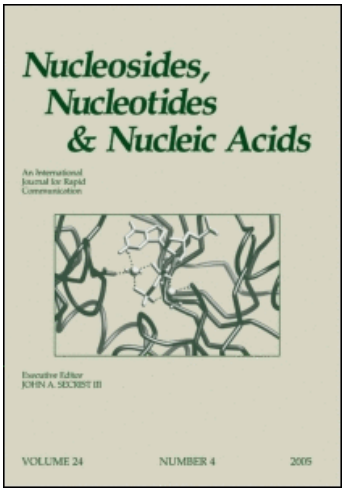

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SYNTHESIS OF NEW 5'-SULFONYLAMIDO DERIVATIVES OF 3'-AZIDO-3'-DEOXYTHYMIDINE (AZT)

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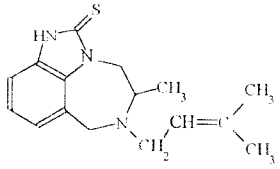
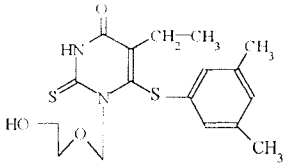
ABSTRACT: A series of 5'-N-methanesulfonyl derivatives of 3'-azido-5'-(alkylamino)-3',5'-dideoxythymidine was synthesised. The first step of the synthesis involved the reaction of 1-(2,5-dideoxy-5-O-tosyl-β-D-*threo*-pentofuranosyl)thymine **1** with an appropriate amine to give 1-[5-(alkylamino)-2,5-dideoxy-β-D-*threo*-pentofuranosyl]thymines **2a-e** and 1-(2,5-dideoxy-β-*threo*-pent-4-enofuranosyl)thymine **3** as a by-product. Compounds **2a-e** were treated with an excess of methanesulfonyl chloride to yield intermediates 1-[5-(dimethylamino)-3-O-methanesulfonyl-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl]-thymine **4a** and 1-[5-(N-alkyl-N-methanesulfonyl)-3-O-methanesulfonyl-2,3,5-trideoxy-β-D-*threo*-penfuranosyl]thymines **4b-e**. The reaction of **4a-e** with lithium azide in dimethylformamide afforded the final compounds 1-[3-azido-5-(N-methyl-N-methanesulfonyl)-2,3,5-trideoxy-β-D-*erythro*-penofuranosyl]thymine **5a** and 1-[3-azido-5-(N-alkyl-N-methanesulfonyl)-2,3,5-trideoxy-β-D-*erythro*-penofuranosyl]thymines **5b-e**. The independent synthesis of 4',5'-unsaturated product **3** was also described.

The life cycle of the human immunodeficiency virus (HIV) is dependent upon HIV-encoded reverse transcriptase (RT) which has been a major target for the design of anti-HIV agents.[1,2] In this regard, 3'-azido-3'-deoxythymidine (AZT) has been developed as a drug for the treatment of acquired immunodeficiency syndrome (AIDS).[3,4] AZT acts as an inhibitor of viral reverse trancriptase after its conversion to AZT-5'-triphosphate by host cell kinase.[5] Although AZT has proved to be very effective against viral replication in laboratory tests, it shows some toxicity and causes the development of drug-resistant virus mutants.[6,7] Furthermore, the ability of AZT to cross the blood brain barrier (BBB) is less than optimal. Therefore, AZT does not effectively suppress viral replication in the brain.[8] Currently, the development of new anti-HIV agents is focused on discovering of AZT

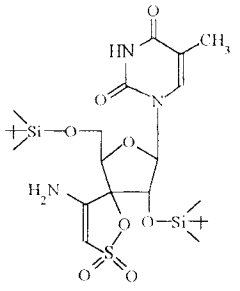
prodrugs (or other first generation anti-HIV nucleosides) and compounds active through new mechanism of action.[9] A number of AZT prodrugs have been investigated, which can more readily penetrate into the central nervous system due to their enhanced ability to cross the BBB. These studies involved esterification of the 5'-hydroxyl group of AZT,[10,11] attachment of lipophilic functional groups to the base moiety[12,13] and utilization of masked phosphate nucleotides.[14,15] A second major class of HIV RT inhibitors is represented by the so called "nonnucleoside" agents (for example TIBO and HEPT derivatives).[2] These compounds interact with a specific allosteric ("non-substrate") binding site of HIV RT.[2] However, among these inhibitors are some nucleoside analogues with substituted 5' position, namely TSAO derivatives.[16]



