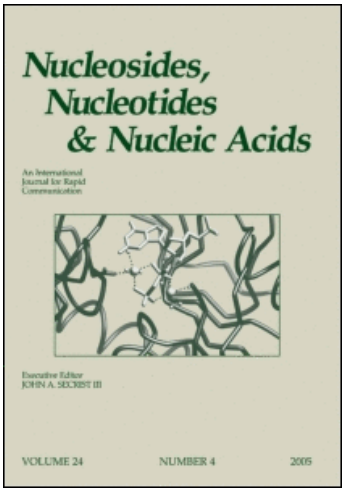

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Ochoa, Carmen , Provencio, Rafael , Jimeno, Maria Luisa , Balzarini, Jan and De Clercq, Erik(1998) 'Synthesis and Anti-HIV Properties of 1,2,4,6-Thiatriazin-3-one 1,1-Dioxtoe Nucleosides', Nucleosides, Nucleotides and Nucleic Acids, 17: 5, 901 — 910
To link to this Article: DOI: 10.1080/07328319808003462
URL: http://dx.doi.org/10.1080/07328319808003462

NUCLEOSIDES & NUCLEOTIDES, 17(5), 901-910 (1998)

SYNTHESIS AND ANTI-HIV PROPERTIES OF 1,2,4,6-THIATRIAZIN-3-ONE 1,1-DIOXIDE NUCLEOSIDES

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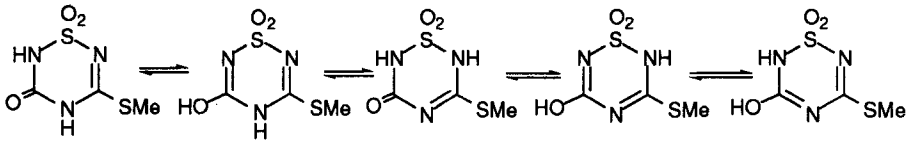
ABSTRACT: Synthesis of 1,2,4,6-thiatriazine 1,1-dioxide nucleosides is now reported for the first time. In order to know the conformation of the nucleosides, a NMR study has been carried out. Anti-HIV-1 and HIV-2 properties of the nucleosides have been tested. These compounds have not shown activity at subtoxic concentrations.

Following our studies on glycosylation reactions of heterocycles containing the sulfamido moiety,[1-7] results on the synthesis of glucosyl and ribosyl derivatives of 5-methylthio-4H-1,2,4,6-thiatriazin-3-one 1,1-dioxide (**1**)[8] are now reported, being the first examples of 1,2,4,6-thiatriazine dioxide nucleosides.

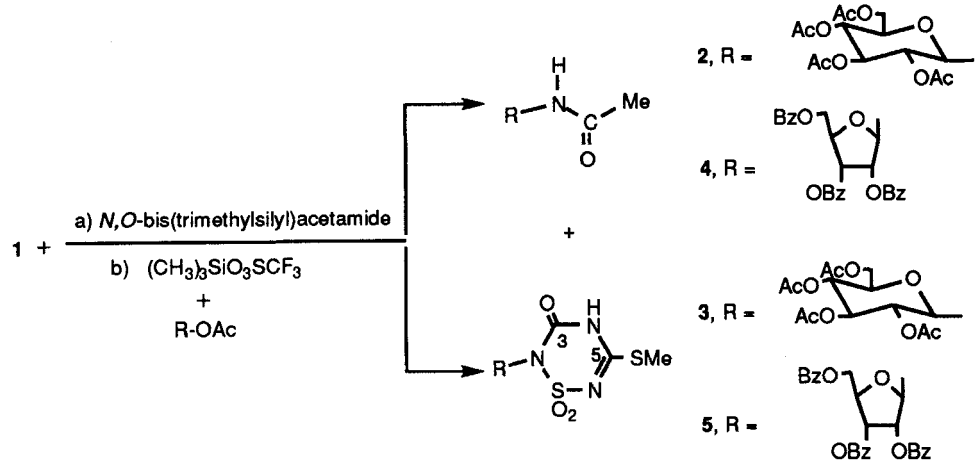
Compound **1** could exist in five tautomeric forms (**1A**, **1B**, **1C**, **1D** and **1E**). Methylation of the parent compound (1,2,4,6-thiatriazine 1,1-dioxide) afforded 4-methyl derivative as unique reaction product.[9] However, glycosylation of **1** could yield N-2, N-4, N-6 and O-mononucleoside isomers as well as several dinucleosides.



