1',2',6'-THIADIAZINE 1',1'-DIOXIDE AND IMIDAZO [4',5'-*c*][1',2',6']-THIADIAZINE 2',2'-DIOXODE 1,3-OXATHIOLANE NUCLEOSIDE ANALOGUES: SYNTHESIS AND ANTI-HIV-1 ACTIVITY

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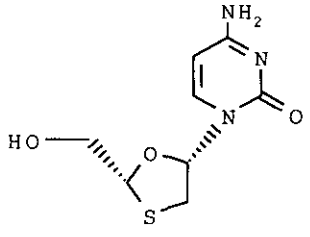
Abstract - A series of 1,3-oxathiolanes containing the 1,2,6-thiadiazine dioxide moieties were synthesized by various coupling conditions of the oxathiolane sugar (**3**) and silylated 1,2,6-thiadiazine dioxides (**4-7**) as bases. The compounds were evaluated for their potential anti-HIV activities in MT-4 cells and were found to lack activity at 100 μg/ml.

The hetero-substituted 2',3'-dideoxynucleoside analogues have emerged as an important class of antiviral agents,[1] particularly against the inhibition of the replication of the human immunodeficiency virus (HIV), the causative agent of AIDS, and hepatitis B virus (HBV). (-)-2'-Deoxy-3'-thiacytidine[2] (**1**, Lamivudine, 3TC™) and its 5-fluoro congener[3] have high therapeutic indices for HIV and HBV[4] relative to that of 2',3'-dideoxycytidine[5] (ddC). As part of our research program aimed at modifications in the nucleobase ring, we undertook the synthesis of 1,3-oxathiolanyl nucleosides containing the 1,2,6-thiadiazine 1,1-dioxides as pyrimidine and purine mimetics. Approaches involving base modifications have become useful in identifying novel therapeutic agents, particularly oligonucleotides. We report herein the synthesis and anti-HIV activity[6] of a series of racemic 1',2',6'-thiadiazine dioxide-1,3-oxathiolane nucleoside analogues of the general formula (**2**).



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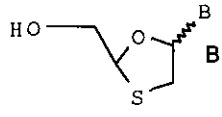
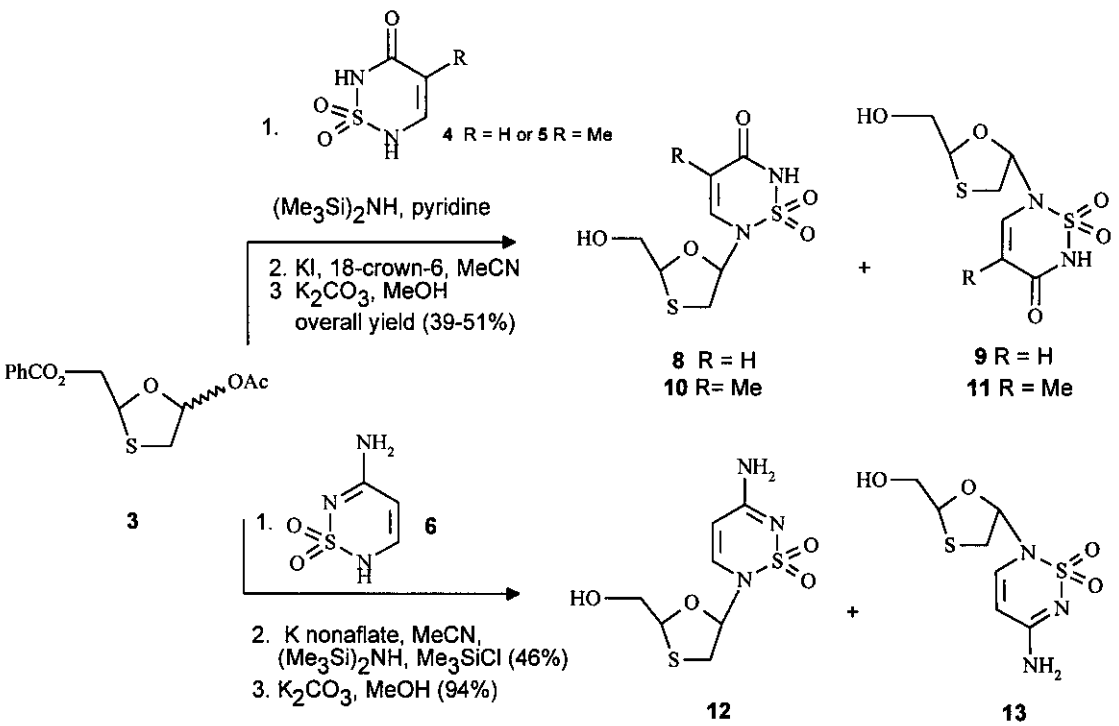