TIBO



HEPT

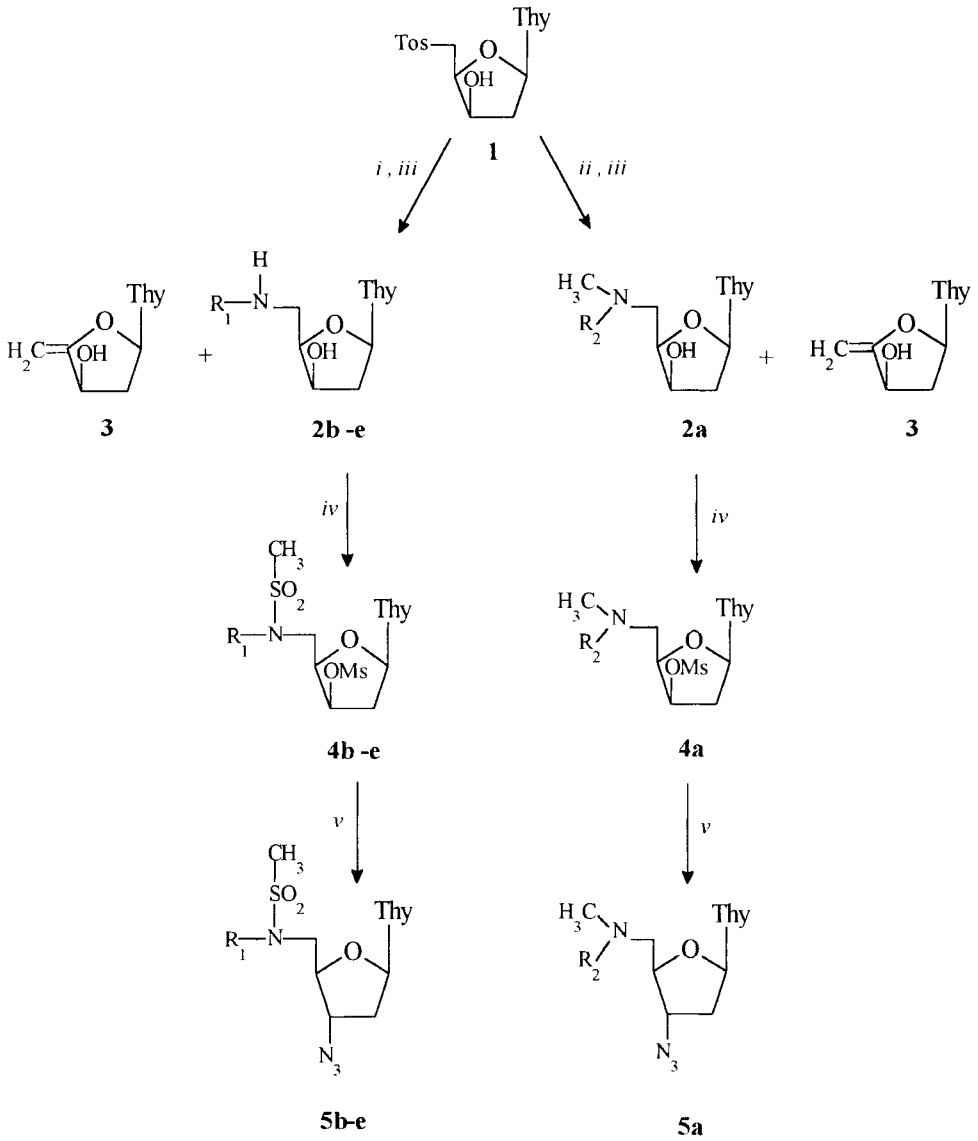


TSAO

There are some examples illustrating antiviral activity of 5'-deoxy-5'-N-substituted nucleosides. 5'-Amino-5'-deoxythymidine[17-19] and 5'-N-methanesulfonyl derivative of 5'-amino-2',5'-dideoxy-5-iodouridine[19] were reported to inhibit selectively replication of Herpes Simplex Virus (HSV) in cultured cells. Pathack and coworkers reported the synthesis of 3'-substituted 5'-alkylamino-3',5'-dideoxythymidines by the reaction of 3',5'-dimethanesulfonylthymidine with secondary amines.[20]

A variety of nucleosides have been synthesised which contain a 5'-extended -SO_2- moiety. Among these are sulfamoyl derivatives of nucleosides[21-23] and 5'-N-methanesulfonyl derivatives of 5'-amino-2',5'-dideoxy-5-iodouridine.[19]

In this paper, continuing our interest in the area of aminonucleosides[24,25], we present the method of the synthesis of 5'-N-methanesulfonyl derivatives of 3'-azido-5'-(alkylamino)-3',5'-dideoxythymidine. Compounds **2a-e** were obtained by the reaction of 1-(2,5-dideoxy-5-O-tosyl-β-D-*threo*-pentofuranosyl)thymine **1** with the appriopriate amine in acetonitrile at 120°C in 70-76 % isolated yield (Scheme). This reaction, however, gave also β-elimination by-product 1-(2,5-dideoxy-β-D-*threo*-pent-4-enofuranosyl)thymine **3**



(*i*) R_1-NH_2, CH_3CN, 120°C, 16 hrs; (*ii*) R_2-$NHCH_3$, CH_3CN, 120°C, 16 hrs; (*iii*) Dowex 50Wx2; (*iv*) MsCl, Py, 0-4°C, 6 hrs; (*v*) LiN_3, DMF, 90°C, 45 min.
Thy = thymin-1-yl, Ms = methanesulfonyl, Ts = *p*-toluenesulfonyl
$R_1 = CH_3$, CH_2CH_3, $CH_2CH{=}CH_2$, CH_2-Ph
$R_2 = CH_3$

Scheme

in about 20 % yield. Similarly, we have observed that the reactions of 1-(3,5-dideoxy-3-O-mesyl-5-O-trityl-β-D-*threo*-pentofuranosyl)thymine with alkylamines in acetonitrile at 120°C afford the substitution products 3'-alkylamino-5'-O-trityl-3',5'-dideoxythymidines and the β-elimination product 1-(2,3-dideoxy-5-O-trityl-β-D-glycero-pent-2-enofuranosyl)thymine.[24] The desired products **2a-e** were easily separated from by-product **3** by treatment of the reaction mixture with the cation-exchange resin (Dowex 50Wx2). The identity of compound **3** was confirmed by spectroscopic means as well as by independent synthesis. Compound **3** was prepared by reaction of **1** with potassium *t*-butoxide in dimethyl sulfoxide at 80°C in 68 % yield. It should be mentioned that this reaction does not proceed at room temperature. Literature methods of the synthesis of 4',5'-unsaturated pyrimidine nucleosides involve dehydrohalogenation reaction of the acylated 5'-iodo-5'-deoxy nucleosides using either silver fluoride in pyridine[26] or potassium fluoride in hot dimethyl sulfoxide[27,28] and reaction of 5'-O-tosyl-2',3'-O-isopropylideneuridine with potassium *t*-butoxide in *t*-butyl alkohol.[29]

Treatment of compounds **2a-e** with 2.5 equivalents of methanesulfonyl chloride in anhydrous pyridine at 0-4°C afforded the corresponding 1-[5-(dimethylamino)-3-O-methanesulfonyl-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl]thymine **4a** and 1-[5-(N-alkyl-N-methanesulfonyl)-3-O-methanesulfonyl-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl]thymines **4b-e.** The reaction of compounds **4a-e** with lithium azide in dimethylformamide at 90°C provided the final compounds **5a-e**. It is worth noting that during the last reaction only the 3'-O-mesyl group undergoes substitution by azide and 5'-(N-alkyl-N-methanesulfonyl) group remains intact.