1A **1B** **1C** **1D** **1E**

Glycosylation reactions of compound **1** were carried out by using the silyl method in the presence of Friedel-Crafts catalysts. Penta-*O*-acetyl-β-D-glucopyranose, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose and tetra-*O*-acetyl-β-D-ribofuranose were tried as glycosylating agents.

Reactions of **1** with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose were carried out, in refluxing acetonitrile, using *N,O*-bis(trimethylsilyl)acetamide as silylating agent[10] and trimethylsilyl triflate as catalyst (SCHEME 1).



SCHEME 1

Reactions were checked by tlc until the sugar disappeared completely. In the first case, neither starting base nor sugar are visualized under UV light and therefore reaction products were only seen by carbonizing the sugar moiety. Two reaction products were detected in the reaction mixture. However, the absence of sulphur in one of them indicated that only one of the compounds could be a nucleoside of thiatriazine derivative **1**.

Analytical and NMR data confirmed that the *N*-glucopyranosylacetamide **2** together with the nucleoside derivative **3** were obtained. The excess of *N,O*-bis(trimethylsilyl)acetamide used, as well as the fact that acetamide was not removed after the silylation step, allowed the sugar acyloxonium ion to react with trimethylsilylacetamide to yield compound **2**, following the same mechanism as proposed for glycosylation of silylated bases.[11] To our knowledge, the formation of **2** in this type of reaction has not been previously reported, probably due to the fact that this compound is not visualized under UV light and therefore not isolated.

An NMR study of the unique regioisomer nucleoside **3**, allowed its structure to be assigned. ^{1}H- and ^{13}C-NMR data appear in Tables 1 and 2, respectively. Proton and carbon assigments were made by COSY, HMQC and HMBC experiments. Proton H-2' appeared more deshielded than H-1' and the chemical shift of the latter (5.65 ppm) confirmed the presence of an N-nucleoside. Glycosylation position at N-2 was unequivocally established by the correlation shown between the anomeric proton and C-3 in an HMBC experiment.

Two facts are worth mentioning: a) The ^{1}H-NMR spectrum of **3**, registered at 22 °C in DMSO-d6, showed four broadened signals (H-1', H-2', H-3' and H-5'), while the other ones appeared as well resolved sharp multiplets. When the spectrum was registered at 100 °C the broad signals became narrow (Table 1). These facts indicated that a dynamic process took place. In order to reject a tautomeric equilibrium, a few drops of TFA were added and the spectrum

Table 1. ^{1}H-NMR data[a] of nucleosides

Compound	H-1'	H-2'	H-3'	H-4'	H-5'	H-6A'	H-6B'	Others
3[b]	5.65 (d)[c] $J_{1',2'}$=8.6	5.82 (t)[c] $J_{2',3'}$=9.3	5.38 (t)[c] $J_{3',4'}$=9.0	4.92 (t)	4.15 (t)[c]	4.11 (m)	4.11 (m)	2.42 (SCH_3), 2.00, 1.99 1.94, 1.91 (CO-CH_3)
5[d]	6.06 (d) $J_{1',2'}$=2.9	6.13 (dd) $J_{2',3'}$=6.3	6.01 (t) $J_{3',4'}$=6.3	4.61 (m)	4.59 (m)	—	—	7.99, 7.31 (C_6H_5) 2.32 (SCH_3)
6[d]	5.78 (d) $J_{1',2'}$=2.8	5.70 (dd) $J_{2',3'}$=6.4	5.43 (t) $J_{3',4'}$=6.3	3.96 (m)	4.14 (m)	—	—	2.32 (SCH_3), 2.15, 2.09 2.06 (CO-CH_3)
7[d]	5.15 (d) $J_{1',2'}$=8.5	4.75 (t)	4.15(t)	3.75 (m)	3.75 (m)	3.30 (m)	3.15 (m)	7.10 (OH), 2.30 (SCH_3)
8[d]	4.92 (d) $J_{1',2'}$=4.5	4.65 (dd) $J_{2',3'}$=6.5	4.30 (t) $J_{3',4'}$=6.5	3.8-3.6 (m)	3.8-3.6 (m)	—	—	2.40 (SCH_3)

a) δ in ppm and J in Hz.
b) DMSO-d_6 at 100° C.
c) These signals appeared broadened in the spectrum at 22° C.
d) DMSO-d_6 at 22° C.

