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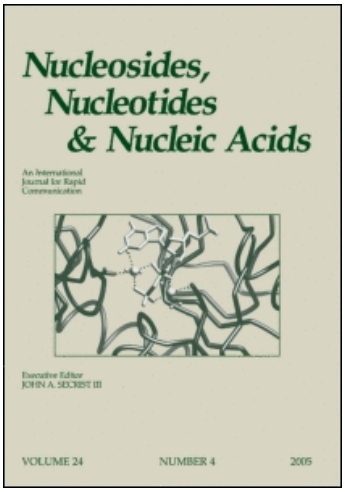

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Synthesis and Antiviral Activity of Modified 1,2,6-Thiadiazine Dioxide Acyclonucleosides

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF MODIFIED 1,2,6-THIADIAZINE DIOXIDE ACYCLONUCLEOSIDES

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ABSTRACT: Modified 1,2,6-thiadiazine dioxide acyclonucleosides were synthesized using the silylation method. All the compounds were tested as antiviral agents in a wide variety of assay systems. With two compounds, some activity (20, 35 and 14 μg/mL, respectively) was noted against herpes simplex virus, human cytomegalovirus and varicella-zoster virus.

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INTRODUCTION

In the past few years, a large number of acyclonucleosides have been synthesized in an attempt to develop new antiviral agents.[1-2] Active compounds are generally considered to exhibit antiviral activities after being converted to their triphosphates. For example, the anti-HSV agent acyclovir, 9-[(2-hydroxyethoxymethyl]guanine,[3] is monophosphorylated by HSV thymidine kinase[4] and then further converted to the corresponding triphosphate by cellular enzymes. Recent observations with new antiviral acyclonucleoside, especially those related to HEPT,[5] suggest that the presence of a terminal hydroxyl group in the side chain is not necessary for activity.[6] Based on this assumption, a great variety of acyclonucleoside analogues in which the acyclic portion is altered so that it cannot be phosphorylated[7] have been developed. Introduction in the acyclic portion of unsaturated and lipophilic moieties have resulted in compounds with a promising antiviral activity.[8-9]

Considering this background and continuing our work in this field,[10] we report here the synthesis and antiviral activities of modified 1,2,6-thiadiazine dioxide acyclonucleosides.[11]

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As base selectivity is an important problem frequently associated with the design of new biologically active nucleosides and acyclonucleosides,[12] we have chosen SO_2 analogs of natural pyrimidinic bases, cytosine and uracil, and related compounds (Figure 1). Those compounds that contain a NH-SO_2-NH moiety, as well as the nucleosides thereof, have shown interesting biological properties.[13-15]

RESULTS AND DISCUSSION

The thiadiazine dioxides were synthesized according to described procedures,[16-18] which normally involves in the first step, the cyclocondensation of sulfamide with ethoxymethylendicarboxylates in alkaline medium.

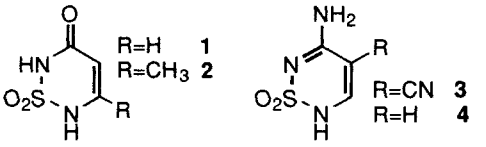
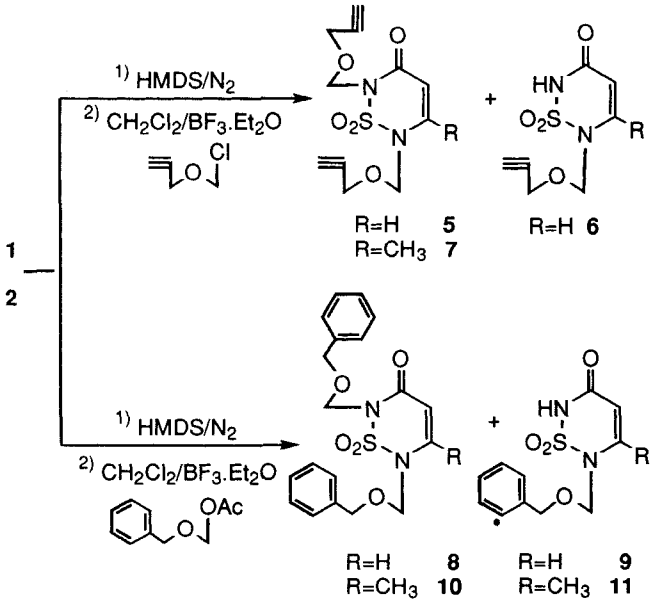


Figure 1

The synthesis of the modified acyclonucleosides was achieved using the silylation procedure,[19] thus uracil related thiadiazines **1** and **2** were first silylated using hexamethyldisilazane under nitrogen atmosphere.



Scheme 1

Reaction of these silyl derivatives with (propargyloxy)methyl chloride[8] or acetoxymethyl benzyl ether,[20] in dichloromethane and boron trifluoride as catalyst, afforded a mixture of compounds from which N(2),N(6)-disubstituted analogs and the N(6)-monosubstituted derivatives could be isolated (Scheme 1).