B = 1,2,6-thiadiazine dioxide base

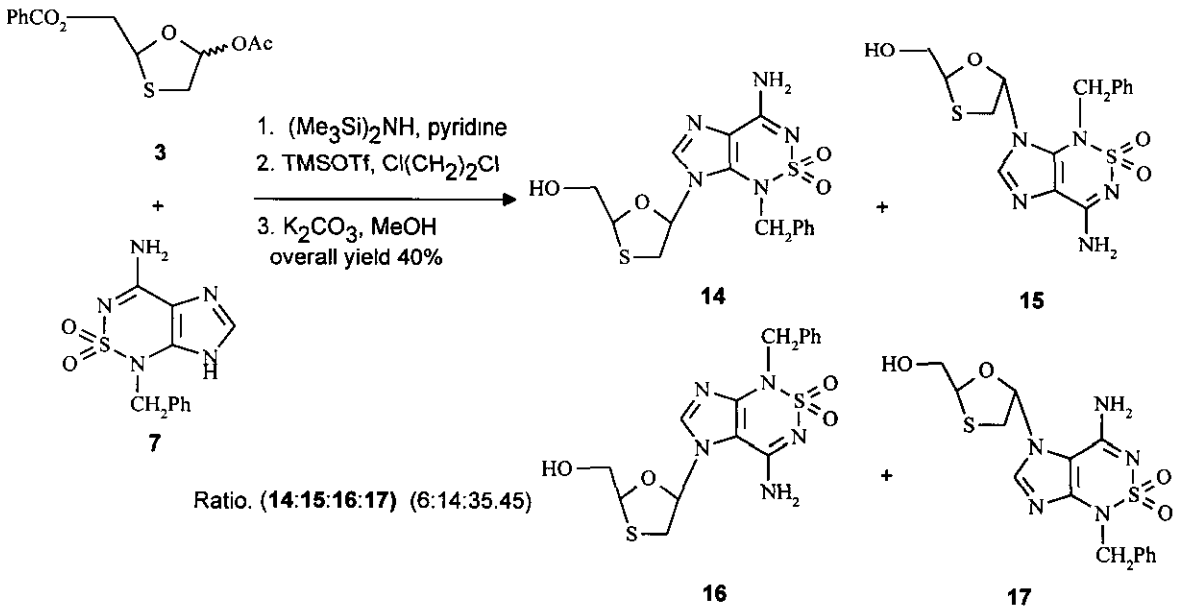
2

The general protocol for the preparation of the desired nucleosides is patterned after the established glycosylation of 1,3-oxathiolanyl sugar surrogates such as **3** with silylated pyrimidine[1,7] or purine bases.[1,8] The required thiadiazine bases were prepared by a [3+3] reaction of 1,3-bissilyl sulfamide with a suitable 1,3-dielectrophile.[9,10] Treatment of the persilylated derivative of **4** with **3** followed by addition of one equivalent of each of KI and 18-crown-6 in acetonitrile under reflux, afforded a mixture of N6 *cis* and *trans* nucleosides (**8**) and (**9**) respectively (1:1 ratio). Separation of the two isomers was performed by reverse phase preparative hplc after K_2CO_3/MeOH deprotection (Scheme 1). The preparation of the thymine analogues (**10**) and (**11**) was accomplished in a similar fashion. However, in the case of 3-amino 1,2,6-thiadiazine-1,1-dioxide (**6**), glycosylation was best achieved using potassium nonaflate-1,1,1,3,3,3-hexamethyldisilazane-trimethylsilyl chloride mixtures[11] to afford the expected mixture of N6 nucleosides in no stereoselectivity (Scheme 1). In this particular case, the persilyated derivative of **6** is formed *in situ* with 1,1,1,3,3,3-hexamethyldisilazane and glycosylated with **3** in the presence of trimethylsilyl nonaflate which, in turn, is generated *in situ* by the reaction of potassium nonaflate and trimethylsilyl chloride. That glycosylation occurred at N6 and not N2 was deduced easily from the ^1H nmr spectral data of the nucleoside analogues, particularly those of the anomeric proton. Assignment of the relative stereochemistry of the nucleosides was based on the well established ^1H nmr shifts and multiplicities of the anomeric proton[8] which appears in the *trans* isomer as a doublet approximately 0.3 ppm downfield from the doublet of doublet of the corresponding *cis* isomer.

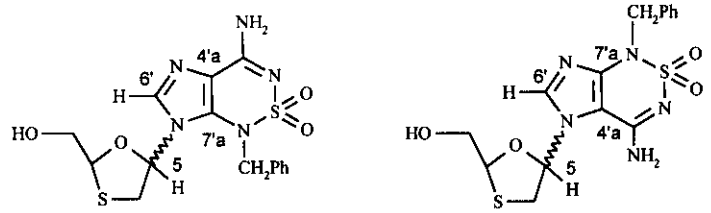


Scheme 1 . The synthesis of nucleosides containing pyrimidine base analogues (**4**, **5** and **6**).