Table 2. ^{13}C-NMR chemical shifts of nucleosides

Compound	C-3	C-5	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	Others
3[a]	—	169.0	80.7	68.0	72.3	67.5	72.7	61.4	169.6, 169.1 (*CO*-CH_3) 20.1, 20.0, 19.9 (CO-*CH_3*) 13.2 (SCH_3)
3[b]	146.2	169.0	81.0	68.2	72.4	67.6	73.0	61.4	169.6,169.1,168.9 167.3 (*CO*-CH_3), 20.1, 20.0, 19.9 19.8 (CO-*CH_3*), 13.2 (SCH_3)
5[c]	152.7	172.8	86.4	73.8	70.4	77.8	63.7	—	165.5,164.5,164.4 (*CO*-C_6H_6) 133.8-128.5 (C_6H_5) 13.5 (SCH_3)
6[c]	151.5	171.7	86.2	72.4	69.5	78.3	63.0	—	170.1, 169.5, 169,2 (*CO*-CH_3) 22.4, 20.7, 20.2 (CO-*CH_3*) 13.5 (SCH_3)

a) DMSO-d_6 at 80° C. b) DMSO-d6 + F_3C-COOH at 70° C. c) DMSO-d_6 22° C.

registered once more. No changes were observe. Thus, the existence of a restricted rotation about the glycosidic bond at room temperature seemed more probable. A slow *syn-anti* equilibrium at room temperature has been previously described for 1,2,6-thiadiazine 1,1-dioxide nucleosides.[6] b) In the ^{13}C-NMR spectrum registered at 80 °C, the signal corresponding to C-3, which should appear near of 150 ppm,[8] was not observed. By adding a few drops of TFA a broad signal at 146.2 ppm could be seen. This fact indicated that a prototropic equilibrium among possible tautomers took place. This equilibrium was slow enough to be observed in ^{13}C-NMR but not in ^{1}H-NMR.

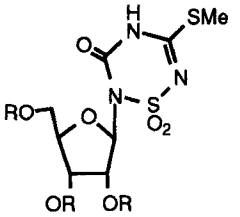
In the reaction of **1** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, regioselective glycosylation took place, as well, and one mononucleoside **5** together with the *N*-ribofuranosylacetamide **4** were obtained.

^{1}H- and ^{13}C-NMR data of compound **5** appear in Tables 1 and 2, respectively. Proton and carbon assigments were made as before. Glycosylation position was established by the correlation shown between the anomeric proton and C-3 in an HMBC experiment. No restricted rotation about the glycosidic bond was observed at room temperature. However, in the ^{13}C-NMR broad signals corresponding to C-3 and C-5 appeared indicating a tautomeric equilibrium among possible **A**, **C** and **E** tautomers.

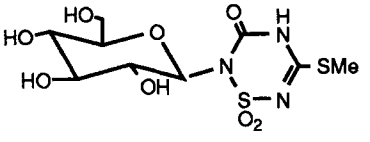
Reactions of **1** with tetra-*O*-acetyl-β-D-ribofuranose were carried out using the same silylating and catalyst agents as mentioned above. Again the reaction was regioselective with only mononucleoside **6** being produced. In this case no glycosylated acetamide was detected, probably due to the fact that the sugar reacted with **1** more quickly than in the other cases.

^{1}H- and ^{13}C-NMR data are gathered in Tables 1 and 2 respectively. The signals corresponding to C-3 and C-5 appear broadened in the ^{3}C-NMR spectrum indicating, once again, a slow tautomeric equilibrium.