Elemental analysis and spectral data (UV, MS, ^{1}H-NMR and ^{13}C-NMR) are consistent with the structures shown. The ^{1}H-NMR spectrum of **3** in deuteriochloroform shows the 5'-methylene group as two peaks at δ 4.20 (as doublet of doublets) and δ 4.83 (as quartet). The ^{1}H-NMR of compounds **2a-e** and **4a-e** display a doublet of doublets at δ range from 6.06 to 6.27 for H-1' ($J_{1',2'}$ ~ 3 Hz, $J_{1',2''}$ ~ 8 Hz). The signals for H-2' and H-2" are widely separeted multiplets with δ ~ 1.84 and δ ~ 2.55 for compound **2a-e** and with δ ~ 2.50 and δ ~2.83 for **4a-e** what indicates a cis relationship between H-1' and H-3'.[30] The ^{1}H-NMR of compounds **5a-e** in contrast display a pseudo-triplet at δ ~ 6.20 for H-1' and closely spaced multiplets for the H-2' and H-2" protons centered at δ 2.44.

In conclusion, we have developed a method of the synthesis of 5'-N-methanesulfonyl derivatives of 3'-azido-5'-N-alkyl-3',5'-dideoxythymidine. We have demonstrated that 5'-(N-alkyl-N-methanesulfonyl) group does not undergo substitution reaction with azide anion during the last step of the synthesis.

EXPERIMENTAL SECTION

Melting points were determined on a Boetius and are uncorected. Micro-analyses were obtained on an elemental analyser Perkin-Elmer 240. UV spectra were recorded on a Shimadzu UV-160 spectrophotometer. IR spectra were recorded on a Perkin-Elmer 180 infrared spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were determined on Varian-Gemini 300 MHz spectrometer. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} precoated (0.2 mm) plates and column chromatography was performed on Merck silica gel 60 H (5-40 μm). Analytical HPLC was carried out on a Waters Nova-Pak C_{18} reverse phase column (3.9 x 150 mm, 4 μm particle size), eluent: water (70 %) - methanol (30 %), flow rate: 1 ml/min, detection at 275 nm. Compound **1** was prepared from thymidine according to the literature methods.[31,32] Compounds **2a-e** were prepared by our method described previously.[25] The spectral data of compounds **2a** and **2c** were reported previously[25] and the synthesis of compound **2e** was modified.

Preparation of compounds 2b and 2d

To a solution of **1** (1.5 g, 3.79 mmol) in acetonitrile (35 ml), an appropriate amine (22.56 mmol) was added. The reaction mixture was heated in a sealed glass tube at 120°C for 18 hrs. After cooling, the tube was opened and the reaction mixture was evaporated under reduced pressure. The residue was dissolved in water (18 ml) and was applied to a column (4 x 6 cm) of Dowex 50Wx2 (H^+) (50-100 mesh). The column was eluted with methanol (250 ml), then with water (450 ml) in order to remove compound **3** and *p*-toluenosulfonic acid and finally with 1N ammonium hydroxide. The fractions containing **2b** (or **2d**) were combined and evaporated under reduced pressure. The residue was dissolved in 100 ml of methanol - water (1:1), treated with charcol and the mixture was refluxed for 10 min. Then the mixture was filtered through a Celite pad, evaporated and crystallized from ethanol - ethyl acetate (2:1) to give compound **2b** (or **2d**), which was dried in vacuo over phosphorus pentoxide.

1-[2,5-Dideoxy-5-(methylamino)-β-D-*threo*-pentofuranosyl]thymine (2b). m.p. 182-184°C (EtOH : AcOEt 2:1). UV (CH_3OH) λ_{max} 266 nm, ε_{max} 9200. ^{1}H-NMR (DMSO-d_6) δ 1.78 (d, 3H, J = 1.1 Hz, 5-CH_3), 1.84 (dd, 1H, J = 2.4 Hz, J = 14.6 Hz, H-2'), 2.31 (s, 3H, 5'N-CH_3), 2.55 (m, 1H, H-2''), 2.77 (dd, 1H, J = 5.9 Hz, J = 12.5 Hz, H-5'), 2.84 (dd, 1H, J = 5.4 Hz, J = 12.1 Hz, H-5''), 3.82 (m, 1H, H-4'), 4.21 (dd, 1H, H-3'), 6.06 (dd, 1H, J = 2.5 Hz, J = 8.6 Hz, H-1'), 7.83 (d, 1H, J = 1.1 Hz, H-6).

^{13}C-NMR (DMSO-d_6) δ 13.2 (5-CH_3), 35.7 (C-2'), 40.7 (C-3'), 47.0 (5'N-CH_3), 68.1 (C-5'), 81.9 (C-1'), 83.1 (C-4'), 108.7 (C-5), 136.8 (C-6), 150.3 (C-2), 162.3 (C-4). IR (KBr) ν_{max} 3400 (OH), 3200 (NH), 3060, 1700-1660 (C=O), 1470, 1380, 1270, 1060 (C-O-C), 840, 650, 550 cm^{-1}. Anal. Calcd for $C_{11}H_{17}N_3O_4$: C, 51.75; H, 6.71; N, 16.46. Found: C, 51.68; H, 6.62; N, 16.31.

