3 g, 8.35 mmoL) and sodium azide (1.12 g, 17.3 mmoL) were suspended in DMF (30 mL) and the mixture was heated in an oil bath at 110 °C for 7 hrs. The homogenous mixture was poured into water (75 mL) containing 5% aqueous hydrochloric acid (6 mL). The solution was extracted with ethyl acetate (3 x 20 mL) and the combined ethyl acetate extracts were washed with water followed by saturated brine solution. After drying with anhydrous sodium sulfate the solvent was evaporated *in vacuo* to give a foamy solid. Yield (2.70 g. 77.1%) ^{1}H NMR (DMSO-d_6)ppm: 1.63 (s, 3, CH_3), 2.39-2.51 (m, 2, H2'), 3.83 (s, 3, OCH_3), 4.12 (m, 1, H4'), 4.41-4.64 (overlapping m, 3, H3', H5'), 6.16 (t, 1, H1'), 7.03, (d, 2, ar-H), 7.94 (d, 2, ar-H), 7.41 (s, 1, H6), 11.37 (br s, 1, NH); ^{13}C NMR (DMSO-d_6)ppm: 11.8, 35.7, 55.4, 59.9, 63.3, 80.6, 83.4, 109.9, 114.0, 121.3, 131.3, 135.6, 150.2, 163.3, 163.5, 165.0.

3'-Amino-5'-O-anisoyl-3'-deoxythymidine (7c)

Azide **(7b)** (1 g, 2.78 mmol) was dissolved in ethyl acetate (150 mL), and 10% Pd/C (0.7 g) was added, and the mixture was shaken under 40 psi H_2 for 36 hrs. TLC showed no starting material. The solution was filtered through celite and the solution was concentrated to dryness, on which the amine **(7c)** was obtained as a solid. Yield 0.93 g (82.7%) m.p 128-132 °C; ^{1}H NMR (CD_3OD)ppm: 1.61 (s, 3, CH_3) , 2.27-2.36 (m, 2, H2'), 3.62 (m, 1, H4'), 3.85 (s, 3, OCH_3), 4.01 (m, 1, H3'), 3.99-4.70 (dd, 2, H5'), 6.19 (t, 1, H1'), 7.00 (d, 2, ar-H), 7.42 (s, 1, H6), 7.99 (d, 2, ar-H); ^{13}C NMR

(CD_3OD)ppm: 12.4, 41.3, 52.3, 56.1, 64.5, 86.0, 86.1, 111.4, 115.0, 123.1, 132.7, 137.3, 152.1, 165.4, 166.3, 167.5

5'-Dimethoxytritylthymidinyl-(3'-N(β)-carbamoyl)-5'-(β-aminoethyl)amino-5'-deoxythymidine (9a).

Imidazolide **8a** (2.0 g, 3.12 mmol) and amine **6** (0.98 g, 3.44 mmol) were dissolved in dry pyridine and evaporated *in vacuo* to dryness. The residue was redissolved in pyridine (10 mL) and the mixture was stirred at room temperature for 36 hrs. The solvent was removed and the resulting glass, on purification by chromatography (0-10% MeOH in CH_2Cl_2), gave compound **9a** (1.12 g, 42%). R_f 0.38 (20% MeOH in $CHCl_3$ v/v). ^1H NMR (DMSO-d_6)ppm: 1.37 (s, 3, CH_3), 1.77 (s, 3, CH_3), 1.97-2.41 (overlapping m, 4, 2 x H2'), 2.60 (m, 2, $CONHCH_2C\underline{H}_2$), 2.72 (m, 2, H5''), 3.09 (m, 2, $CONHC\underline{H}_2CH_2$), 3.17-3.22 (m, 2, H5'), 3.71-3.72 (overlapping s, m, 7, 2 x OMe, H4''), 4.02 (m, 1, H4'), 4.12 (m, 1, H3''), 5.24 (m, 1, H3'), 6.14 (m, 1, H1'), 6.21 (m, 1, H1'), 6.87-7.32 (m, 13, ar-H), 7.52 (s, 1, H6), 7.57 (s, 1, H6), 11.30 (br, 2, 2 x NH); ^{13}C NMR (DMSO-d_6)ppm: 11.5, 12.1, 36.5, 39.1, 39.4, 49.0, 51.1, 54.8, 55.0, 64.0, 71.1, 83.4, 83.5, 83.5, 85.5, 86.0, 109.5, 109.8, 113.2, 126.7, 127.6, 127.8, 129.6, 135.0, 135.2, 136.1, 144.4, 150.3, 150.4, 155.3, 158.1, 163.5, 163.6

Thymidinyl-(3'-N(β)-carbamoyl)-5'-(β-aminoethyl)amino-5'-deoxythymidine (3).

