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The Synthesis and Biological Evaluation of Novel Bridging Nucleoside Analogues

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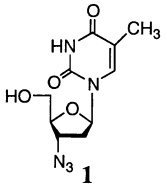
Abstract—Novel bridging nucleoside analogues were prepared by cycloaddition reactions between pyranose glycals and barbiturate-derived, reactive thionoimides in modest yields. In all of the reactions conducted, the major cycloadducts obtained were the bottom faced adducts resulting from endo addition to the glycal. The adducts were stable to a variety of acidic reaction conditions and several of the compounds showed moderate activities against HIV-1 in primary human lymphocytes. One compound displayed anti-herpes simplex virus type-1 activity in Vero cells. Cytotoxicity measurements were also obtained.

Introduction

The discovery that modified nucleoside analogues are potentially effective therapeutic agents for the treatment of acquired immune deficiency syndrome (AIDS) has spurred research into new chemistry for the synthesis of these molecules. Recent examples of selective nucleoside-based antiviral agents are 3′-azido-3′-deoxythymidine (AZT, **1**),[1] lamivudine (3TC, **2**),[3] 9-(2-hydroxyethoxymethyl)guanine (acyclovir, ACV, **3**)[2] and oxetanocin A[4]**4**. In addition to the potential antiviral properties of nucleoside analogues, they are also a very important class of compounds due to their wide range of biological activities as antitumor and antibiotic agents.



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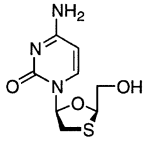

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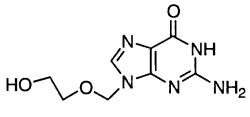

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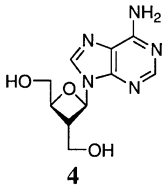

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In recent years, the chemical modification of nucleosides and nucleotides has resulted in compounds that possess improved selectivity in vitro and in vivo, improved activity against mutant viruses, increased oral bioavailability, enhanced cellular uptake and the appropriate hybridization to target genes on mRNA.[5] The substitution of the ring atoms of the sugar moiety with other heteroatoms has also lead to analogues with greater potency. For example, dioxolane[6] and oxathiolane[7] nucleosides have exhibited promising antiviral and anticancer properties. Other changes in the sugar moiety have also been effective. Hexopyranosyl nucleoside analogues have been prepared by Eschenmoser[8] and were found to be highly efficient at duplex formation. Locked nucleic acids in which the conformation of the ring is fixed due to bridging are also believed to be active because of entropically more favorable duplex formation.[9]

In this paper, we describe our results on the synthesis and antiviral activities of a new class of bridging nucleoside analogues. The compounds described are tricyclic derivatives consisting of pyranose sugars, oxathienes and nitrogen-containing heterocyclic rings fused together. These conformationally-restricted nucleoside analogues were prepared by the cycloaddition reactions of glycals with thionoimide precursors. The effectiveness of these compounds against HIV and herpes simplex virus type-1 (HSV-1) and their cytotoxicity in several cell lines will be discussed.

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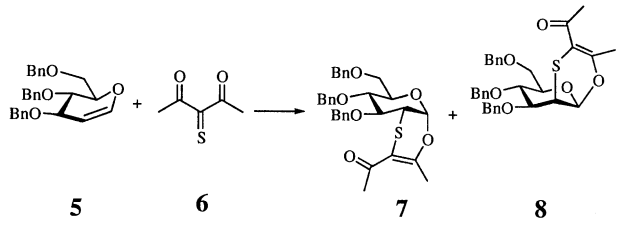
Background and Significance

The barbiturates are a class of compounds closely related to the pyrimidine bases found in many nucleoside analogues; the key difference being an additional carbonyl group present in the heterocyclic ring. *N*-glucuronidation of barbiturates has been determined as the major pathway for the metabolism of these compounds in vivo.[10] However, the *N*-glucuronides are not stable and have consequently not been studied as potential therapeutic agents.[11] Following *N*-glycosylation, the barbiturate rings are more susceptible to hydrolysis and decompose to their corresponding malonurates.[12] *O*-Glucuronidation is normally not a major metabolic pathway for the barbiturates.