1-[2,5-Dideoxy-5-(allylamino)-β-D-*threo*-pentofuranosyl]thymine (2d).
m.p. 181-183°C (EtOH : AcOEt 2:1). UV (CH_3OH) λ_{max} 267 nm, ε_{max} 9400. ^{1}H-NMR (DMSO-d_6) δ 1.70 (d, 3H, J = 1.0 Hz, 5-CH_3), 1.83 (dd, 1H, J = 3.0 Hz, J = 14.8 Hz, H-2'), 2.42 (m, 3H, H-2", 5'N-CH_2), 2.79 (dd, 1H, J = 5.7 Hz, J = 12.6 Hz, H-5'), 2.85 (dd, 1H, J = 5.3 Hz, J = 12.2 Hz, H-5"), 3.89 (m, 1H, H-4'), 4.17 (dd, 1H, H-3'), 5.02-5.19 (m, 2H, =CH_2), 5.70-5.88 (m, 1H, -CH=), 6.15 (dd, 1H, J = 2.5 Hz, J = 8.9 Hz, H-1'), 7.77 (d, 1H, J = 1.0 Hz, H-6). ^{13}C-NMR (DMSO-d_6) δ 13.5 (5-CH_3), 40.6 (C-2'), 47.7 (C-3'), 51.9 (5'N-CH_2), 69.5 (C-5'), 81.9 (C-1'), 83.0 (C-4'), 108.6 (C-5), 115.1 (=CH_2), 136.3 (-CH=), 137.4 (C-6), 154.5 (C-2), 161.8 (C-4). IR (KBr) ν_{max} 3400 (OH), 3200 (NH), 3060, 1690-1660 (C=O), 1600, 1520, 1470, 1400, 1270, 1120, 1060 (C-O-C), 960, 910, 790, 650, 560, 510 cm^{-1}. Anal. Calcd for $C_{13}H_{19}N_3O_4$: C, 55.50; H, 6.81; N, 14.94. Found: C, 55.66; H, 6.73; N, 15.04.

Preparation of compound 2e from 1

A mixture of **1** (1.5 g, 3.79 mmol) and benzylamine (15.16 mmol) in acetonitrile (27 ml) was heated in a sealed glass tube at 120°C for 16-17 hrs. After cooling, the tube was opened and the reaction mixture evaporated under reduced pressure. The residue was dissolved in CH_3OH : H_2O (1:1) (20 ml) and the solution was applied to a column (4 x 8 cm) of Dowex 50Wx2 (H^+) (50-100 mesh). The column was eluted with CH_3OH (400 ml), then with H_2O (300 ml) in order to remove compound **3** and *p*-toluenesulfonic acid. Finally, the aminonucleoside **2e** was eluted with mixture of 1N NH_4OH : CH_3OH (1:1). The fractions containing **2e** were combined, evaporated under reduced pressure. The residue as white solid foam was dried in vacuo over phosphorus pentoxide to afford product **2e** in pure form. Yield about 76 %.

1-[2,5-Dideoxy-5-(benzylamino)-β-D-*threo*-pentofuranosyl]thymine (2e).
UV (CH_3OH) λ_{max} 267 nm, ε_{max} 9600. ^{1}H-NMR (DMSO-d_6) δ 1.72 (d, 3H, J = 1.1 Hz, 5-CH_3), 1.85 (dd, 1H, J = 2.4 Hz, J = 14.7 Hz, H-2'), 2.55 (m, 1H, H-2"), 2.76-2.90 (m, 2H, H-5', H-5"), 3.74 (m, 2H, 5'N-CH_2), 3.87 (m, 1H, H-4'), 4.22 (dd, 1H, H-3'), 6.06 (dd, 1H, J = 2.4 Hz, J = 8.4 Hz, H-1'), 7.26 (m, 5H, Ph), 7.80 (d, 1H, J = 1.1 Hz, H-6), 11.23 (br s, 1H, 3N-H). ^{13}C-NMR (DMSO-d_6) δ 12.5 (5-CH_3), 40.6 (C-2'), 47.4 (C-3'),

53.0 (5'N-CH_2), 69.1 (C-5'), 83.0 (C-1'), 83.2 (C-4'), 108.5 (C-5), 126.4 (arom), 127.7 (arom), 127.9 (arom), 137.0 (C-6), 140.4 (arom.), 150.3 (C-2), 163.5 (C-4). IR (KBr) ν_{max} 3400 (OH), 3200 (NH), 3050, 1690 (C=O), 1470, 1270, 1120, 1060 (C-O-C), 750 (arom), 690 (arom), 550 cm^{-1}. Anal. Calcd for $C_{17}H_{21}N_3O_4$: C, 61.62; H, 6.39; N, 12.68. Found: C, 61.87; H, 6.22; N, 12.59.

Method for separation of compound 3

The fractions containing compound **3** and *p*-toluenesulfonic acid obtained from Dowex 50Wx2 column (see preparation of compound **2b, 2d** and **2e** from **1**) were concentrated under reduced pressure. The residue solution was extracted with $CHCl_3$ (5 x 30 ml) and combined organic extracts were washed with water (2 x 20 ml), dried over Na_2SO_4, filtered and evaporated under reduced pressure. Analytically pure sample of compound **3** was obtained by crystallization from ethanol and dried in vacuo over phosphorus pentoxide.