Removal of the acetyl protecting groups of nucleosides **3** and **6** with methanolic/ammonia solution yielded the deblocked nucleosides **7** and **8**, respectively. Their ^{1}H-NMR data appear in Table 1. As a consequence of the lower steric hindrance in the deprotected nucleoside **7** comparing to **3**, the *syn-anti* equilibrium is faster in **7**, therefore averaged narrow signals for all protons appeared in its ^{1}H-NMR spectrum at room temperature.



6, R=OAc
8, R=H



7

In order to increase into the knowledge of ribofuranose nucleosides, a study on the conformation adopted by ribofuranose ring of nucleosides **5** and **8**, in DMSO solution, was carried out.

Combination of the pseudorotation concept,[12,13] with solid-state data in furanose rings have shown that, in general, this type of 5-membered ring only appears in two relatively narrow ranges of the total pseudorotational circuit, with N and S conformers,[14] while in solution an N/S equilibrium is possible . The relationships between vicinal coupling constants of the ring protons with the interprotonic torsion angles can be established by the generalized Karplus equation of Altona.[15] Equations to relate the exocyclic proton-proton torsion angles ($\varnothing_{H,H}$) and the endocyclic torsion angles (ν_0-ν_4), the latter interrelated *via* the pseudorotation parameters P and τ, have been parametrized empirically by Altona *et al*[16] for different sugar moieties.

From the experimental data for vicinal coupling constants of **5** and **8**, the pseudorotation parameters corresponding to the ribose conformer present in DMSO solution were calculated (Table 3).

Calculations for nucleoside **5** agree with the existence of a β-nucleoside in which the ribose is found to exist between a twist ($_3T^4$) and an envelope (C4'-exo) conformation, the population of the S conformer being negligible.

Since vicinal coupling constants of nucleoside **6** are very similar to those of **5**, the same conformation for furanose ring is supossed in **6**.

Calculations for **8** showed that its ribose ring has a twist conformation ($_4T^O$), the population of the S conformer being negligible. The conformers of nucleosides **5**, **6** and **8** are outside of the range preferred by most the purine and pyrimidine nucleosides (C3'-*endo*) and that preferred by anti-HIV agents (C3'-*exo*).[17]

Compounds **3**, **5**, **6**, and **7** were evaluated for anti-HIV-1 and anti-HIV-2 activity in human T-lymphocyte (CEM/0) cell cultures (Table 4). None of the nucleosides showed antiviral activity at subtoxic concentrations.

Substitution of a ribosyl for a glucosyl moiety increased the cytotoxicity as well as activity mainly against HIV-1.

EXPERIMENTAL

Microanalyses were obtained with a Hearaeus CHN-O-RAPID instrument and are uncorrected. ^{1}H-NMR spectra were recorded in a Varian-Unity 500 at 500 MHz. ^{13}C-NMR spectra were registered in a Bruker AM-200 at 50 MHz. Bidimensional experiments (COSY, HMQC and HMBC) were obtained under standard conditions. Pseudorotational analysis was performed using the program PSEUROT.[18] Analytical TLC was performed on silica gel 60 F_{254} (Merck). Flash column chromatography was performed with silica gel 60 (230-400 mesh) (Merck). Compounds were detected with with UV light (254 nm) or by spraying the plate with ethanol/sulphuric acid (3/1 v/v) and heating.

Glycosylation Reactions.

General method

To a solution of 1.8 mmol of 5-methylthio-1,2,4,6-thiatriazin-3-one 1,1-dioxide (**1**) in 20 mL of dry acetonitrile, 2.5 mL of *N,O*-bis(trimethylsilyl)acetamide were added. The mixture was heated at 80 °C and stirred during 1 h. Then, a solution of

Table 3. Calculated Pseudorotation Parameters for nucleoside **5** and **8**

Compound	P_N	τ_N	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	RMS[a]
5	45	20	3.04[b]	6.26[b]	6.37[b]	0.115
	2.9[c]	6.3[c]	6.3[c]			
8	72	26	4.35[b]	6.55[b]	6.53[b]	0.115
			4.5[c]	6.5[c]		

a) Residual mean square, in Hz, of calculated coupling constants. b) Calculated constants. c) Experimental constants