The structures of all new compounds were elucidated according to analytical and spectroscopic data, which are presented in the Experimental Section. The site of glycosylation was determined on the basis of nOe experiments. Thus, irradiation in the thiadiazine ring 5-substituent (H or CH_3) showed nOe effect (8-15%) on the singlets at

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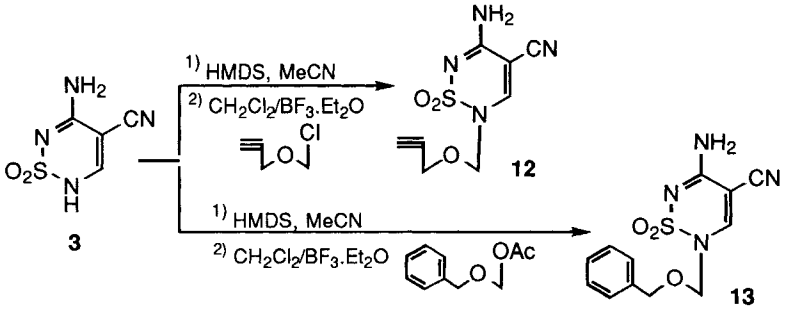
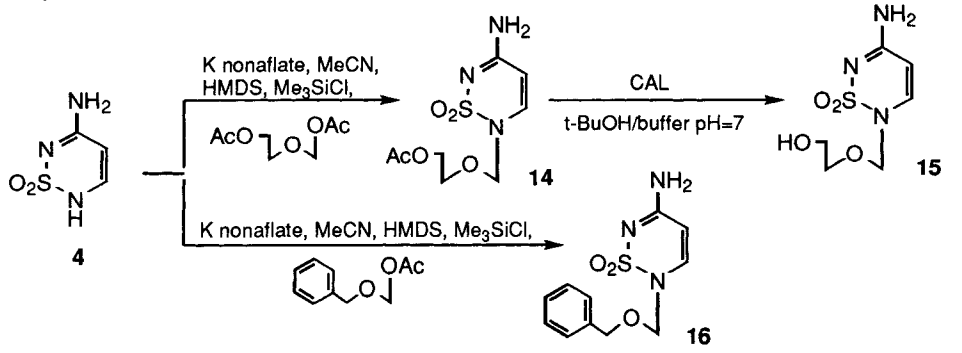
5-5.5 ppm which confirms that the O-CH_2 protons were linked to N(6). Sequences of HMQC for one bond correlation and HMBC for long distance correlations were used for unequivocal assignment of all chemical shifts.

The preparation of the cyanoaminothiadiazine **3** derivatives was accomplished in a similar fashion. It is worth mentioning that acetonitrile as co-solvent was necessary in the silylation step. In both cases, only the N(6)-monoacyclonucleoside was obtained in good yields (Scheme 2).



Scheme 2

However, synthesis of cytosine-related acyclonucleosides was only achieved using potassium nonaflate-1,1,1,3,3,3-hexamethyldisilazane-trimethylsilyl chloride[21] to afford the expected N(6)-derivatives (Scheme 3). This different behavior is probably due to the heterocycle basicity.[17] Deprotection of acyclonucleoside **14** using a lipase-mediated deacylation afforded the acyclonucleoside **15** quantitatively. This previously described methodology,[22] has been applied to the regioselective deacylation of a diacyclic nucleoside of **2**.[23]



Scheme 3

The analytical and spectrospic data of all the newly synthesized compounds are collected in the Experimental Section. NOe experiments were used to determine the site of glycosylation. The ^1H NMR spectra of cyanoacyclonucleosides **12** and **13** show that the protons of the 4-amino group are not equivalent as a result of the hindered rotation around the C-N bond.

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In order to obtain acyclonucleosides with lipophilic side chains, the *tert*-butyl-dimethylsilyl group was introduced by treatment in alkaline medium of the corresponding 2-(hydroxyethoxy)methylderivatives[10] with the *tert*-butyl-dimethylsilyl chloride (Figure 2).