Compound **9a** (0.7 g, 0.819 mmol) was dissolved in 80% acetic acid (10 mL) and the solution was stirred at room temperature. The progress of the reaction was monitored by TLC and detritylation was complete after 3 hrs. Acetic acid was removed *in vacuo* and the residue was chromatographed, eluting with 5-20% methanol in chloroform, on which compound **3** was obtained as a glass. The product was washed with anhydrous ether (10 mL) and dried. Yield 0.32 g (71%); R_f 0.08 (20% MeOH in $CHCl_3$); ^1H NMR (DMSO-d_6)ppm: 1.78 (overlapping s, 6, 2 x CH_3), 2.12-2.19 (overlapping m, 4, 2 x H2'), 2.63 (m, 2, H5''), 2.71 (dd, 2, H5'), 3.10 (m, 2,

$CONHCH_2C\underline{H}_2$), 3.22 -3.48 (br, 1, NH), 3.62 (m, 2, $CONHC\underline{H}_2CH_2$), 3.75 (m, 1, H4''), 3.93 (m, 1, H4'), 4.25 (m, 1, H3''), 5.11 (m, 1, H3'), 5.20-5.23 (overlapping br, 2, 5'OH, 3'OH), 6.11-6.28 (overlapping t, 2, 2 x H1'), 7.33 (t, 1, NH carbamate), 7.74 (overlapping s, 2, 2 x H6), 11.3 (br, 2, 2 x NH); ^{13}C NMR (DMSO-d_6)ppm: 12.1, 12.2, 36.7, 38.6, 49.0, 50.8, 61.3, 71.1, 74.6, 83.4, 83.5, 84.8, 85.5, 109.4, 109.6, 135.7, 136.1, 150.4, 150.4, 155.4, 163.2, 163.6

N-(5'-Anisoyl-3'-deoxythymidin-3'-yl)-N'-(β-(5'-deoxythymidin-5'-yl)amino)ethylurea (9b).

Amine **7c** (0.6 g, 1.59 mmol) was dissolved in pyridine and evaporated. This process was repeated twice. It was again redissolved in pyridine (10 mL), 1,1'-carbonyldiimidazole (0.32 g, 2 mmol) was added, and the solution was stirred for 16 hours. Water (3 mL) was added, and the mixture was shaken for 5 minutes. Solvents were removed on rotary evaporator. The residue was dissolved in pyridine and evaporated. This process was again repeated three times. The residue was taken in dry pyridine (10 mL), amine **6** was added, and the solution was stirred for 30 hrs. The solvent was removed and the residue was purified on a silica gel column eluted with a gradient of 5-15% methanol in chloroform, on which compound **9b** was isolated. Yield 0.158 g (15.8%). R_f 0.21 (20% MeOH in $CHCl_3$ v/v); ^1H NMR(DMSO-d_6)ppm: 1.63 (s, 3, CH_3), 1.78 (s, 3, CH_3), 2.05-2.50 (overlapping m, 4, H2', H2''), 2.58-2.69 (m, 2, $CONHCH_2C\underline{H}_2$), 2.71-2.82 (m, 2, H5''), 3.06-3.10 (m, 2, $CONHC\underline{H}_2CH_2$), 3.75 (m, 1, H4''), 3.83 (s, 3, OCH_3), 3.98 (m, 1, H4''), 4.11-4.19 (m, 1, H3''), 4.31-4.38 (m, 1, H3'), 4.53 (m, 2, H5'), 6.01 (t, 1, $NHCON\underline{H}CH_2$-), 6.12-6.23 (overlapping m, 2, 2 x H1'), 6.55 (d, 1, $N\underline{H}CONHCH_2$-), 7.06 (d, 2, ar-H), 7.44 (s, 1, H6), 7.58 (s, 1, H6), 7.92 (d, 2, ar-H); ^{13}C NMR (DMSO-d_6)ppm: 11.8, 12.0, 37.3, 39.1, 39.4, 49.6, 51.3, 55.4 64.3, 71.2, 79.1, 82.5, 83.4, 83.5, 85.6, 109.5, 109.7, 135.7, 136.1, 114.0, 121.5, 131.2, 157.6, 150.2, 150.3, 163.2, 163.5, 163.6, 165.1

N-(3'-Deoxythymidin-3'-yl)-N'-(β-(5'-deoxythymidin-5'-yl)-amino)ethylurea (4).