Glycosylation of the silylated derivative of **7** with **3** under Vorbrüggen's conditions[11] (TMSOTf, 1,2-dichloroethane) followed by deprotection and separation afforded two pairs of N7 **14, 15** and N5 regioisomers **(16), (17)** in a ratio of 1:4 (Scheme 2). In their uv spectra, the N5 regioisomers with a linear conjugated system gave a significant bathochromic shift of 18 nm in comparison to the cross conjugated N7 isomers. The higher ratio of the N5 regioisomer reflects the dominance of kinetic control in the coupling reaction due to the shielding effect of the N7 site by the bulky benzyl group. Each of the N7 and N5 regioisomers consisted of a mixture of *cis* and *trans* isomers in a ratio of 3:7 and 7:9, respectively. Long range proton-carbon decoupling experiments proved to be useful in verifying the structures of **14-17**. In each case, a C6'-H5 long range coupling constant was detected, confirming that the sugar ring was attached either on N5 or N7. The magnitude of this three-bond coupling was not substantially different between the corresponding N5 and N7 regioisomers, however it was useful in eliminating other regioisomers arising from the possible attachment of the 1,3-oxathiolane at different centres of the thiadiazine skeleton . The C4'a-H6' and C7'a- H6' coupling constants gave further supportive evidence for the structures (Figure 1), since the planar H6'-C=N-C=C moiety gave a larger coupling constant (11-13 Hz), than the less planar H6'-C-N-C=C system (3-4 Hz). The nucleosides (**8-17**) were assayed against the inhibition of HIV-1 replication (RF strain) in whole cell assays using MT-4 cell lines. None of the compounds exhibited anti-HIV activity at concentrations lower than 100 μg/ml and were not cytotoxic at that concentration. The lack of activity could be attributed to the inability of the triphosphates to inhibit the HIV-1 replication or due to the difficulty in phosphorylating the analogues.[12]



Scheme 2. Synthesis of nucleosides containing purine base analogue (7).