1-[(2,5-Dideoxy-β-D-*threo*-pent-4-enofuranosyl)thymine (3). m.p. 190-192°C. UV (CH_3OH) λ_{max} 267 nm, ε_{max} 9500. ^{1}H-NMR ($CDCl_3$) δ 1.96 (d, 3H, J = 1.2 Hz, 5-CH_3), 2.52 (m, 2H, H-2', H-2"), 4.20 (dd, 1H, H-5'), 4.83 (q, 1H, H-5"), 4.98 (m, 1H, H-3'), 5.57 (m, 1H, 3'-OH), 6.73 (dd, 1H, J = 5.1 Hz, J = 5.7 Hz, H-1'), 8.05 (q, 1H, J = 1.2 Hz, H-6), 8.67 (br s, 1H, 3N-H). ^{13}C-NMR ($CDCl_3$) δ 12.8 (5-CH_3), 38.2 (C-2'), 76.0 (C-3'), 80.6 (C-1'), 87.2 (C-5'), 88.8 (C-4'), 111.7 (C-5), 136.3 (C-6), 151.1 (C-2), 163.9 (C-4). MS, m/z (rel. int.) 224 (19), 126 (39), 125 (55), 98 (100), 83 (28). IR (KBr) ν_{max} 3420 (OH), 3180 (NH), 3080 (CH_2=C), 1700-1670 (C=O), 1460, 1410 (CH_2=C), 1260, 1230, 1150, 1080 (C-O-C), 950, 860, 750, 550 cm^{-1}. Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.56; H, 5.40; N, 12.50. Found: C, 53.84; H, 5.62; N, 12.61.

Preparation of compound 3

To a solution of **1** (0.1 g, 0.25 mmol) in DMSO (4 ml) was added *t*-BuOK (0.5 mmol). The mixture was stirred at 80°C for 8 hrs and then neutralized with 1N HCl. After cooling to the solution was added water (20 ml) and the mixture was extracted with chloroform (4 x 15 ml). Combined organic extracts were washed with water (2 x 10 ml), dried over Na_2SO_4, filtered and evaporated under reduced pressure. Analitically pure sample of product **3** was obtained by crystallization from methanol in 68 % yield (m.p. 194-195°C).

TABLE. Yields of compounds **2a-e**, **4a-e** and **5a-e**

Compund **2, 4, 5**	Substitutent		Isolated yield (%)		
	R_1	R_2	**2**	**4**[a)]	**5**[a)]
a	CH_3	CH_3	78[23]	64	52
b	CH_3	-	73	64	55
c	CH_2CH_3	-	70[23]	61	54
d	$CH_2CH{=}CH_2$	-	71	58	49
e	CH_2-Ph	-	76	62	52

[a)] Total yields of compounds **4a-e** and **5a-e**.

Preparation of compounds 4a-e from 2a-e

Compound **2** (0.5 g) was stirred with anhydrous pyridine (13 ml) and methanesulfonyl chloride (2.5 equivalents) at 0-4°C. After 6 hrs the mixture was pured into cold water (50 ml) and the solution was extracted with chloroform (3 x 15 ml). Combined organic extracts were washed with aqueous $NaHCO_3$ and then with water, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (40 g) using as eluent $CHCl_3$: CH_3OH (120 : 1). The fractions containing the product were evaporated and dried in vacuo over phosphorus pentoxide (yield see Table).

1-[5-(Dimethylamino)-3-O-methanesulfonyl-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl]thymine (4a). UV (CH_3OH) λ_{max} 266 nm, ε_{max} 9400. ^{1}H-NMR ($CDCl_3$) δ 1.91 (d, 3H, J = 1.1 Hz, 5-CH_3), 2.34 (m, 1H, H-2'), 2.52 (t, 6H, J = 1.7 Hz, 5'N-$(CH_3)_2$), 2.93 (m, 1H, H-2"), 3.35 (s, 3H, 3'O-SO_2CH_3), 3.52 (m, 2H, H-5', H-5"), 4.59 (m, 1H, H-4'), 5.36 (m, 1H, H-3'), 6.27 (dd, 1H, J = 3.8 Hz, J = 7.9 Hz, H-1'), 7.43 (d, 1H, J = 1.1 Hz, H-6). ^{13}C-NMR ($CDCl_3$) δ 12.5 (5-CH_3), 37.9 (3'O-SO_2CH_3), 38.0 (C-2'), 43.1 (C-3'), 55.5 (5'N-$(CH_3)_2$), 75.8 (C-5'), 80.0 (C-1'), 83.3 (C-4'), 110.1 (C-5), 135.5 (C-6), 150.3

(C-2), 163.4 (C-4). IR (KBr) ν_{max} 3200 (NH), 3040, 1680-1660 (C=O), 1470, 1320 (SO_2), 1270, 1140 (SO_2), 1050 (C-O-C), 840, 760, 540 cm^{-1}. Anal. Calcd for $C_{13}H_{21}N_3O_6S$: C, 44.95; H, 6.09; N, 13.10. Found: C, 45.21; H, 6.18; N, 13.33.

1-[5-(N-Methyl-N-methanesulfonyl)-3-O-methanesulfonyl-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl]thymine (4b). m.p. 173-175°C (CH_3OH). UV (CH_3OH) λ_{max} 266 nm, ε_{max} 9500. ^{1}H-NMR (DMSO-d_6) δ 1.78 (d, 3H, J = 1.1 Hz, 5-CH_3), 2.34 (dd, 1H, J = 2.5 Hz, J = 15.8 Hz, H-2'), 2.84 (s, 3H, 5'N-SO_2CH_3), 2.82 (m, 1H, H-2"), 2.95 (s, 3H, 3'O-SO_2CH_3), 3.31 (s, 3H, 5'N-CH_3), 3.49 (m, 2H, H-5', H-5"), 4.32 (m, 1H, H-4'), 5.30 (m, 1H, H-3'), 6.13 (dd, 1H, J = 2.5 Hz, J = 8.0 Hz, H-1'), 7.45 (d, 1H, J = 1.1 Hz, H-6), 11.39 (s, 1H, 3N-H). ^{13}C-NMR (DMSO-d_6) δ 12.5 (5-CH_3), 35.2 (5'N-SO_2CH_3), 35.3 (3'O-SO_2CH_3), 37.7 (C-2'), 38.7 (C-3'), 48.8 (5'N-CH_3), 79.6 (C-5'), 79.7 (C-1'), 83.4 (C-4'), 109.3 (C-5), 135.3 (C-6), 150.2 (C-2), 163.5 (C-4). IR (KBr) ν_{max} 3180 (NH), 3040, 1680 (C=O), 1470, 1320 (SO_2), 1270, 1170 (SO_2), 1140 (SO_2), 1090 (C-O-C), 960, 900, 770, 520 cm^{-1}. Anal. Calcd for $C_{13}H_{21}N_3O_8S_2$: C, 37.95; H, 5.15; N, 10.21. Found: C, 38.13; H, 5.38; N, 10.50.