Table 4. Anti-HIV-1 and -HV-2 activity of nucleosides in cell culture

Compound	EC_{50} (μg/mL)[a]		CC_{50} (μg/mL)[b]
	HIV-1	HIV-2	
3	>200	>200	>200
5	>40	>40	82±2.1
6	>40	>200	170
7	>200	>200	>200

a) 50% Effective concentration or concentration required to protect CEM cells against the cytopathogenecity of HIV by 50%. b) Cytotoxic concentration or concentration required to reduce CEM cell viability by 50%.

the appropriate sugar (3.6 mmol) in dry acetonitrile (10 mL) and trimethylsilyl triflate (3.6 mol) were added. Reaction mixture was stirred under reflux until the sugar disappeared. Once the reaction finished, ice was added into the flask and the mixture was neutralized at pH 7 with sodium bicarbonate. The aqueous layer was extracted several times with ethyl acetate. The organic phase was dried with sodium sulfate, filtered off and evaporated to dryness. The syrup thus obtained was purified by column chromatography.

5-Methylthio-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-4*H*-1,2,4,6-thiatriazin-3-one 1,1-Dioxide (3). Following the general method, compound **1** (345 mg, 1.8 mmol) was made to react with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (1.3 g, 3.6 mmol). The resulting syrup was chromatographed on a column using hexane/ethyl acetate (1/1) as eluent. The fraction of Rf=0.48 corresponded to nucleoside **3**, which was isolated as a white solid (324 mg, yield 27%), m.p. 160-61 °C.

Anal. Calcd. for $C_{17}H_{23}N_3O_{12}S_2$: C, 38.86; H, 4.38; N, 14.00; S, 12.19. Found: C, 38.61; H, 4.25; N, 13.89; S, 12.15.

***N*(1-deoxy-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranos-1-yl)acetamide (2).** From the above reaction the fraction of Rf=0.31 corresponded to pyranosylacetamide **2** (287 mg, yield 46%), m.p. 161-63 °C (lit,[19] m.p. 161-63 °C). ^{1}H-NMR (DMSO-d_6) δ ppm: 8.60 (d, 1 H, $J_{NH,1'}$=9.6 Hz, NH), 5.35 (t, 1 H, $J_{1',2'}$=9.6 Hz, H-1'), 5.31 (t, 1 H, $J_{2',3'}$=9.6 Hz, H-2'), 4.87 (t, 1 H, $J_{4',5'}$=9.6 Hz, H-4'), 4.80 (t, 1 H, $J_{3',4'}$=9.6 Hz, H-3'), 4.13 (dd, 1 H, J_{gem}=12.2 Hz, H-6a'), 4.04 (t, 1 H, $J_{5',6a'}$=4.5 Hz, H-5'), 3.95 (dd, 1 H, H-6b'), 1.98, 1.97, 1.93, 1.92 (s, 12 H, CH_3COO), 1.82 (s, 3 H, CH_3CONH). ^{13}C-NMR (DMSO-d6) δ: 170.1 (CONH), 170.0, 169.6, 169.4, 169.1 (COO), 76.9 (C-1'), 72.0 (C-5'), 67.8 (C-4'), 61.7 (C-6'), 22.6 ($\underline{CH_3}CONH$), 20.6, 20.4 ($\underline{CH_3}COO$).

The same reaction avoiding the presence of heterocycle **1** was attempted. Compound **2,** identical to that previously obtained, was isolated in 57% yield.

5-Methylthio-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-4H-1,2,4,6-thiatriazin-3-one 1,1-dioxide (5). Following the general method, compound **1** (380 mg, 2 mmol) was made to react with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (2 g, 4 mmol). The resulting syrup was chromatographed on a column using hexane/ethyl acetate (1/1) as eluent. The fraction of Rf=0.38 corresponded to nucleoside **5**, which was isolated as a glass (356 mg, yield 27%), m.p. 86-8 °C.

Anal. Calcd. for $C_{29}H_{25}N_3O_{10}S_2$: C, 54.46; H, 3.91; N, 6.57; S, 10.01. Found: C, 54.39; H, 3.64; N, 6.36; S, 9.85.