14 and **15** **16** and **17**

C6' - H5	3-4 Hz	3 Hz
C7'a - H6'	3-4 Hz	13 Hz
C4'a - H6'	11 Hz	4 Hz

Figure 1. Long range carbon-proton coupling constants of nucleosides (**14**, **15**, **16** and **17**).

In conclusion, we have demonstrated that different glycosylation conditions can be employed for the coupling of thiadiazine dioxide bases with 1,3-oxathiolane sugar and that suggested regioselectivity can be achieved only in the pyrimidine-like bases with no control on the stereoselectivity of glycosylation. The mere replacement of the C=0 in cytosine by SO_2 abolished the antiviral activity of BCH-189 (racemic form of **1**).[2,4,13]

EXPERIMENTAL

General Procedures - Melting points were determined with a Mel-Temp II melting point apparatus and were uncorrected. TLC was performed on 0.20 mm thick Merck silica gel 60 F254. Components were located by spraying with 2% ceric sulphate in 2N sulphuric acid and heating with a hot gun until coloration took place. Flash column chromatography was performed on Merck silica gel particle size 0.04-0.063 mm (230-400 mesh) with the solvent systems specified. Evaporations were conducted *in vacuo*. The ^{1}H and ^{13}C nmr spectra were recorded on a Brüker AM250 nmr spectrometer. Chemical shifts are reported in ppm downfield from internal TMS. Preparative hplc separations were performed on a Waters instrument using Partisil ODS-3 SU column; 1 ml/min flow rate; Eluent: 3% (0.04% trifluoroacetic acid (TFA) in acetonitrile (MeCN)) in 0.04% TFA in water. Microanalyses were performed at Guelph Chemical Laboratories Ltd., Guelph, Ontario, Canada.

***cis* and *trans*-2-Hydroxymethyl-5-(5',6',-dihydro-1',1',5'-trioxo-2'*H*-1',2',6'-thiadiazin-2'-yl)-1,3-oxa-thiolane (8 and 9).** 2*H*,6*H*-1,2,6-thiadiazin-3-one 1,1-dioxide (**4**) (1.11 g, 7.50 mol) and hexamethyldisilazane (67 ml, 0.32 mol) were refluxed in pyridine (22 ml) for 8 h, then the solution was evaporated *in vacuo* to dryness and the residual solid was left on high vacuum for 2 h. To this solid was added 20 ml of MeCN, oxathiolane (**3**) (1.41 g, 5.00 mmol), potassium iodide (0.83 g, 5.00 mmol), 18-crown-6 (0.53 g, 2.00 mmol) and toluene (20 ml). The solution was then refluxed for 14 h and concentrated to dryness *in vacuo*. The