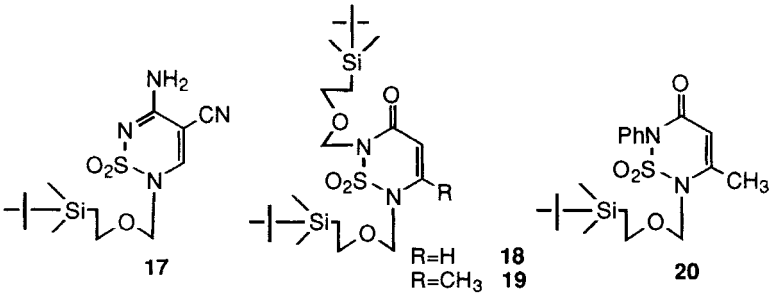

Figure 2

BIOLOGICAL EVALUATION

The new modified 1,2,6-thiadiazine dioxide acyclonucleosides (**5-20**) were evaluated for their antiviral activity in a wide variety of assay systems: herpes simplex virus type 1 (strains KOS, F, McIntyre), herpes simplex virus type 2 (strains G, 196, Lyons), thymidine kinase-deficient (TK^-) herpes simplex virus type 1 (strains B 2006, VMW 1837), vaccinia virus and vesicular stomatitis virus in human embryonic skin-muscles fibroblasts (E_6SM); vesicular stomatitis virus, poliovirus type 1 and Coxsackie B4 virus in HeLa cells; parainfluenza virus type 3, reovirus type 1, Sindbis virus, Coxsackie B4 virus and Semliki forest virus in Vero Cells; human immunodeficiency virus (HIV) types 1 and 2 in T-lymphocyte (MT-4) cells. However, no antiviral activity was noted in any system (at compound concentrations up to 400 μg/mL). Worth mentioning is the activity of compound **17** against HSV-1 (KOS) and HSV-2 (G). This activity was modest (MIC_{50}: 20 and 40 μg/mL, respectively; MCC_{50} > 400 μg/mL), but confirmed in different experiments, and thus may be considered reproducible.

In addition, the acyclonucleosides **5-20** were also evaluated for their activity against cytomegalovirus (CMV, strains AD-169 and Davis) and varicella-zoster virus (VZV, strains OKA, YS, 07/1 and YS/R) in human embryonic lung (HEL) cells. Although the great majority of the compounds did not show an appreciable antiviral activity in this essays (at compound concentrations up to 400 μg/mL), compound **8** showed some activity against CMV and VZV at concentrations (35 and 14 μg/mL, respectively) that were 3- to 10-fold below the cytotoxic concentrations for the host cells.

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These results suggest that the modified 1,2,6-thiadiazine dioxide acyclonucleosides **8** and **17** may serve as new lead compounds in the development of antiviral agents.

EXPERIMENTAL SECTION

Melting points were determined with a Reichert-Jung Thermovar and are uncorrected. CC was performed on Merck silica gel 60 (70-230 mesh).^{1}-H NMR spectra were obtained at 298K using TMS as internal standard on a Varian-Gemini 200 and a Brucker Am-200 at 200 MHz. Double dimension experiments were done with a Varian-Gemini 500 at 500 MHz. The ^{13}-C NMR were recorded with a Varian-Gemini 200 and a Brucker Am-200 at 50 MHz and using TMS as internal reference. *Candida antarctica* lipase used was Novo Nordisk's immobilized preparation Novozym 435.

The heterocyclic bases **1-4** were prepared according to described procedures[16,18].

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General procedure for glycosylation.- To a solution in CH_2Cl_2 (25 mL) of the silyl derivative of the 1,2,6-thiadiazine 1,1-dioxide (1 mmol) prepared by refluxing the base in hexamethyldisilazane (3 mL) under nitrogen using suitable catalyst and co-solvents, the dissolved acyclic moiety precursor (25 mL) was added. The mixture was cooled and BF_3Et_2O was added under vigorous stirring and exclusion of moisture. The resulting mixture was stirred at room temperature for 1 to 3 hours, and then was shaken with saturated $NaHCO_3$ solution (50 mL). The organic phase was separated, dried over sodium sulfate, and evaporated under reduced pressure. The residue was purified in each particular case.

2,6-[di-(propargyloxymethyl)]-1,2,6-thiadiazin-3(2H)-one 1,1-dioxide **(5)** and ***6-propargyloxymethyl-1,2,6-thiadiazin-3(2H)-one 1,1-dioxide*** **(6).-** Following the general procedure, the silyl derivative of **1** (0.296 g, 0.002 mol) [catalyst:TCS (1mL)] in CH_2Cl_2, was treated with (propargyloxy)methyl chloride[8] (0.208 g, 0.002 mol). The mixture was stirred for 1 hour at room temperature. After work-up, the residue was purified on silicagel CC and eluted with CH_2Cl_2:MeOH (100:1) to give **5** (0.068 g, 12%) as a syrup. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.36 (d, 1H, $J_{H\text{-}4,H\text{-}5}$=8.3 Hz, H-5), 5.77 (d, 1H, $J_{H\text{-}4,H\text{-}5}$=8.3 Hz, H-4), 5.40 (s, 2H, N(2)-CH_2O), 5.21 (s, 2H, N(6)-CH_2O), 4.28 (m, 4H, CHCCH_2,), 2.56 (t, 1H, N(2)-CHCCH_2), 2.48 (t, 1H, N(6)-CHCCH_2). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 162.00 (C-3), 104.94 (C-4), 140.48 (C-5), 78.61 (N(6) CHCCH$_2$), 77.44 (N(2)-CHCCH$_2$), 77.30 (N(6)-CH_2O), 71.00 (N(2)-CH_2O), 76.71 (N(6)-CHCCH$_2$), 75.26 (N(2)-CHCCH$_2$)), 57.08 (N(6)-CHCCH_2)), 56.10 (N(2) -CHCCH_2). $C_{11}H_{12}N_2O_5S$. Anal. Calc. C 46.47 H 4.26 N 9.86 S 11.28. Anal. Found. C 46.48 H 4.57 N 9.84 S 11.38.