Barbituric acid and its *N*-alkylated derivatives possess an enolizable center; two hydrogens on a carbon alpha to two imidic carbonyls. Recently, it was demonstrated that the reagent phthalimidosulfenyl chloride reacts with compounds that possess enolizable hydrogens to produce reactive acylthiones that can be trapped with electron-rich alkenes.[13] Cycloadducts were prepared from a variety of acyl thiones and alkenes. Glycals, which contain a vinyl ether moiety, gave excellent yields of cycloadducts.[14]

For example, when reacted with the acylthione derivative of 2,4-pentanedione **6** was reacted with tri-*O*-benzyl-D-glucal (Scheme 1), both the regioselectivity and facial selectivity of addition to the glycal was high. Some adducts proved to be remarkably stable and only underwent ring opening when further derivatized and activated with strong acids.[15]



Scheme 1.

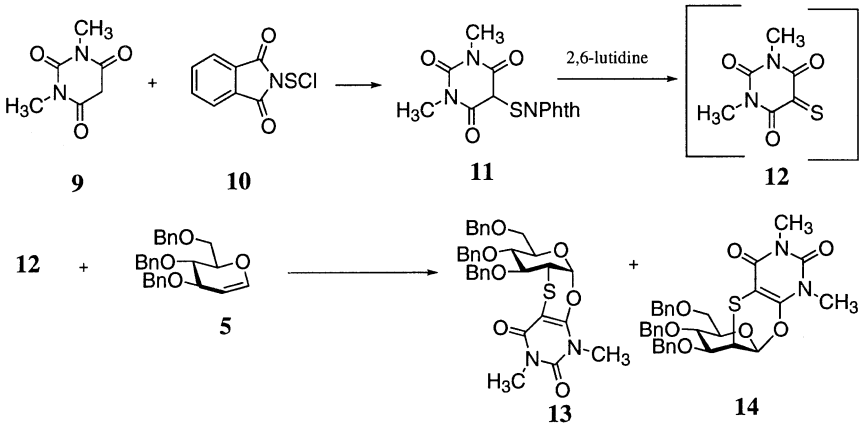
Because of the structural similarity of the barbiturates with the pyrimidine bases and because of the potential high stability of the resulting adducts, we also prepared *O*-linked nucleoside analogues from barbiturate-derived thionoimides and tri-*O*-benzyl-D-glucal using a cycloaddition route.[14] Herein, we report further, detailed results of these synthetic studies with other glycals derived from pyranose and furanose sugars and thionoimides prepared from *N*-protected and unprotected barbituric acid.

Results and Discussion

Synthesis

Treatment of 1,3-dimethylbarbituric acid **9** with phthalimidosulfenyl chloride **10** afforded sulfenylated derivative **11** (Scheme 2). This compound was stable and could be stored in the freezer for months without significant decomposition. When needed, thionoimide **12** was generated in situ by treatment of crude **11** with 2,6-lutidine. When **12** was formed in the presence of glycals, the appearance of products was observed over time. The cycloaddition reactions were monitored by taking aliquots at various time intervals and analyzing them by ^{1}H NMR (300 MHz, $CDCl_3$). Two unique resonances were observed over time corresponding to the anomeric protons of two cycloadducts. Both resonances were doublets; the anomeric proton signal of the bottom face adduct (α-D-anomer) appeared further down field (5.7–5.9 ppm) and had a coupling constant of 2–3 Hz. The minor adduct (β-D-anomer) had a C1 ^{1}H resonance which was more shielded (5.4–5.6 ppm) and a smaller ^3J (1–2 Hz). Both resonances were well separated from the glycal olefinic ^{1}H resonances. When no additional change in the proton NMR was observed, the reaction was stopped.

When **12** was reacted with 3,4,6-tri-*O*-benzyl-D-glucal **5,** a mixture of α-gluco **13** and β-manno cycloadducts **14** (9:1; 64%) was obtained after 48 h. Prolonging the reaction time gave rise to reduced yields of products. Attempts to optimize the reaction yields by changing the reaction solvent from DMF to THF or CH_2Cl_2 were



Scheme 2.

also unsuccessful. It seems likely that the decomposition of the intermediate thionoimide under the reaction conditions of the cycloaddition is responsible for the modest yields of adducts from these reactions. The cycloadducts obtained were easily purified from residual starting materials by silica gel column chromatography.