***N*(1-deoxy-2,3,5-tri-*O*-benzoyl-β-D-ribofuranos-1-yl)acetamide (4).** From the above reaction the fraction of Rf=0.58 corresponded to furanosylacetamide **4** (440 mg, yield 22%), m.p. 155-56 °C (lit,[20] m.p. 156-58 ° C). ^{1}H-NMR (DMSO-d_6) δ ppm: 8.25 (d, 1 H, $J_{NH,1'}$=10 Hz, NH), 8.15-7.85 (m, 6 H, H_o), 7.67-7.36 (m, 9 H, H_m, H_p), 6.02-5.85 (m, 2 H, H-1', H-2'), 5.65 (t, 1 H, $J_{3',2'}$=$J_{3',4'}$=5.5 Hz, H-3'), 4.70-4.59 (m, 3 H, H-4', H-5a'H-5b'), 1.91 (s, 3 H, CH_3CONH). ^{13}C-NMR (DMSO-d6) δ: 170.0 (CONH), 165.5, 164.8, 164.7,133.8-133.5 (C_i), 129.5-128.6 (C_o, C_m, C_p), 81.7 (C-1'), 77.5 (C-4'), 73.8 (C-3'), 64.2 (C-5'), 22.8 ($\underline{CH_3}CONH$).

The same reaction avoiding the presence of heterocycle **1** was attempted. Compound **4,** identical to that previously obtained, was isolated in 44% yield.

5-Methylthio-2-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-4H-1,2,4,6-thiatriazin-3-one 1,1-dioxide (6). Following the general method, compound **1** (380 mg, 2 mmol) was made to react with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (1.28 g, 4 mmol). The resulting syrup was chromatographed on a column using hexane/ethyl acetate (1/2) as eluent. Nucleoside **6** was isolated as a glass (656 mg, yield 41%), m.p. 70-2 °C.

Anal. Calcd. for $C_{14}H_{19}N_3O_{10}S_2$: C, 37.09 H, 4.19; N, 9.27; S, 15.50. Found: C, 36.87; H, 4.00; N, 8.95; S, 15.36.

5-Methylthio -2-(β -D-glucopyranosyl)-4*H*-1,2,4,6-thiatriazin-3-one 1,1-dioxide (7). Compound **3** (600 mg, 0.9 mmol) was treated with a saturated solution of ammonia/methanol (40 mL) and stirred at room temperature for 4 h. The solution was evaporated to dryness and the residue dissolved in methanol, $CHCl_3$ was added dropwise until the solution became clouded and then cooled in a refrigerator. The solid ammonium acetate was removed by filtration and the solution evaporated to dryness yielding compound **7** as a glass (276 mg, yield 86 %), m.p. 62-4 °C.

Anal. Calcd. for $C_9H_{15}N_3O_8S_2$: C, 30.25; H, 4.20; N, 11.76; S, 17.93. Found: C, 30.18; H, 4.17; N, 11.54; S, 17.52.

5-Methylthio-2-(β-D-ribofuranosyl)-4*H*-1,2,4,6-thiatriazin-3-one 1,1-dioxide (8). From compound **6** (450 mg, 1 mmol) following the same procedure as above compound **8** was obtained as a white solid (252 mg, yield 80 %), m.p.75-6 °C.

Anal. Calcd. for $C_7H_{13}N_3O_7S_2$: C, 26.67; H, 4.13; N, 13.33; S, 20.32. Found: C, 26.53; H, 4.19; N, 13.21; S, 20.14.

Antiretroviral evaluation. CEM cells were obtained from the American Tissue Culture Collection (Rockville, MD). HIV-1 (III_B) and HIV-2 (ROD) were generously provided by Dr. R. C. Gallo (National Cancer Institute, NIH, Betheseda, MD.) and Dr. L. Montaigner (Pasteur Institute, Paris, France), respectively.

The CEM cells were suspended at 250,000 cells/mL of cell culture medium and infected with HIV-1 (III_B) or HIV-2 (ROD) at 100 times the 50% cell culture infective dose ($CCID_{50}$) for mL. Then, 100 µL of the infected cell suspension were added to 200 µL microtiter plate wells containing 100 µL of an appropriate dilution of the test compounds. After 4 days incubation at 37 °C, the cell cultures were examined for syncytium formation. The EC_{50} was determined as the compound concentration required to inhibit syncytium formation by 50%.

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