From the last fractions using CH_2Cl_2:MeOH (25:2) the monoacyclonucleoside **6** (0.082 g, 20%) was obtained as a syrup. ^{1}H-NMR (200 MHz, CD_3OD): δ 7.40 (d, 1H, $J_{H\text{-}4,H\text{-}5}$=8.1 Hz, H-5), 5.59 (d, 1H, $J_{H\text{-}4,H\text{-}5}$=8.1 Hz, H-4) , 5.50 (s, 2H, NCH_2O), 4.28 (m, 2H, CHCCH_2), 2.56 (t, 1H, *CH*CCH$_2$). ^{13}C-NMR (50 MHz,CD_3OD): δ 154.51 (C-3), 143.46 (C-5), 101.21 (C-4), 77.62 (CH*C*CH$_2$), 75.54 (*CH*CCH$_2$), 70.57 (OCH_2N), 57.03 (CHC*CH*$_2$). $C_7H_8N_2O_4S$. Anal. Calc. C 38.89 H 3.73 N 12.96 S 14.83. Anal. Found. C 38.98 H 3.58 N 12.92 S 14.58.

2,6 -[di-(propargyloxymethyl)]-5-methyl-1,2,6-thiadiazin-3(2H)-one 1,1-dioxide **(7).-** Following the general procedure, the silyl derivative of **2** (0.486 g, 0.003 mol) [catalyst:$SO_4(NH_4)_2$] in CH_2Cl_2, was treated with (propargyloxy)methyl chloride[8] (0.314 g, 0.003 mol). The mixture was stirred for 1 hour at room temperature. After work-up, the residue was purified on silicagel CC and eluted with CH_2Cl_2:MeOH (100:1) to give **7** (0.375 g, 42%) as a syrup. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.74 (s, 1H, H-4), 5.36 (s, 2H, N(2)-CH_2O), 5.23 (s, 2H, N(6)-CH_2O), 4.27 (d, 2H, $J_{CH,CH2}$=2.2 Hz, N(2) CHC*CH*$_2$), 4.21 (d, 2H, $J_{CH,CH2}$=2.2 Hz, N(6) CHC*CH*$_2$), 2.48 (m, 2H, *CH*CCH$_2$), 2.27 (s, 3H, CH_3-5). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 161.95 (C-3), 108.04 (C-4), 151.01 (C-5), 79.20 (N(6)-CH*C*CH$_2$), 78.31 (N(2)-CH*C*CH$_2$), 75.17 (N(6)-CH_2O), 71.33 (N(2)-CH_2O), 76.27 (N(6)-*CH*CCH$_2$), 75.58 (N(2)-*CH*CCH$_2$)) 57.44 (N(6)-CHC*CH*$_2$), 56.97 (N(2)-CHC*CH*$_2$), 20.14 (CH_3-5). $C_{12}H_{14}N_2O_5S$. Anal. Calc. C 48.31 H 4.73 N 9.39 S 10.75. Anal. Found. C 48.47 H 4.76 N 9.44 S 10.86.

2,6-[di-(benzyloxymethyl)]-1,2,6-thiadiazin-3(2H)-one 1,1-dioxide **(8)** and ***6-benzyloxymethyl-1,2,6-thiadiazin-3(2H)-one 1,1-dioxide*** **(9).-** According to the general procedure, the silyl derivative of **1** (0.296 g, 0.002 mol) [catalyst:TCS (1mL)] in CH_2Cl_2, was treated with acetoxymethyl benzyl ether[20] (0.360 g, 0.002 mol). The mixture was stirred for 1 hour at room temperature. After work-up, the residue was purified on silicagel CC and eluted with CH_2Cl_2:MeOH (100:1) to give **8** (0.078 g, 10%) as a syrup. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.41-7.25 (m, 10H, Ph), 7.07 (d, 1H, $J_{H\text{-}4,H\text{-}5}$=8.3 Hz, H-5), 5.74 (d, 1H, $J_{H\text{-}4,H\text{-}5}$=8.3 Hz, H-4), 5.38 (s, 2H, N(2)-CH_2O), 5.11 (s, 2H, N(6)-CH_2O), 4.67 (s, 2H , N(2)-CH_2-Ph), 4.61 (s, 2H, N(6)-CH_2-Ph). ^{13}C-NMR(50 MHz, $CDCl_3$) : δ 162.67 (C-3), 105.46 (C-4), 140.68 (C-5), 137.45 (C*i*), 136.36 (C*i*), 129.17 (C*p*), 128.92 (C*m*), 128.54 (C*o*), 78.60 (N(6)-CH_2O), 72.31 (N(2)-CH_2O), 71.98 (N(6)-CH_2-Ph), 71.72 (N(2)-CH_2-Ph). $C_{19}H_{20}N_2O_5S$ Anal. Calc. C 58.75 H 5.19 N 7.21 S 8.25. Anal. Found. C 58.45 H 5.40 N 7.14 S 8.20.