The stereochemistry of the adducts was further confirmed by NOESY experiments (400 MHz). Irradiation of H1 in adduct **13** produced only a single cross peak (NCH_3), whereas irradiation of H1 in adduct **14** showed four cross-peaks (NCH_3, H2, H3, and H5).

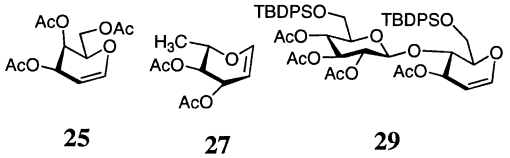
The barbiturate-derived thionoimide **12** reacted with a variety of other protected glucals to give mixtures of adducts (Table 1). In all instances, the bottom-face adduct was obtained as the major product. In addition, the regioselectivity remained constant in all of the reactions tried.

Table 1. Reaction of thionoimide **12** with different protected glucals

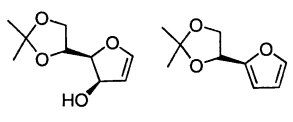
Glucal	Reaction time (days)	Isolated yield of bottom-face adduct	Isolated yield of top-face adduct
$R_1=R_2=R_3=$Bn, **5**	2	58 %, **13**	6 %, **14**
$R_1=R_2=R_3=$Ac, **15**	6	39 %, **16**	10 %, **17**
$R_1=R_2=R_3=$TBDMS, **18**	1	31 %, **19**	< 5 %, **20**
$R_1=$H; $R_2=R_3=$DTBS, **21**	7	46 %, **22**	Nd[a]
$R_1=$H; $R_2=R_3=C(CH_3)_2$, **23**	3	23 %, **24**	Nd

[a]Nd, none detected.

Glycals of other sugars also gave modest yields of cycloadducts (Table 2). The bottom-face cycloadduct **26** was obtained exclusively when tri-*O*-acetyl-D-galactal **25** was used as the glycal. Other sugars that were successfully used were 3,4-di-*O*-acetyl-L-rhamnal **27** and lactal derivative **29.** Attempts to prepare cycloadducts from the ribofuranose glycal **31** were unsuccessful. After 24 h, substantial amounts of decomposition of the sugar had occurred leading to the formation of furan **32**.



25 **27** **29**



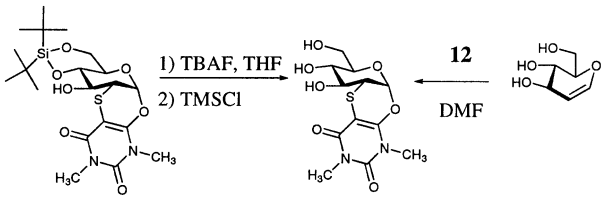
31 **32**

Reaction of thionoimide **12** with the unprotected sugar, D-glucal **33** in DMF, appeared to give rise to one major cycloadduct when monitored by ^1H NMR, however the isolation of the adducts from the reaction mixture proved difficult. In order to obtain the unprotected gluco adduct **34,** compound **22** was desilylated using TBAF[16] (Scheme 3) and the resulting trihydroxy compound was purified by prep TLC (C18).

Table 2. Reaction of thionoimide with other glycals

Glycal	Reaction time (days)	Isolated yield of bottom-face adduct	Isolated yield of top-face adduct
25	4	33 %, **26**	Nd[a]
27	7	11 %, **28**	Nd
29	2	37 %, **30**	Nd
31	1	Nd	Nd

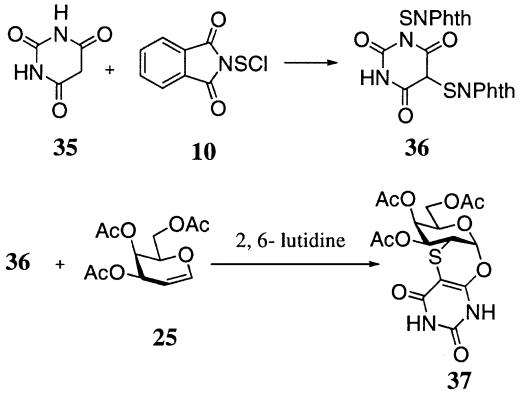
[a]Nd, none detected.