residue was dissolved in a saturated solution of sodium bicarbonate (50 ml) and washed with dichloromethane (4 x 10 ml). The water phase was concentrated to dryness *in vacuo* and the traces of water were removed by azeotropic distillation with ethyl acetate. Methanol (15 ml) was added to the dry residue and the mixture was stirred overnight at 20°C. The insoluble solids were filtered and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (10% methanol in ethyl acetate) to afford 0.69 g (51.2%) of a yellow oil as a mixture of **8** and **9** isomers, which were separated by preparative hplc as outlined in the general procedures. **8** mp 126-130°C (decomp.): ^{1}H Nmr (DMSO -d_6) δ 3.03 (dd, 1H, 6.9 Hz, 11.3 Hz), 3.22 (dd, 1H, 5.7 Hz, 11.0 Hz), 3.33 (s, 1H), 3.61 (m, 2H), 5.06 (t, 1H, 5.7 Hz), 5.10 (d, 1H, 8.8 Hz), 5.20 (t, 1H, 5.9 Hz), 5.72 (t, 1H, 6.2 Hz), 7.11 (d, 1H, 8.2 Hz); ^{13}C nmr (DMSO-d_6) δ 34.9, 64.2, 83.6, 87.5, 102.0, 136.2, 168.2;uv:λ_{max} (EtOH)= 245, 265 nm. Anal. Calcd for $C_7H_{10}N_2O_5S_2$· C 31.57; H 3.79; N 10.52, Found C 31.75; H 3.89; N 10.33. **9** mp 126-130°C (decomp.): ^{1}H Nmr (DMSO-d_6) δ 3.10 (dd, 1H, 4.2 Hz, 11.6 Hz), 3.31 (s), 3.37 (dd, 1H, 6.1 Hz, 11.6 Hz), 3.44 (q, 1H, 5.8 Hz), 3.56 (q, 1H, 5.7 Hz), 5.05 (d, 1H, 8.2 Hz), 5.16 (t, 1H, 5.8 Hz), 5.28 (t, 1H, 5.3 Hz), 5.97 (t, 1H, 4.5 Hz), 7.50 (d, 1H, 8.2); ^{13}C nmr (DMSO-d_6) δ 35.7, 65.2, 85.6, 87.8, 101.8, 136.3, 168.3;uv:λ_{max} (EtOH)=245, 266 nm. Anal. Calcd for $C_7H_{10}N_2O_5S_2$. C 31.57; H 3.79; N 10.52, Found C 31.64; H 3.99, N 10.60.

***cis* and *trans*-2-Hydroxymethyl-5-(5',6',-dihydro-4'-methyl-1',1',5'-trioxo-2'*H*-1',2',6'-thiadiazin-2'-yl)-1,3-oxathiolane (10 and 11).** 3-Methyl-2*H*,6*H*-1,2,6-thiadiazin-3-one 1,1-dioxide **(5)** (0.97 g, 6.00 mmol) and hexamethyldisilazane (60 ml, 0.28 mol) were refluxed in pyridine (20 ml) for 8 h, then the solution was evaporated *in vacuo* to dryness and the residual solid was left on high vacuum for 2 h. To this solid **3** (1.41 g, 5.00 mmol) was added MeCN (20 ml), potassium iodide (0.83 g, 5.00 mmol), 18-crown-6 (0.26 g, 1.00 mmol) and toluene (20 ml) and refluxed for 25 h. Then the cold reaction mixture was treated with triethylamine (1.04 ml, 7.50 mmol) and filtered through a short silica gel column to remove inorganic salts. The filtrate was concentrated to dryness and purified by column chromatography (ethyl acetate, followed by gradient addition of 1-10% methanol in ethyl acetate). The fractions containing the products were concentrated to dryness and the residue was suspended in a small volume of ethyl acetate, filtered and washed with cold ethyl acetate. The filtrate was concentrated to dryness to give the protected nucleosides. The mixture of the protected nucleoside (0.75 g, 1.95 mmol) and potassium carbonate (0.20 g, 1.46 mmol) was dissolved in methanol (45 ml) and stirred for 2 h. Ion exchange resin (Amberlite, IRC-50, 4.00 g) was added and further stirring continued for 15 min. The resin was filtered and the filtrate was evaporated to dryness *in vacuo*. The crude product consisting of **10** and **11** was purified by silica gel chromatography (ethyl acetate, followed by gradient addition of 5-20% methanol in ethyl acetate). After purification, the isomeric mixtures (0.55 g, 39.0%) were separated by preparative hplc as outlined in the general procedures. **10** mp 127-128°C: ^{1}H Nmr (DMSO-d_6), δ 1.66 (s, 3H), 3.03 (dd, 1H, 7.4 Hz, 11.0 Hz), 3.16 (dd, 1H, 5.5 Hz, 11.0 Hz), 3.61 (m, 2H), 5.05 (t, 1H, 4.9 Hz), 5.19 (t, 1H, 5.9 Hz), 5.69 (dd, 1H, 5.8 Hz, 6.7 Hz), 6.95 (s, 1H); ^{13}C nmr (DMSO-d_6) δ 15.5, 34.3, 64.4, 83.0, 87.6, 109.1, 131.9, 168.6;