1-[5-(N-Ethyl-N-methanesulfonyl)-3-O-methanesulfonyl-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl]thymine (4c). m.p. 169-170°C (CH_3OH). UV (CH_3OH) λ_{max} 266 nm, ε_{max} 9300. ^{1}H-NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.1 Hz, 5'-C-CH_3), 1.97 (d, 3H, J = 1.3 Hz, 5-CH_3), 2.52 (dd, 1H, J = 2.9 Hz, J = 16.1 Hz, H-2'), 2.84 (m, 1H, H-2"), 2.91 (s, 3H, 5'N-SO_2CH_3), 3.11 (s, 3H, 3'O-SO_2CH_3), 3.26-3.50 (m, 2H, 5'N-CH_2), 3.54-3.76 (m, 2H, H-5', H-5"), 4.24 (m, 1H, H-4'), 5.25 (m, 1H, H-3'), 6.27 (dd, 1H, J = 3.0 Hz, J = 8.1 Hz, H-1'), 7.47 (d, 1H, J = 1.3 Hz, H-6), 8.82 (s, 1H, 3N-H). ^{13}C-NMR ($CDCl_3$) δ 12.7 (5-CH_3), 14.0 (5'N-CH_2-CH_3), 38.8 (5'N-SO_2CH_3), 39.0 (3'O-SO_2CH_3), 39.7 (C-2'), 43.4 (C-3'), 45.8 (5'N-CH_2), 78.5 (C-5'), 81.3 (C-1'), 83.7 (C-4'), 111.5 (C-5), 135.0 (C-6), 150.2 (C-2), 163.2 (C-4). IR (KBr) ν_{max} 3200 (NH), 3020, 1680 (C=O), 1470, 1320 (SO_2), 1270, 1170 (SO_2), 1140 (SO_2), 1090 (C-O-C), 960, 900, 770, 520 cm^{-1}. Anal. Calcd for $C_{14}H_{23}N_3O_8S_2$: C, 39.52; H, 5.45; N, 9.88. Found: C, 39.43; H, 5.61; N, 10.04.

1-[5-(Allyl-N-methanesulfonyl)-3-O-methanesulfonyl-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl]thymine (4d). m.p. 163-164°C (EtOH). UV (CH_3OH) λ_{max} 266 nm, ε_{max} 9500. ^{1}H-NMR ($CDCl_3$) δ 1.96 (d, 3H, J = 1.0 Hz, 5-CH_3), 2.51 (dd, 1H, J = 2.7 Hz, J = 16.0 Hz, H-2'), 2.83 (m, 1H, H-2"), 2.94 (s, 3H, 5'N-SO_2CH_3), 3.09 (s, 3H, 3'O-SO_2CH_3), 3.66 (m, 2H, 5'N-CH_2), 3.96 (m, 2H, H-5', H-5"), 4.28 (m, 1H, H-4'), 5.23 (m, 1H, H-3'), 5.28-5.36 (m, 2H, =CH_2), 5.79-5.92 (m, 1H, –CH=), 6.25 (dd, 1H, J = 2.5 Hz, J = 7.9 Hz, H-1'), 7.46 (d, 1H, J = 1.0 Hz, H-6), 9.20 (s, 1H, 3N-H). ^{13}C-NMR ($CDCl_3$) δ 12.7 (5-CH_3), 38.8 (5'N-SO_2CH_3), 39.5 (3'O-SO_2CH_3), 39.7 (C-2'), 45.8 (C-3'), 51.0 (5'N-CH_2), 78.4 (C-5'), 81.2 (C-1'), 83.9 (C-4'), 111.3 (C-5),

119.6 (=CH_2), 132.2 (-CH=), 135.0 (C-6), 150.3 (C-2), 163.5 (C-4). IR (KBr) ν_{max} 3180 (NH), 3020, 1690 (C=O), 1470, 1320 (SO_2), 1270, 1170 (SO_2), 1140 (SO_2), 1080 (C-O-C), 960, 900, 790, 510 cm^{-1}. Anal. Calcd for $C_{15}H_{23}N_3O_8S_2$: C, 41.18; H, 5.30; N, 9.61. Found: C, 41.25; H, 5.38; N, 9.76.