21 **34** **33**

Scheme 3.

The free imido adducts were also accessible from barbituric acid **35** (Scheme 4). Reaction of **35** with an excess of phthalimidosulfenyl chloride afforded **36** in which one of the nitrogens as well as the imide carbon had been sulfenylated. Treatment of **36** with 2,6-lutidine in the presence of 3,4,6-tri-*O*-acetyl-D-galactal **25** for 3 days at rt afforded, after chromatography, 57% of the α-adduct **37** as a single isomer. Apparently, the N–S bond was readily hydrolyzed prior to isolation. The free imido adduct was also prepared from 3,4-di-*O*-acetyl-L-rhamnal **27** (Table 3).



35 **10** **36**

25 **37**

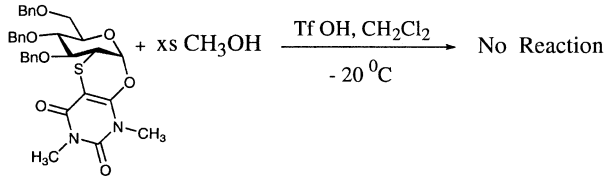
Scheme 4.

Table 3. Reaction of bis-phthalimidosulfenylated barbituric acid with glycals

Glucal	Reaction time (days)	Isolated yield of bottom-face adduct	Isolated yield of top-face adduct
25	3	57 %, **37**	Nd[a]
27	5	35 %, **38**	Nd

[a]Nd, none detected.

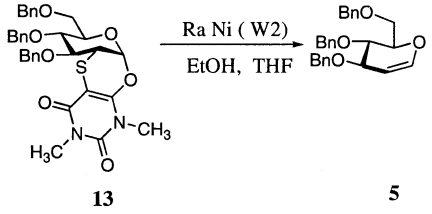
Heteroaryl substituted anomeric groups have been reported to act as excellent glycosyl donors.[17] For this reason, we sought to evaluate the reactivity of our adducts with a variety of glycosylation promoters in methanol. Adduct **13** was treated with triflic acid (1 equiv) in the presence of a large excess of methanol in dichloromethane at −20 °C (Scheme 5). After 3.5 h, only unreacted starting material was obtained following workup of the reaction mixture. Similar results were realized when stoichiometric amounts of TMSOTf were employed with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside (2 equiv) at rt in dichloromethane. When the minor, top faced adduct **14** was subjected to similar conditions, analogous results were obtained.



13

Scheme 5.

We also attempted to cleave the C–S bond of the cycloadduct in order to prepare the 2-deoxy derivatives. Treatment of adduct **13** with Raney nickel (W2) in THF/ethanol resulted in substantial overreduction and formation of 3,4,6-tri-*O*-benzyl-D-glucal **5** as the major product (Scheme 6).



13 **5**

Scheme 6.

Biological evaluation

Several of the compounds prepared were tested against HIV-1 in primary human peripheral blood mononuclear (PBM) cells, and the antiviral activity was expressed by the concentrations (μM) that inhibit 50% of viral replication (EC_{50}) and 90% of viral replication (EC_{90}) (Table 4). In addition the effects of the compounds on the growth of uninfected human PBM, CEM and Vero cells were also determined. Compounds **13**, **14**, **26**, **28**, **30**, and **34** were also tested against HSV-1 using a plaque assay in Vero cells.

As can be seen from the data, four of the compounds (**26**, **28**, **30**, and **38**) showed activity against HIV-1 in human PBM cells. Note that while these compounds are moderately effective against HIV-1, they are also cytotoxic against human PBM and CEM cells. Only one of the compounds tested, **26** showed activity against HSV-1. However, the anti-HSV activity is secondary to the cytotoxic effects in Vero cells; therefore the activity is not specific.

Conclusions

Novel bridging nucleoside analogues were prepared by cycloaddition reactions between glycals and barbiturate-derived reactive thionoimides in modest yields. In all of the reactions carried out, the major cycloadducts obtained were the α-anomeric adducts arising from the preferred endo addition. The cycloaddition reactions were unaffected by changes in the sugar protecting groups or in the nature of the pyranose sugar. Furanose derivatives decomposed to the corresponding furans under the reaction conditions employed. The solubilities of the reactants and the stabilities of the thionoimides had an impact on the yields of adducts obtained. The resulting cycloadducts were stable to acid. Attempts to cleave the C2 carbon–sulfur bond were unsuccessful.