uv:λ_{max}(EtOH)=245, 272 nm. Anal. Calcd for $C_8H_{12}N_2O_5S_2$: C 34.29; H 4.32; N 10.00, Found C 34.07; H 3.97; N 10.21 **11** mp 129-130°C (decomp.): ^{1}H Nmr (DMSO-d_6) δ 1.80 (s, 3H) 3.10 (dd, 1H, 4.7 Hz, 11.5 Hz), 3.34 (dd, 1H, 6.0 Hz, 11.5 Hz), 3.51 (m, 2H), 5.16 (t, 1H, 5.8 Hz), 5.28 (t, 1H, 5.2 Hz), 5.96 (t, 1H, 4.9 Hz), 6.96 (s, 1H); ^{13}C nmr (DMSO-d_6) δ 15.6, 35.3, 65.2, 85.3, 87.7, 108.7, 132.4, 168.8; uv:λ_{max} (EtOH)=245, 273 nm. Anal. Calcd for $C_8H_{12}N_2O_5S_2$: C 34.29; H 4.32; N 10.00, Found C 34.01; H 4.16; N 9.69.

***cis* and *trans*-2-Hydroxymethyl-5-(5'-amino-1',1'-dioxo-2'*H*-1',2',6'-thiadiazin-2'-yl)-1,3-oxathiolane (12 and 13).** 3-Amino-6*H*-1,2,6-thiadiazine 1,1-dioxide **(6)** (0.74 g, 5.00 mmol), oxathiolane **(3)** (1.41 g, 5.00 mmol) and potassium nonaflate (4.06 g, 12.00 mmol) were dissolved in dry MeCN (7 ml), then hexamethyldisilazane (0.74 g, 3.50 mmol) and trimethylsilylchloride (1.9 ml, 15.00 mmol) were added. After refluxing for 18 h, the reaction mixture was cooled to 20°C and poured onto a saturated solution of sodium bicarbonate (50 ml), extracted with dichloromethane (4 x 50 ml) and the combined organic phases were washed with water (50 ml), dried over sodium sulfate and concentrated to dryness. The monobenzoated derivatives were separated by column chromatography on silica gel (5-20% ethyl acetate in toluene). To the solution of the protected nucleoside (0.83 mmol) in methanol (100 ml) was added potassium carbonate (82 mg, 0.60 mmol) and the solution was stirred overnight at 20°C. The solvent was evaporated *in vacuo* and the crude product was purified by column chromatography on silica gel using ethyl acetate as eluent. **12** mp 46-48°C: ^{1}H Nmr (DMSO-d_6) δ 3.18 (dd, 1H, 5.6 Hz, 11.6 Hz), 3.43 (dd, 1H, 5.6 Hz, 11.6 Hz), 3.70 (m, 2H), 5.19 (t, 1H, 4.7 Hz), 5.32 (t, 1H, 5.9 Hz), 5.61 (d, 1H, 8.2 Hz), 5.88 (t, 1H, 5.7 Hz), 7.64 (d, 1H, 8.2 Hz), 7.86 (br s, 1H), 7.91 (br d, 2H); ^{13}C nmr (DMSO-d_6) δ 36.1, 63.6, 85.2, 87.1, 93.9, 141.2, 162.6; uv: λ_{max} (EtOH)=254, 282 nm. Anal. Calcd for $C_7H_{11}N_3O_4S_2$: C 31.70; H 4.18; N 15.95, Found C 32.07, H 4.21, N 15.55. **13** mp 48-50°C: ^{1}H Nmr (DMSO-d_6) δ 3.25 (dd, 1H, 3.5 Hz, 12.0 Hz), 3.53 (dd, 1H, 5.9 Hz, 11.9 Hz), 3.59 (m, 2H), 5.26 (br s, 1H), 5.44 (t, 1H, 5.0 Hz), 5.59 (d, 1H, 8.0 Hz), 6.12 (dd, 1H, 3.4 Hz, 5.8 Hz), 7.52 (d, 1H, 8.0 Hz), 7.89 (br d, 2H), 7.95 (br s, 1H); ^{13}C nmr, (DMSO-d_6), δ 36.3, 65.0, 86.7, 88.3, 93.6, 141.5, 162.8; uv:λ_{max} (EtOH)=251, 283 nm. Anal. Calcd for $C_7H_{11}N_3O_4S_2$: C 31.70; H 4.18; N 15.95, Found C 32.03, H 4.16, N 15.53.