1-[5-(N-Benzyl-N-methanesulfonyl)-3-O-2,3,5-trideoxy-β-D-*threo*-pentofuranosyl]-thymine (4e). UV (CH_3OH) λ_{max} 265 nm, ε_{max} 9400. ^{1}H-NMR ($CDCl_3$) δ 1.93 (d, 3H, J = 1.1 Hz, 5-CH_3), 2.46 (dd, 1H, J = 3.0 Hz, J = 16.2 Hz, H-2'), 2.73 (m, 1H, H-2"), 2.94 (s, 3H, 5'N-SO_2CH_3), 3.02 (s, 3H, 3'O-SO_2CH_3), 3.64 (m, 2H, H-5', H-5"), 4.12 (m, 1H, H-4'), 4.41 (d, 1H, J = 15.2 Hz, 5'N-CH_A), 4.59 (d, 1H, J = 15.2 Hz, 5'N-CH_B), 5.01 (m, 1H, H-3'), 6.21 (dd, 1H, J = 2.9 Hz, J = 8.1 Hz, H-1'), 7.36 (m, 6H, H-6, Ph), 8.85 (s, 1H, 3N-H). ^{13}C-NMR ($CDCl_3$) δ 12.7 (5-CH_3), 38.8 (3'O-SO_2CH_3), 39.5 (5'N-SO_2CH_3), 39.7 (C-2'), 46.1 (C-3'), 52.0 (5'N-CH_2), 78.3 (C-5'), 80.7 (C-1'), 83.9 (C-4'), 111.4 (C-5), 128.3 (arom), 128.4 (arom), 128.9 (arom), 135.0 (C-6), 135.2 (arom), 150.2 (C-2), 163.3 (C-4). IR (KBr) ν_{max} 3200 (NH), 3020, 1680 (C=O), 1460, 1320 (SO_2), 1260, 1170 (SO_2), 1140 (SO_2), 1090 (C-O-C), 960, 900, 780, 750 (arom), 690 (arom), 510 cm^{-1}. Anal. Calcd for $C_{19}H_{25}N_3O_8S_2$: C, 46.81; H, 5.17; N, 8.62. Found: C, 46.97; H, 5.02; N, 8.84.

Preparation of compounds 5a-e from 4a-e

To a solution of **4** (0.3 g) in dimethylformamide (10 ml) was added lithium azide (2 equivalents) and the reaction mixture was stired at 90°C for 45 min. The cooled reaction mixture was evaporated under reduced pressure and the crude product was applied to a column of silica gel (25 g) and chromatographed using as eluent $CHCl_3$: CH_3OH (140-120 : 1). The white solid foam was dried in vacuo over phosphorus pentoxide to afford product **5** in pure form (yield, see Table).

1-[3-Azido-5-(dimethylamino)-2,3,5-trideoxy-β-D-*erythro*-pentofuranosyl]thymine (5a). UV (CH_3OH) λ_{max} 265 nm, ε_{max} 9300. ^{1}H-NMR ($CDCl_3$) δ 1.93 (d, 3H, J = 1.1 Hz, 5-CH_3), 2.35-2.50 (m, 8H, 5'N-$(CH_3)_2$, H-2', H-2"), 2.63 (dd, 1H, J = 4.7 Hz, J = 14.3 Hz, H-5"), 2.67 (dd, 1H, J = 4.7 Hz, J = 14.3 Hz, H-5'), 3.97 (m, 1H, H-4'), 4.12 (m, 1H, H-3'), 6.08 (t, 1H, J = 6.3 Hz, H-1'), 7.34 (d, 1H, J = 1.1 Hz, H-6), 9.82 (br s, 1H, 3N-H). ^{13}C-NMR ($CDCl_3$) δ 12.8 (C-5), 37.4 (C-2'), 46.3 (C-3'), 61.0 (C-5'), 61.9 (N-$(CH_3)_2$), 82.1 (C-1'), 85.5 (C-4'), 111.1 (C-5), 135.9 (C-6), 150.3 (C-2), 163.9 (C-4). IR (KBr) ν_{max} 3200 (NH), 3050, 2100 (N_3), 1700-1680 (C=O), 1460, 1270, 1070 (C-O-C), 1040, 760, 550 cm^{-1}. Anal. Calcd for $C_{12}H_{18}N_6O_3$: C, 48.97; H, 6.16; N, 28.56. Found : C, 48.71; H, 6.32; N, 28.69.

1-[3-Azido-5-(N-methyl-N-methanesulfonyl)-2,3,5-trideoxy-β-D-*erythro*-pentofuranosyl]thymine (5b). UV (CH_3OH) λ_{max} 264 nm, ε_{max} 9100. ^{1}H-NMR ($CDCl_3$) δ 1.97 (d, 3H, J = 1.2 Hz, 5-CH_3), 2.44 (m, 2H, H-2', H-2"), 2.89 (s, 3H, 5'N-CH_3), 2.97 (s, 3H, 5'N-SO_2CH_3), 3.33 (dd, 1H, J = 4.4 Hz, J = 14.8 Hz, H-5"), 3.75 (dd, 1H, J = 4.4 Hz, J = 14.8 Hz, H-5'), 3.90 (m, 1H, H-4'), 4.43 (m, 1H, H-3'), 6.26 (t, 1H, J = 6.2 Hz, H-1'), 7.25 (d, 1H, J = 1.2 Hz, H-6), 9.02 (br s, 1H, 3N-H). ^{13}C-NMR ($CDCl_3$) δ 12.5 (5-CH_3), 35.4 (C-2'), 37.0 (5'N-SO_2CH_3), 37.2 (C-3'), 50.7 (5'N-CH_3), 60.1 (C-5'), 82.2 (C-1'), 84.7 (C-4'), 112.1 (C-5), 135.2 (C-6), 150.1 (C-2), 163.4 (C-4). IR (KBr) ν_{max} 3200 (NH), 3050, 2100 (N_3), 1690 (C=O), 1470, 1320 (SO_2), 1270, 1140 (SO_2), 1080 (C-O-C), 960, 780, 520 cm^{-1}. Anal. Calcd for $C_{12}H_{18}N_6O_5S$: C, 40.22; H, 5.06; N, 23.45. Found: C, 40.51; H, 5.18; N, 23.61.