Four of the cycloadducts showed moderate activity against HIV-1 in human PBM cells. These compounds were the bottom face adducts of 1,3-dimethyl barbituric acid with tri-*O*-acetyl-D-galactal (**26**), di-*O*-acetyl-L-

Table 4. Antiviral activity and cytotoxicity of selected cycloadducts[a]

	Anti-HIV-1 activity in PBM cells		Anti-HSV-1 activity in vero cells		Cytotoxicity in:		
					PBM	CEM	Vero
Adduct	EC_{50}, (μM)	EC_{90}, (μM)	EC_{50}, (μM)	EC_{90}, (μM)	IC_{50}, (μM)	IC_{50}, (μM)	IC_{50}, (μM)
13	>100	100	>100	>100	>100	36.5	>100
14	>100	100	>100	>100	>100	>100	>100
34	>100	100	>100	>100	>100	>100	>100
26	13.6	47.7	61.0	>100	39.0	16.7	61.7
30	107	331	>100	>100	100	>100	>100
28	29.0	123	>100	→100	46.2	12.6	>100
37	>100	>100	—	—	>100	>100	>100
38	41.4	100	—	—	70.0	14.3	>100

[a]AZT and acyclovir used as positive controls for the HIV and HSV-1 assays, had an EC_{50} of 0.004 and 0.1 μM, respectively.

rhamnal (**28**), 6,6-di-*O*-(*tert*-butyldiphenylsilyl)-3,2,3,4-tetra-*O*-acetyl-D-lactal (**30**) and the β-adduct of barbituric acid with di-*O*-acetyl-L-rhamnal (**38**). One of these compounds **26**, also showed activity against HSV-1 in Vero cells. From a structure–activity perspective, all of these compounds possess an axially disposed substituent at the C4 position of the sugar in the $^4C_1$ conformation that may account for the observed activities. Deprotection of the hydroxyl groups in the gluco series (**34**) and of the imide nitrogens in both the galacto (**37**) and rhamno (**38**) adducts gave rise to either static or diminished antiviral activities. These compounds were also shown to be cytotoxic in several mammalian cell lines resulting in a therapeutic index of approximately two for the best candidate, the galacto adduct **28**.

Experimental

All reagents were obtained from commercial sources and were used without further purification. Dry DMF was purchased from Aldrich Chemical Company. THF was distilled from Na/benzoquinone ketyl and CH_2Cl_2 was distilled from P_2O_5. Column chromatography was carried out on silica gel (Merck; 230–400 mesh) using gradients of ethyl acetate in petroleum ether. ^1H and ^{13}C NMR spectra were recorded on a Varian EM360 (300 MHz) instrument. These spectra are reported in ppm relative to tetramethylsilane as internal standard. NOESY spectra were recorded on a Jeol 400 MHz spectrometer. Optical rotations were measured in a Rudolph Autopol II polarimeter under standard conditions. Chemical ionization and FAB mass spectra were obtained in the positive ion mode. Microanalyses were performed at Robertson MicrolitLaboratory (Madison, NJ, USA).

1,3-Dimethyl-2-thiophthalimido-barbituric acid (11). To a solution of 1, 3-dimethylbarbituric acid **9** (0.33 g, 2.1 mmol) in dry THF (4 mL) at 5 °C, a solution of phthalimidosulfenyl chloride **10** (0.65 g, 2.3 mmol) in dry CH_2Cl_2 (4 mL) was added. The mixture was stirred for 1 h, then was triturated with *n*-pentane (50 mL) and was warmed to rt. A beige solid was formed and was collected by vacuum filtration and dried in vacuo to afford **11** (0.77g, 1.94 mmol, 92%): ^1H NMR (DMSO-d_6) δ 11.31 (br s), 7.81 (s, 4H), 3.14 (s, 3H), 3.09 (s, 3H); ^{13}C NMR δ 168.9, 163.8, 151.9, 134.1, 132.5, 122.7, 28.3, 28.2.