From the last fractions using CH_2Cl_2:MeOH (25:2) the monoacyclonucleoside **9** (0.178 g, 33%) was obtained as a syrup. ^{1}H-NMR (200 MHz, CD_3OD): δ 7.54-7.45 (m, 10H, Ph), 7.39 (d, 1H, $J_{H\text{-}4,H\text{-}5}$=8.1 Hz, H-5), 5.61 (d, 1H $J_{H\text{-}4,H\text{-}5}$=8.1 Hz, H-4,), 5.30 (s, 2H, NCH_2O), 4.97 (s, 2H, CH_2-Ph). ^{13}C-NMR (50 MHz, CD_3OD) : δ 100.97

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(C-4), 143.60 (C-5), 138.78 (C*i*), 129.38 (C*m*), 129.13 (C*p*), 128.85 (C*o*), 78.73 (NCH_2O), 71.98 (CH_2-Ph). $C_{11}H_{12}N_2O_4S$. Anal. Calc. C 49.24 H 4.51 N 10.44 S 11.95. Anal. Found. C 49.48 H 4.58 N 10.38 S 11.84.

2,6-[di-(benzyloxymethyl)]-5-methyl-1,2,6-thiadiazin-3(2H)-one 1,1-dioxide **(10)** and ***6-benzyloxymethyl-5-methyl-1,2,6-thiadiazin-3(2H)-one 1,1-dioxide*** **(11).-** According to the general procedure, the silyl derivative of **2** (0.364 g, 0.002 mol) [catalyst:$SO_4(NH_4)_2$], was treated with acetoxymethyl benzyl ether[20] (0.352 g, 0.002 mol). The mixture was stirred for 2 hours at room temperature. After work-up, the residue was purified on silicagel CC and eluted with CH_2Cl_2:MeOH (100:1) to give **10** (0.140 g, 18%) as a syrup. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.27-7.17 (m, 10H, Ph), 5.69 (d, 1H $J_{H\text{-}4,CH3}$=1.0 Hz, H-4,), 5.29 (s, 2H, N(2)-CH_2O), 5.14 (s, 2H, N(6)-CH_2O), 4.60 (s, 2H , N(2)-CH_2-Ph), 4.53 (s, 2H, N(6)-CH_2-Ph), 2.21 (d, 3H, $J_{H\text{-}4,CH3}$=1.0 Hz, CH_3-5). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 161.68 (C-3), 150.64 (C-4), 137.08, 136.28, 128.58, 128.37, 127.98, 127.86 (C-arom), 107.39 (C-4), 75.66 (N(6)-CH_2O), 71.66 (N(2)-CH_2O), 71.51 (N(6)-*C*H_2-Ph), 71.30 (N(2)-*C*H_2-Ph). 19.70 (CH_3-5). $C_{20}H_{22}N_2O_5S$. Anal. Calc. C 59.69 H 5.51 N 6.96 S 7.97. Anal. Found. C 59.71 H 5.56 N 7.01 S 8.10.

From the last fractions using CH_2Cl_2:MeOH (25:2) the monoacyclonucleoside **11** (0.024 g, 4%) was obtained as a syrup. ^{1}H-NMR (200 MHz, CD_3OD): δ 7.54-7.45 (m, 10H, Ph), 5.61 (s, 1H, H-4), 5.44 (s, 2H, NCH_2O), 4.84 (s, 2H, C*H*$_2$-Ph), 2.41 (s, 3H, CH_3-5). ^{13}C-NMR (50 MHz,CD_3OD): δ 153.23 (C-3), 139.07 (C-5), 129.76, 129.37, 129.06, 128.79 (C-arom), 102.73 (C-4), 74.74 (NCH_2O), 71.34 (C*H*$_2$-Ph), 19.43 (CH_3-5). $C_{12}H_{14}N_2O_4S$. Anal. Calc. C 51.05 H 5.00 N 9.92 S 11.36. Anal. Found. C 51.12 H 4.82 N 10.00 S 11.40.