1-[3-Azido-5-(N-ethyl-N-methanesulfonyl)-2,3,5-trideoxy-β-D-*erythro*-pentofuranosyl]thymine (5c). UV (CH_3OH) λ_{max} 265 nm, ε_{max} 9300. ^{1}H-NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7.2 Hz, 5'N-C-CH_3), 1.96 (d, 3H, J = 1.1 Hz, 5-CH_3), 2.44 (m, 2H, H-2', H-2"), 2.92 (s, 3H, 5'N-SO_2CH_3), 3.28-3.51 (m, 3H, 5'N-CH_2, H-5"), 3.58 (dd, 1H, J = 6.0 Hz, J = 15.2 Hz, H-5'), 3.94 (m, 1H, H-4'), 4.36 (m, 1H, H-3'), 6.16 (t, 1H, J = 6.4 Hz, H-1'), 7.24 (d, 1H, J = 1.1 Hz, H-6), 9.47 (s, 1H, 3N-H). ^{13}C-NMR ($CDCl_3$) δ 12.4 (5-CH_3), 13.5 (5'N-CH_2-CH_3), 36.7 (C-2'), 38.9 (5'N-SO_2CH_3), 43.6 (C-3'), 48.0 (5'N-CH_2), 60.8 (C-5'), 82.1 (C-1'), 85.5 (C-4'), 111.7 (C-5), 135.0 (C-6), 150.2 (C-2), 163.6 (C-4). IR (KBr) ν_{max} 3200 (NH), 3040, 2100 (N_3), 1700-1680 (C=O), 1470, 1320 (SO_2), 1270, 1190, 1140 (SO_2), 1080 (C-O-C), 1060, 960, 770, 520 cm^{-1}. Anal. Calcd for $C_{13}H_{20}N_6O_5S$: C, 41.93; H, 5.41; N, 22.57. Found: C, 42.13; H, 5.34; N, 22.73.

1-[3-Azido-5-(N-allyl-N-methanesulfonyl)-2,3,5-trideoxy-β-D-*erythro*-pentofuranosyl]thymine (5d). UV (CH_3OH) λ_{max} 265 nm, ε_{max} 9300. ^{1}H-NMR ($CDCl_3$) δ 1.97 (d, 3H, J = 1.2 Hz, 5-CH_3), 2.42 (m, 2H, H-2', H-2"), 2.93 (s, 3H, 5'N-SO_2CH_3), 3.48 (dd, 1H, J = 4.8 Hz, J = 15.1 Hz, H-5"), 3.60 (dd, 1H, J = 5.9 Hz, J = 15.2 Hz, H-5'), 3.82-4.08 (m, 3H, 5'N-CH_2, H-4'), 4.34 (m, 1H, H-3'), 5.33 (m, 2H, =CH_2), 5.78-5.92 (m, 1H, –CH=), 6.18 (t, 1H, J = 6.3 Hz, H-1'), 7.24 (d, 1H, J = 1.2 Hz, H-6), 8.55 (s, 1H, 3N-H). ^{13}C-NMR ($CDCl_3$) δ 12.4 (5-CH_3), 36.5 (5'N-SO_2CH_3), 38.9 (C-2'), 46.0 (C-3'), 53.2 (5'N-CH_2), 61.0 (C-5'), 81.9 (C-1'), 86.0 (C-4'), 111.5 (C-5), 120.1 (=CH_2), 133.5 (–CH=), 135.4 (C-6), 150.2 (C-2), 163.5 (C-4). IR (KBr) ν_{max} 3200 (NH), 3030, 2100 (N_3), 1690 (C=O), 1470, 1320 (SO_2), 1270, 1140 (SO_2), 1080 (C-O-C), 960, 900, 790, 550 cm^{-1}. Anal. Calcd for $C_{14}H_{20}N_6O_5S$: C, 43.74; H, 5.24; N, 21.86. Found: C, 43.91; H, 5.40; N, 21.72.

1-[3-Azido-5-(N-benzyl-N-methanesulfonyl)-2,3,5-trideoxy-β-D-*erythro*-pentofuranosyl]-thymine (5e). UV (CH_3OH) λ_{max} 265 nm, ε_{max} 9300. ^{1}H-NMR ($CDCl_3$) δ 1.96 (d, 3H, J = 1.1 Hz, 5-CH_3), 2.37 (m, 2H, H-2', H-2"), 2.87 (s, 3H, 5'N-SO_2CH_3), 3.43

(dd, 1H, J = 4.6 Hz, J = 15.3 Hz, H-5''), 3.60 (dd, 1H, J = 7.1 Hz, J = 15.3 Hz, H-5'), 3.88 (m, 1H, H-4'), 4.14 (m, 1H, H-3'), 4.34 (d, 1H, J = 14.8 Hz, 5'N-CH_A), 4.61 (d, 1H, J = 14.8 Hz, 5'N-CH_B), 6.11 (t, 1H, J = 6.2 Hz, H-1'), 7.20 (d, 1H, J = 1.1 Hz, H-6), 7.37 (m, 5H, Ph), 9.28 (s, 1H, 3N-H). ^{13}C-NMR ($CDCl_3$) δ 12.5 (5-CH_3), 36.6 (5'N-SO_2CH_3), 39.4 (C-2'), 48.5 (C-3'), 52.0 (5'N-CH_2), 61.1 (C-5'), 81.7 (C-1'), 85.8 (C-4'), 111.8 (C-5), 128.4 (arom), 128.9 (arom), 128.9 (arom), 134.8 (C-6), 135.5 (arom), 150.0 (C-2), 163.4 (C-4). IR (KBr) ν_{max} 3200 (NH), 3030, 2100 (N_3), 1700-1680 (C=O), 1470, 1450, 1320 (SO_2), 1270, 1140 (SO_2), 1080 (C-O-C), 1060, 960, 750 (arom), 690 (arom), 510 cm^{-1}. Anal. Calcd for $C_{18}H_{22}N_6O_5S$: C, 49.76; H, 5.11; N, 19.35. Found: C, 49.51; H, 5.20; N, 19.27.

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