***N*-2-Bis-thiophthalimido-barbituric acid (36).** To a solution of barbituric acid **35** (0.10 g, 0.78 mmol) in THF (2 mL) at 5 °C was added a solution of phthalimidosulfenyl chloride **10** (0.65 g, 3.0 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 45 min, then warmed to rt and stirred for an additional 15 min. It was triturated with *n*-pentane (20 mL) and the resulting white powder was collected by vacuum filtration (0.59 g, 0.90 mmol): ^1H NMR (DMSO-d_6) δ 11.29 (br s, 1H), 8.93–8.88 (m, 1H), 8.10–7.79 (m, 4H), 2.52 (s, 1H); ^{13}C NMR δ 167.2, 165.8, 146.1, 141.7, 135.5, 134.3, 132.8, 132.0, 127.7, 124.3, 123.1.

General procedure for cycloaddition reactions. To a stirred suspension of glycal (1 equiv) and barbiturate-*S*-phthalimide (1.1 equiv) in dry solvent (0.5–1.0 M concentration) and molecular sieves (3 Å), 2,6-lutidine (1 equiv) was added as a single portion. The mixture was stirred at rt and the reaction progress was monitored by ^1H NMR (300 MHz, $CDCl_3$) until no change in glycal concentration was detected (1–7 days). The mixture was quenched with saturated aq NH_4Cl, and was washed with CH_2Cl_2 (3×). The combined organics were washed with water, then with brine, and were dried ($MgSO_4$), filtered and concentrated in vacuo.

Cycloaddition with 3,4,6-tri-*O*-benzyl-D-glucal. To a solution of 3,4,6-tri-*O*-benzyl-D-glucal **5** (0.19 g, 0.47 mmol) and barbiturate-*S*-phthalimide **11** (0.21 g, 0.52 mmol) in dry DMF (2.5 mL), powdered sieves (0.3 g) and 2,6-lutidine (0.053 mL, 0.47 mmol) were added. The mixture was stirred at rt for 2 days, then was quenched with aq NH_4Cl and worked up as previously decribed. A crude product (0.41 g) was obtained which was chromatographed (SiO_2; 33–55% ethyl acetate in petroleum ether) to afford 3,4,6-tris-*O*-(phenylmethyl)-2-thio-1-*O*,2-*S*-(1,2,3,6 - tetrahydro - 1,3 - dimethyl - 2,6 - dioxo - 4,5 - pyrimidinediyl)-α-D-glucopyranose (**13**) as a white powder (0.16 g, 0.28 mmol, 58%): mp 60–63 °C; $[\alpha]_D$ +84.1° (*c* 0.9, $CHCl_3$). IR (thin film) 2918, 1742, 1702, 1646, 1456, 1362, 1199, 1130, and 1028 cm^{-1}. ^1H NMR δ 7.40–7.26 (m, 13H), 7.17–7.13 (m, 2H), 5.85 (d. 1H, $J=2.7$ Hz), 4.97–4.65 (m, 3H), 4.63–4.52 (m, 3H), 3.95 (dd, 1H, $J=10.1$, 2.7 Hz), 3.86–3.70 (m, 3H), 3.63 (dd, 1H, $J=10.8$, 8.7 Hz), 3.38 (s, 3H), 3.37 (s, 3H), 3.31 (dd, 1H, $J=10.8$, 3.0 Hz); ^{13}C NMR δ 160.3, 151.1, 150.1, 137.5, 137.4, 128.4, 128.3, 127.9, 127.8, 99.8, 80.7, 77.8, 77.1, 75.3, 74.1, 73.6, 67.8, 42.1, 29.1, 28.3. MS (DEP/PCI) (*m*/*z*) (rel. intensity) 434 (100) ($M-C_6H_6O_3N_2S + NH_4^+$). Anal. calcd For $C_{33}H_{34}O_7N_2S{\cdot}H_2O$: C, 63.86; H, 5.80, N, 4.51. Found: C, 63.72, H, 5.93, N, 4.33. Further elution afforded 3,4,6-tris-*O*-(phenylmethyl)-2-thio-1-*O*,2-*S*-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-4,5-pyrimidinediyl)-β-D-mannopyranose **(14)** as an oil (0.02 g, 3.0×10^{-5} mol, 6%): $[\alpha]_D$ +42.9 (*c* 0.3, $CHCl_3$). IR (neat) 3012, 2942, 2883, 1731, 1701, 1637, 1454, 1366, 1261, 1184, 1096, and 1014 cm^{-1}. ^1H NMR δ 7.35–7.26 (m, 13H), 7.17–7.15 (m, 2H), 5.47 (d, 1H, $J=0.9$ Hz), 4.80 (Abq, 2H), 4.57–4.49 (m, 4H), 3.98 (m, 2H), 3.83 (d, 1H, $J=1.8$ Hz), 3.76–3.65 (m, 3H), 3.37 (s, 3H), 3.36 (s, 3H); ^{13}C NMR δ 160.6, 150.1, 149.4, 137.8, 137.7, 137.0, 128.5, 128.4, 128.1, 127.9, 127.8, 123.6, 94.5, 79.7, 76.6, 74.9, 73.5, 73.1, 71.3, 69.1, 40.2, 29.4, 28.4. MS (DEP/PCI) (*m*/*z*) (rel. intensity) 434 (100) ($M-C_6H_6O_3N_2S + NH_4^+$). Anal. calcd for $C_{33}H_{34}O_7N_2S$: C, 65.76; H, 5.69; N, 4.64. Found: C, 65.49; H, 5.94; N, 4.38.