***cis* and *trans*-2-Hydroxymethyl-5-(4'-amino-1'-benzyl-2',2'-dioxo-1'*H*,7'H-imidazo-[4',5'-*c*][1',2',6']- thiadiazin-7'-yl)-1,3-oxathiolane (14, 15) and *cis* and *trans*-2-hydroxymethyl-5-(4'-amino-1'-benzyl-2',2'-dioxo-1'*H*,5'*H*-imidazo[4',5'-*c*][1',2',6']thiadiazin-5'-yl)- 1,3-oxathiolanes (16, 17).** The mixture consisting of base **(7)** (3.00 g, 10.82 mmol), pyridine (6 ml) and hexamethyldisilazane (90 ml, 0.43 mol) was refluxed for 2 h, then the solution was evaporated to dryness *in vacuo*. Oxathiolane **(3)** (3.39 g, 12.00 mmol) in 1,2-dichloroethane (60 ml) and trimethylsilyl triflate (0.5 ml, 2.64 mmol) were then added to the residue and the mixture was refluxed for 2 h. The reaction mixture was then poured onto a saturated solution of sodium bicarbonate (60 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic phases were dried over $MgSO_4$ and evaporated to dryness.

The crude product was purified by column chromatography on silica gel (hexanes/ethyl acetate 2/3). The suspension of the protected nucleoside of **14** and **15** (0.50 g, 1.00 mmol), potassium carbonate (0.50 g, 3.62 mmol) in methanol (5 ml) was stirred at ambient temperature for 1 h. Ion exchange resin (Amberlite, IRC 50, 5.00 g) was added and stirring was continued for 15 min. The resin was then filtered and the filtrate was evaporated to dryness to afford a mixture of isomers (**14** and **15**) which were separated by hplc as outlined in the general procedure section. **14** mp 211-213°C: ^{1}H Nmr (DMSO-d_6) δ 3.2-3.8 (m, 4H), 4.85 (d, 1H, 14.4 Hz), 4.95 (d, 1H, 14.4 Hz), 5.19 (t, 1H, 4.8 Hz), 5.50 (br s, 1H), 6.07 (t, 1H, 4.3 Hz), 7.30 (s, 5H), 8.12 (s, 1H), 8.18 (br s, 1H); ^{13}C nmr (DMSO-d_6) δ 35.3, 54.5, 63.4, 85.8, 86.3, 119.1, 127.9, 128.3 (overlapping 3 carbons), 134.7, 135.6, 139.4, 158.8; uv:λ_{max} (EtOH)= 227, 281 nm. Anal. Calcd for $C_{15}H_{17}N_5O_4S_2$: C 45.57; H 4.33; N 17.72; S 16.19, Found C 45.16, H 4.61, N 17.49, S 16.13. **15** mp 194-196°C: ^{1}H Nmr (DMSO-d_6) δ 3.2-3.7 (m, 2H), 4.85 (d, 1H, 15.6 Hz), 4.97 (d, 1H, 15.6 Hz), 5.30 (t, 1H, 5.2 Hz), 6.41 (t, 1H, 3.5 Hz), 7.25 (s, 5H), 8.03 (s, 1H) 8.18 (br s, 2H); ^{13}C nmr (DMSO-d_6) δ 35.7, 54.6, 64.2, 86.2, 86.3, 119.4, 128.0, 128.2, 128.4, 134.3, 135.4, 139.2, 158.8; uv:λ_{max} (EtOH)= 226, 281 nm. Anal. Calcd for $C_{15}H_{17}N_5O_4S_2$: C 45.57; H 4.33; N 17.72; S 16.19, Found C 