5-amino-2-propargyloxymethyl-4-cyano-1,2,6-tiadiazin 1,1-dioxide **(12).-** Following the general procedure, the silyl derivative of **3** (0,344 g (0.002 mol) [catalyst: 0.5 ml TCS, cosolvent: 2 ml CH_3CN] in CH_2Cl_2, was treated with (propargyloxy)methyl chloride[8] (0.210g, 0.002 mol). The mixture was stirred for 2 hours at room temperature. After work-up, the residue was purified by crystalization with CH_2Cl_2 to give **12** (0.200 g, 42%).m.p.:148-150°C. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 8.62, 8.20 (s, s, 1H, 1H, NH_2), 8.50 (s, 1H, H-3), 5.15 (s, 2H, OCH_2N), 4.25 (d, 2H, $J_{CH\text{-}CH2}$=1.6 Hz, CHCC*H*$_2$,), 3.54 (t, 1H, $J_{CH\text{-}CH2}$=1.6 Hz, *CH*CCH$_2$). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 159.30 (C-5), 78.47 (C-4), 155.54 (C-3), 114.52 (CN), 78.96 (CH*C*CH$_2$), 78.59 (*C*HCCH$_2$), 78.35 (OCH_2N), 56.08 (CHC*C*H$_2$). $C_8H_8N_4O_3S$. Anal. Calc. C 39.99 H 3.36 N 23.32 S 13.35. Anal. Found. C 39.81 H 3.22 N 23.45 S 12.98.

5-amino-2-benzyloxymethyl-4-cyano-1,2,6-thiadiazine 1,1-dioxide **(13).-** As indicated in the general procedure, the silyl derivative of **3** (0,344 g (0.002 mol)

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[catalyst: 0.5 ml TCS, co-solvent: 2 ml CH_3CN] in CH_2Cl_2, was treated with acetoxymethyl benzyl ether[20] (0.360 g, 0.002 mol). The mixture was stirred for 2 hours at room temperature. After work-up, the residue was purified by crystalization with CH_2Cl_2 to give **13** (0.300 g, 52%).m.p.:158-160°C. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 8.62, 8.20 (s, s, 1H, 1H, NH_2), 8.58 (s, 1H, H-3), 7.33-7.29 (m, 5H, Ph), 5.21 (s, 2H, OCH_2N), 4.59 (s, 2H, CH_2-Ph). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 159.63(C-3). 78.40 (C-4), 155.64 (C-5), 137.17, 128.58, 128.32, 128.12 (C-arom), 114.75 (CN), 80.11 (NCH_2O), 70.49 (CH_2-Ph). $C_{12}H_{12}N_4O_3S$. Anal. Calc. C 49.30 H 4.14 N 19.17 S 10.97. Anal. Found. C 49.28 H 3.94 N 20.05 S 10.86.

Procedure for glycosylation of 3-amino-6*H*-1,2,6-thiadiazine 1,1-dioxide.- To a solution of the base **4** (1 mol), the acyclic moiety precursor (1 mol) and potassium nonaflate (2.4 mol) in 14 ml of dried acetonitrile, hexamethyl disilazane (1 mol) and trimethyl chloro silane (3.1 mol) were added. The mixture was refluxed for 24 hours with exclusion of moisture. After cooling, the mixture was poured into a saturated $NaHCO_3$ solution (25 ml) and extracted with CH_2Cl_2 (5 x 25 ml). The organic layer was dried over sodium sulfate, and evaporated under reduced pressure. The residue was purified as shown in each particular case.

***5-amino-2-[(2-acetoxyethoxy)methyl)-2H-1,2,6-thiadiazine 1,1-dioxide* (14).-** Following the general procedure 0.074 g (0.005 mol) of **4**, 0.406 g (0.012 mol) of potassium nonaflate and 0.088 g (0.005 mol) of 2-acetoxyethyl acetoxy methyl ether,[24] 0.104 ml (0.005 mol) of HMDS and 0.196 ml (0.015 mol) of TCS, were allowed to react. After work-up, the residue was purified on silicagel CC, using as eluent CH_2Cl_2:MeOH (25:1) to give **14** (0.025 g, 20%) as a syrup. ^{1}H-NMR (200 MHz, CD_3OD): δ 7.50 (d, 1H, $J_{H\text{-}3,H\text{-}4}$=8.0 Hz, H-3), 5.79 (d, 1H $J_{H\text{-}3,H\text{-}4}$=8.0 Hz, H-4), 5.28 (s, 2H, NCH_2O), 4.39 (m, 2H, $AcOCH_2$), 3.98 (m, 2H, CH_2O), 2.22 (s, 3H, CH_3CO). ^{13}C-NMR (50 MHz, CD_3OD): δ 172.78 (CO), 150.40 (C-5), 145.73 (C-3), 94.57 (C-4), 80.71 (NCH_2O), 67.83 (CH_2O), 64.34 ($AcOCH_2$), 20.76 (CH_3CO).