Cycloaddition with 3,4,6-tri-*O*-acetyl-D-glucal. To a solution of tri-*O*-acetyl-D-glucal **15** (0.17 g, 0.6 mmol) and barbiturate-*S*-phthalimide **11** (0.21 g, 0.7 mmol) in dry DMF (2 mL) containing powdered 3 Å molecular sieves (0.15 g), 2,6-lutidine (0.07 mL, 0.6 mmol) was added as a single portion. The mixture was stirred at rt for 6 days, then was worked up in the usual manner. The crude product (0.31 g) was chromatographed (SiO_2,

40–80% ethyl acetate in petroleum ether) and afforded 3,4,6-tri-*O*-acetyl-2-thio-1-*O*,2-S-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-4,5-pyrimidinediyl)-α-D-glucopyranose **(16)** as a white powder (0.12g, 0.2 mmol, 39%): mp 173–176; $[\alpha]_D$ +170.8° (*c* 0.56; $CHCl_3$). IR (thin film) 2950, 1749, 1659, 1588, 1507, 1221, 1144 and 1014 cm^{-1}. ^1H NMR δ 5.89 (d, 1H, *J* = 2.7 Hz), 5.18–5.15 (m, 2H), 4.38–4.31 (m, 1H), 4.26–4.18 (m, 2H), 3.45–3.40 (m, 1H), 3.42 (s, 3H), 3.33 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H); ^{13}C NMR δ 170.3, 169.7, 169.2, 159.9, 150.3, 149.9, 98.1, 80.4, 70.7, 68.4, 67.6, 61.2, 39.9, 28.9, 28.2, 20.5, 20.4, 20.3. MS (ES) (*m*/*z*) (rel. intensity) 295 (26), 357 (100), 459 (M + H) (32), 481 (M + Na) (78), 497 (M + K) (3). Anal. calcd for $C_{18}H_{22}O_{10}SN_2$: C, 46.99; H, 5.16; N; 6.08. Found: C, 47.18; H, 4.96; N, 6.08. Further elution afforded 3,4,6-tri-*O*-acetyl-2-thio-1-*O*,2-*S*-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-4,5-pyrimidinediyl)-β-D-mannopyranose **(17)** as a clear oil (0.03 g, 6.0×10^{-5} mol, 10%): $[\alpha]_D$ −16.8° (*c* 0.5;$CHCl_3$). IR (thin film) 2963, 1750, 1703, 1657, 1634, 1486, 1456, 1368, 1227 and 1047 cm^{-1}. ^1H NMR 5.59 (d, 1H, *J* = 1.5 Hz), 5.54 (dd, 1H, *J* = 9.6, 9.3 Hz), 5.29 (dd, 1H, *J* = 9.3, 4.8 Hz), 4.24–4.22 (m, 2H), 3.92 (dd, 1H, *J* = 4.5, 1.5 Hz), 3.93–3.85 (m, 1H), 3.41 (s, 3H), 3.36 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H); ^{13}C NMR δ 170.4, 169.7, 169.0, 160.2, 149.8, 148.9, 93.6, 83.2, 71.6, 64.9, 62.1, 40.6, 29.8, 29.6, 28.6, 20.8, 20.7 (2C). MS (ES) (*m*/*z*) (rel. intensity) 295 (100), 357 (84), 481 (M + Na) (27); HRMS (FAB+) calcd for $C_{18}H_{22}O_{10}SN$: 459.107342; Found: 459.107600