44.94, H 4.51, N 17.35, S 15.98. Deprotection of benzoylated **16** and **17** was performed in a similar fashion. **16** mp 112-114°C: ^{1}H Nmr (DMSO-d_6) δ 3.25-3.75 (m, 2H), 4.99 (s, 2H), 5.36 (t, 1H, 4.3 Hz), 5.52 (t, 1H, 5.2 Hz), 6.38 (t, 1H, 5.5 Hz), 7.20-7.45 (m, 5H), 8.25 (s, 1H); ^{13}C nmr (DMSO-d_6) δ 35.2, 47.1, 62.1, 84.6, 87.6, 102.6, 127.4, 127.8, 128.4, 137.3, 142.5, 152.6, 153.2; uv:λ_{max} (EtOH)=240, 249, 300 nm. Anal. Calcd for $C_{15}H_{17}N_5O_4S_2$: C 45.57; H 4.33; N 17.72; Found C 45.25, H 4.74, N 17.85. **17** mp 121-123°C (decomp.): ^{1}H Nmr (DMSO-d_6) δ 3.2-3.8 (m, 2H), 4.95 (s, 2H), 5.22 (t, 1H, 5.2 Hz), 5.82 (t, 1H, 5.3 Hz), 6.72 (d, 1H, 3 5 Hz), 7.2-7.4 (m, 5H), 8.19 (s, 1H); ^{13}C nmr (DMSO-d_6) δ 34.8, 46.9, 64.3, 85.8, 87.6, 103.0, 127.4, 127.8, 128.3, 137.3, 141.3, 152.7, 152.8; uv:λ_{max} (EtOH)= 238, 248, 300 nm. Anal. Calcd for $C_{15}H_{17}N_5O_4S_2$: C 45.57; H 4.33; N 17.72; Found C 45.31, H 4.73, N 17.72.

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9. Compound (**4**) was prepared by condensation 1,3-bissilysulfamide with 3,3-diethoxyethyl propionate followed by hydrolysis. Compound (**5**) was obtained in a similar fashion using 2-methyl-3,3-diethoxyethyl acetate and **6** was synthesized from ethoxy methylidine malononitrile and the silylsulfamide see: T.L. Su, B. Bennua, H. Vorbrüggen, and H.J. Lindner, Chem. Ber., 1981, **114**, 1269.

10. The benzyl derivative (**7**) was prepared by chemoselective benzylation of the parent heterocycle at N1 ($PhCH_2Br$, $NaOH/H_2O$, 94%) according to the procedure reported in P. Goya, C. Ochoa, and M. Stud., Heterocycles, 1981, **16**, 525. For a review on thiadiazines see: V.J. Aran, P. Goya, and C. Ochoa, "Advances in Heterocyclic Chemistry", Vol. 44, ed. by A.R. Katritzky, Academic Press, Inc., London, 1988, 81-197.

11. H. Vorbrüggen and B. Bennua Chem. Ber., 1981, **114**, 1279.

12. Details of the antiviral assays are given in reference 2.

13. During the revision of this manuscript a derivative of 1,2,4-benzothiadiazine-1-oxide (NSC 287474) was reported to be a specific inhibitor of HIV-1. R.W. Buckheit, Jr., V. Fliakas-Boltz, W.D. Decker, J.L. Roberson, C.A. Pyle, E.L. White, B.J. Bowdon, J.B. McMahon, M.R. Boyd, J.P. Bader, D.G. Nickell, H. Barth and T.K. Antonocci, Antiviral Res., 1994, **25**, 43.

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