The protected dimer **9b** (0.2 g, 0.29 mmol) was dissolved in methanol, sodium methoxide in methanol (4 mL) was added, and the mixture was stirred for 24 hrs. Water (10 mL) was added and the solution was concentrated to dryness. The residue was dissolved in water and neutralized with 50% aqueous acetic acid. The solution was concentrated to dryness. The residue was dissolved in the minimum amount of methanol, applied to a silica gel column, and eluted with a gradient of 10-20% methanol in chloroform. Yield 0.07 g (43.75%); R_f 0.08 (20% MeOH in $CHCL_3$ v/v); ^{1}H NMR (DMSO-d_6)ppm: 1.65 (s, 3, CH_3), 1.77 (s, 3, CH_3), 2.02-2.18 (overlapping m, 4, H2', H2''), 2.50 (m, 2, CONHCH$_2$C$\underline{H}_2$), 2.66 (m, 2, H5''), 2.97 (m, 2, CONHC$\underline{H}_2$CH$_2$), 3.22 (br, 1, H4'), 3.45-4.08 (overlapping m, 4, H5', H4', H3''), 4.12 (br, 1, H3'), 6.09-6.22 (m, 2, H1', H1''), 6.63 (t, 1, NHCONH̲CH$_2$), 7.08 (d, 1, NH̲CONHCH$_2$), 7.60 (s, 1, H6), 7.77 (s, 1, H6); ^{13}C NMR (DMSO-d_6)ppm: 12.2, 37.6, 39.1, 39.4, 49.5, 61.0, 71.8, 83.3, 85.3, 109.1, 109.6, 136.1, 150.5, 150.6, 158.1, 163.9.

3'-O-Acetyl-5'-amino-5'-deoxythymidine (10).

5'-azido-5'-deoxythymidine (0.34 g, 1.29 mmoL) was dissolved in pyridine (5 mL) and acetic anhydride (0.4 mL, 4.23 mmoL) was added and the mixture was stirred for 15 hrs. The reaction was quenched with water (1 mL) and the pyridine was evaporated. The residue was dissolved in chloroform and washed with 5% sodium bicarbonate, followed by water, and saturated brine solution. The organic layer was separated and on evaporation 3'-O-acetyl-5'-azido-5'-deoxythymidine was obtained. Yield (0.36 g, 91%) m.p. 115-117 °C. The acetyl derivative (0.36 g, 1.16 mmoL) was taken in absolute ethanol (30 mL) and 10% palladium on activated carbon (0.21 g) was added. The solution was shaken under hydrogen (40 psi) at room temperature for 12 hrs. The solution was filtered through a celite pad, the solvent was evaporated, and compound (10) was obtained as a glass. Yield (0.28 g, 85.1%); ^{1}H NMR (DMSO-d_6)ppm: 1.79 (s, 3, CH_3), 2.06 (s, 3, $COCH_3$), 2.20-2.36 (m, 2, H2'), 2.78-2.80 (m, 2, H5'), 3.83-3.87 (m, 1, H4'), 5.18-5.20 (m, 1, H3'), 6.13 (t, 1, H1'), 7.77 (s, 1, H6); ^{13}C NMR (DMSO-d_6)ppm: 12.0, 20.7, 35.8, 43.1, 74.6, 83.4, 84.8, 109.7, 136.0, 150.4, 163.6, 169.9.

N-β-(5'-Dimethoxytritylthymidin-3'-yl)ethyl-N'-(3'-O-acetyl-5'-deoxythymidin-5'-yl)urea (12).