***5-amino-2-[(2-hydroxyethoxy)methyl)-2H-1,2,6-thiadiazine 1,1-dioxide* (15).-** To a solution of 0.073 g (0.0003 mol) of **14** dissolved in 30 ml of a solution of *t*-butanol:Buffer pH=7 (10%), 0.300 g of *Candida antarctica* lipase (CAL) were added. The reaction was incubated for 3 hours in an orbital shaker at 250 rpm and 45°C. Then, the enzyme was removed by filtration and solvents were evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water. The organic layer was separated, dried over sodium sulfate and evaporated under reduced pressure to give **15** (0.063 g, 98%) as a syrup. ^{1}H-NMR (200 MHz, CD_3OD): δ 7.52 (d, 1H, $J_{H\text{-}3,H\text{-}4}$=8.0 Hz, H-3), 5.78 (d, 1H, $J_{H\text{-}3,H\text{-}4}$=8.0, H-4), 5.29 (s, 2H, NCH_2O), 3.87 (m, 4H, $OHCH_2CH_2O$). ^{13}C-NMR (50 MHz, CD_3OD): δ 165.32 (C-5), 146.31(C-3), 94.88 (C-4), 80.57 (NCH_2O), 71.93 (CH_2O), 62.41 ($HOCH_2$).

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***5-amino-2-(benzyloxymethyl)-2H-1,2,6-thiadiazine 1,1-dioxide* (16).-** According to the general procedure 0.100 g (0.007 mol) of **4**, 0.552 g (0.016 mol) of potassium nonaflate and 0.088 g (0.005 mol) of acetoxymethyl benzyl ether[20] 0.145 ml (0.005 mol) of HMDS and 0.278 ml (0.015 mol) of TCS, were allowed to react. After work-up, the residue was purified on silicagel CC, using as eluent CH_2Cl_2:MeOH (50:1) to give **16** (0.035 g, 20%), m.p.: 137-39°C. ^{1}H-NMR (200 MHz, CD_3OD): δ 7.55-7.42 (m, 6H, (H-arom+ H-3), 5.76 (d, 1H, $J_{H\text{-}3,H\text{-}4}$=8,0, H-4), 5.31 (s, 2H, NCH_2O), 4.81 (s, 2H, CH_2-Ph). ^{13}C-NMR (50 MHz, CD_3OD): δ 145.74 (C-3), 138.54, 129.41, 129.18, 128.92 (C-arom), 94.56 (C-4), 79.20 (NCH_2O), 71.56 (CH_2-Ph).

General procedure for O-silylation of acyclonucleosides.- To a solution of 0.0001 mol of the deprotected acyclonucleoside[10] in dried pyridine, 0.0004 mol imidazole and 0.0004 mol of a 1.0 M solution of *tert*-butyldimethylsylil chloride (TBDMSCl) in dichloromethane, were added. The mixture was stirred at room temperature. Then, the solvent was evaporated under vacuum and the residue disolved in CH_2Cl_2. This solution was poured into a saturated $NaHCO_3$ solution. The organic layer was washed with brine, dried over SO_4Na_2, filtered and evaporated under reduced pressure and purified as indicated in each case.

***5-amino-4-cyano-2-[2-(t-butyldimethylsilyliloxy)etoxy]methyl]-1,2,6-thiadiazine 1,1-dioxide* (17).-** According to the general procedure, a mixture of 0.235 g (0.009 mol) of 2-hydroxyethoxymethyl derivative,[10] 0.260 g (0.0038 mol) of imidazole and 3.8 ml (0.0038 mol) of TBDMSCl solution, was allowed to react during 24 hours. After work-up the residue was purified by silicagel CC, using as eluent CH_2Cl_2:MeOH (50:1) to give **17** (0.193 g, 55%). m.p.:98-100°C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.62 (s, 1H, NH_2), 8.20 (s, 1H, NH_2), 7.76 (s, 1H, H-3), 5.15 (s, 2H, (NCH_2O), 3.68 (m, 4H, TBDMSCH_2CH_2), 0.82 (s, 9H, $(CH_3)_3C$)), 0.00 (s, 6H, $(CH_3)_2Si$). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 158.90 (C-5), 151.79 (C-3), 113.66 (CN), 79.70 (NCH_2O), 71.59 (CH_2O), 62.28 (TBDMSCH_2), 25.66 (($CH_3)_3C$), 16.31 ($(CH_3)_3C$), 5.36 (($CH_3)_2Si$). $C_{13}H_{24}N_4O_4SSi$. Anal. Calc. C 43.31 H 6.71 N 15.54 S 8.89. Anal. Found. C 42.91 H 6.53 N 15.41 S 8.91

***2,6-[di-[2-(t-butyldimethylsilyloxy)ethoxy]methyl]-1,2,6-thiadiazin-3(2H)-one 1,1-dioxide* (18).-** Following the general procedure, a mixture of 0.288 g (0.1 mol) of 2-hydroxyethoxymethyl derivative,[10] 0.272 g (0.004 mol) of imidazole and 4 ml (0.004 mol) of TBDMSCl solution was stirred during 7 hours. After work-up the residue was purified on silicagel CC, using as eluent hexane:ethyl acetate (2:1) to give **18** (0.360 g, 76%) as a syrup. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.12 (d, 1H, $J_{H\text{-}4\text{-}H\text{-}5}$=8.3 Hz, H-4), 5.75 (d, 1H, $J_{H\text{-}4\text{-}H\text{-}5}$=8.3 Hz, H-5), 5.38 (s, 2H, (N(2)-CH_2O), 5.15 (s, 2H, N(6)-CH_2O), 3.68 (m, 8H, TBDMSCH_2CH_2), 0.88 (s, 18H, $(CH_3)_3C$)), 0.05 (s, 12H,

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$(CH_3)_2Si$). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 162.14 (C-3), 140.13 (C-5), 104.77 (C-4), 79.28 (N(6)-CH_2O), 72.85 (N(2)-CH_2O), 72.85 (N(6)-CH_2O), 71.29 (N(2)-CH_2O), 62.42 (TBDMSCH_2), 25.90 ((CH_3)$_3$C), 18.32 (CH_3)$_3C$), 5.34 ((CH_3)$_2$Si). $C_{21}H_{44}N_2O_7SSi_2$. Anal. Calc. C 48.06 H 8.45 N 5.34 S 6.11. Anal. Found. C 47.70 H 8.16 N 4.70 S 5.71.

5-methyl-2,6-[di-[2-(t-butyldimethylsilyloxy)]ethoxy]methyl-1,2,6-thiadiazin-3(2H)-one 1,1-dioxide **(19).-** Following the general procedure, a mixture of 0.280 g (0.9 mmol) of 2-hydroxyethoxymethyl derivative,[10] 0.246 g (3.6 mmol) of imidazole and 3.6 ml (3.6 mmol) of TBDMSCl solution was stirred during 7 hours. After work-up the residue was purified on silicagel CC, using as eluent hexane:ethyl acetate (2:1) to give **19** (0.365 g, 75%) as a syrup. ^1H-NMR (200 MHz, $CDCl_3$) (): δ 5.68 (d, 1H, $J_{CH3,H-4}$=1,0 Hz, H-4), 5.24 (s, 2H, N(2)-CH_2O), 5.18 (s, 2H, N(6)-CH_2O), 3.64 (m, 8H, TBDMSCH_2CH_2), 2.24 (d, 3H, $J_{CH3,H-4}$=1,0 Hz, CH_3-5,), 0.86 (s, 18H, (CH_3)$_3$C), 0.02 (s, 12H, (CH_3)$_2$Si). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 161.60 (C-3), 150.55 (C-5), 107.16 (C-4), 76.49 (N(6)-CH_2O), 72.66 (N(2)-CH_2O), 71.22 (N(6)-CH_2O), 70.77 (N(2)-CH_2O), 62.36 (N(6)-TBDMSCH_2), 62.23 (N(2)-TBDMSCH_2), 25.87 ((CH_3)$_3$C), 18.14 (CH_3)$_3C$), 5.31, 5.39 ((CH_3)$_2$Si). $C_{22}H_{46}N_2O_7SSi_2$. Anal. Calc. C 49.04 H 8.60 N 5.20 S 5.95. Anal. Found. C 49.44 H 8.95 N 5.11 S 5.61.

5-methyl-2-phenyl-6-[2-(t-butyldimethylsilyloxy)ethoxymethyl]-1,2,6-thiadiazin-3(2H)-one 1,1-dioxide **(20).-** Following the general procedure, to a solution of 0.194 g (0.0006 mol) of 2-hydroxyethoxymethyl derivative,[10] 0.169 g (0.0025 mol) of imidazole and 2.5 ml (0.0025 mmol) of TBDMS solution were added. The mixture was stirred during 48 hours at room temperature. After work-up, the residue was chromatographed on a silicagel column, and eluted with CH_2Cl_2, to give **20** (0.268 g, 98%) as a syrup. ^1H-NMR (200 MHz, $CDCl_3$): δ 7.31-7.48 (m, 5H, H-arom), 5.83 (d, 1H, $J_{CH3,H-4}$=1,0 Hz, H-4), 5.27 (s, 2H, NCH_2O), 3.59 (m, 2H, TBDMSCH_2), 3.71 (m, 2H, CH_2O), 2.30 (d, 3H, $J_{CH3,H-4}$=1,0 Hz, CH_3-5), 0.88 (s, 9H, (CH_3)$_3$C), 0.05 (s, 6H, (CH_3)$_2$Si). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 161.64 (C-3), 149.89 (C-5), 134.0, 129.84, 129.64, 129.43 (C-arom), 108.05 (C-4), 95.73 (NCH_2O), 69.34 (CH_2O), 62.34 (TBDMSCH_2), 25.92 ((CH_3)$_3$C), 18.35 (CH_3)$_3C$), 5.00 ((CH_3)$_2$Si). $C_{19}H_{30}N_2O_5SSi$. Anal. Calc. C 53.49 H 7.09 N 6.57 S 7.52. Anal. Found. C 53.61 H 7.13 N 6.83 S 7.24.

Antiviral Evaluation.- The compounds were evaluated for antiviral activity following established procedures, as reviewed in ref. 25.

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