Amine **10** (0.65 g, 2.29 mmol) was dissolved in dry pyridine and evaporated twice. It was again dissolved in pyridine (15 mL), 1,1'-carbonyldiimidazole was added, and the solution was stirred at room temperature for 24 hours. Water (1 mL) was added and stirred for 15 minutes. The solvent was removed and the residue was dissolved in pyridine and again evaporated. This process was repeated twice. Finally it was taken in pyridine (15 mL), compound **11** (1.34 g, 2.29 mmol) was added and stirring continued for 36 hours. Pyridine was removed on rotary evaporator and the residue was applied to a silica gel column and eluted with a gradient of 0-5% methanol in chloroform. Appropriate fractions were collected and on evaporation, compound **12** was isolated in the form of glass. Yield 1.35 g (65.8%); R_f 0.87 (20% MeOH in $CHCL_3$ v/v); ^{1}H NMR (DMSO-d_6)ppm: 1.45 (s, 3, CH_3), 1.80 (s, 3, CH_3), 2.04 (s, 3, $COCH_3$), 2.22-2.28 (overlapping m, 4, H2', H2''), 3.14-3.27 (overlapping m, 4, H5', H5''), 3.36-3.39 (m, 4, $OC\underline{H}_2C\underline{H}_2NH_2$), 3.73 (s, 6, 2 x OCH_3), 3.92 (m, 1, H4'), 4.01 (m, 1, H4''), 4.18 (m, 1. H3'), 5.13 (m, 1, H3''), 6.05-6.22 (overlapping m, 4, H1', H1'', N$\underline{H}$CON$\underline{H}$), 6.89-7.52 (overlapping m, s, 14, H6, ar-H), 11.37 (overlapping s, 2, NH); ^{13}C NMR (DMSO-d_6)ppm: 11.6, 12.0, 20.7, 35.4, 36.1, 40.8 54.9, 63.1, 68.2, 74.5, 79.1, 79.3, 82.7, 82.9, 83.6, 83.7, 85.9, 109.6, 109.8, 126.7, 127.8, 129.6, 135.1, 135.2, 135.5, 135.8, 144.6, 150.3, 150.3, 157.9, 158.1, 163.5, 163.6, 169.8

N-β-(3'-Deoxythymidin-3'-yl)ethyl-N'-(5'-deoxythymidin-5'-yl) urea (5).

Compound **12** (0.85 g, 0.947 mmol) was dissolved in methanol (20 mL) and 1,4-dioxane (5 mL) and ammonium hydroxide (5 mL) was added, and the solution was stirred overnight. The solvents were removed, the residue was dissolved in chloroform, and the solution was washed with 5% sodium bicarbonate and then with water. Chloroform was evaporated and the resulting glass was dissolved in 80% acetic acid (10 mL) and stirred for 10 hrs. Acetic acid was removed on rotary evaporator, the resulting residue was triturated in water, and the solid was separated by filtration. The filtrate was evaporated to dryness and the product was purified by column chromatography. On eluting with a gradient of 5-15% methanol in chloroform, compound **5** was isolated. Yield 0.22 g (42.3%); R_f 0.40 (20% MeOH in $CHCL_3$ v/v); ^1H NMR (DMSO-d_6)ppm: 1.77 (s, 3, CH_3), 1.80 (s, 3, CH_3), 2.04-2.18 (overlapping m, 4, H2', H2''), 3.14-3.17 (overlapping m, 4, H5'', $OCH_2C\underline{H}_2NH$-), 3.34-3.43 (m, 2, $OC\underline{H}_2CH_2NH$-), 3.55-3.58 (m, 2, H5'), 3.69 (m, 1, H4''), 3.90 (m, 1, H4'), 4.05-4.12 (overlapping m, 2, H3', H3''), 5.10 (t, 1, 5'OH), 5.28 (d, 1, 3'OH), 6.01 (t, 1, $CH_2NHCON\underline{H}CH_2$-5'), 6.10-6.19 (overlapping m, 3, $CH_2N\underline{H}CONHCH_2$-5', H1', H1''), 7.49 (s, 1, H6), 7.69 (s, 1, H6), 11.30 (s, 2, NH); ^{13}C NMR (DMSO-d_6)ppm: 12.0, 12.2, 36.3, 38.4, 39.2, 41.5, 48.5, 61.4, 68.1, 71.0, 79.2, 83.5, 83.7, 84.5, 85.5, 109.4, 109.6, 135.8, 135.9, 150.3, 157.9, 163.6, 163.6

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