Cycloaddition with 3,4,6-tris(*O*-*tert*-butyldimethylsilyl)-D-glucal. To a solution of glucal **18** (0.11 g, 0.2 mmol) and barbiturate-S-phthalimide **11** (0.20 g, 0.34 mmol) in dry DMF (2 mL) containing powdered 3 Å molecular sieves (0.14 g), 2,6-lutidine (0.03 mL, 0.2 mmol) was added as a single portion. The mixture was stirred at rt for 24 h then was worked up as previously described to afford crude product (0.15 g). Column chromatography (SiO_2, 5–20% ethyl acetate in petroleum ether) afforded 3,4,6-tris-*O*-(*tert*-butyldimethylsilyl)-2-thio-1-*O*,2-S-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-4,5-pyrimidinediyl)-α-D-glucopyranose **(19)** (0.05g, 6.9×10^{-5} mol, 31%) as a white powder: mp 125–127 °C; $[\alpha]_D$ +1.8° (*c* 0.5, $CHCl_3$). IR (thin film) 2931, 1701, 1650, 1558, 1540, 1507, 1458, 1257 and 1097 cm^{-1}. ^1H NMR δ 5.65 (d, 1H, *J* = 2.4 Hz), 4.19–4.11 (m, 2H), 4.95 (apparent t, 1H, *J* = 3.6 Hz), 3.79–3.71 (m, 2H), 3.63 (apparent t, 1H, *J* = 3.0 Hz), 3.33 (s, 3H), 3.31 (s, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.76 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.003 (s, 3H); ^{13}C NMR δ 160.3, 150.2, 149.9, 96.7, 83.4, 79.5, 76.9, 74.1, 68.3, 62.9, 36.5, 28.9, 28.1, 25.8 (6C), 25.6 (6C), 18.2, 17.9, 17.8. MS (DEP/PCI) (*m*/*z*) (rel. intensity) 360 (22), 374 (100), 506 (24), 675 (M + H) (1). Anal. calcd for C_{30}, H_{58},O_7, N_2,Si_3: C, 52.02; H, 8.67; N, 4.04. Found: C, 52.43, H, 8.62; N, 3.65.

Cycloaddition reaction with 4,6-*O*-*tert*-butyldimethylsilanyl-D-glucal. To a solution of glycal **21**[15] (0.2 g, 0.7 mmol) and barbiturate-*S*-phthalimide **11** (0.3 g, 0.8 mmol) in dry DMF (3 mL) containing powdered 3 Å mol sieves (0.24 g), 2,6-lutidine (0.08 mL, 0.7 mmol) was added as a single portion. The mixture was stirred at rt for one week, then was worked up as previously described to afford crude product (0.48 g). Column chromatography (SiO_2; 2:1 petroleum ether/ethyl acetate) afforded 4,6-*O*-(*tert*-butyldimethylsilanyl)-2-thio-1-*O*,2-*S*-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-4,5-pyrimidinediyl)-α-D-glucopyranose **(22)** as a white, waxy solid (0.15 g, 0.32 mmol, 46%): mp 135–145 (d); $[\alpha]_D$ +79.1° (*c* 0.85, $CHCl_3$). IR (thin film) 3445, 2936, 2861, 1701, 1688, 1472, 1135, 1090, and 1022 cm^{-1}. ^1H NMR δ 5.83 (d, 1H, *J* = 2.7 Hz), 4.24–4.21 (m, 1H), 3.97–3.85 (m, 3H), 3.63–3.57 (m, 2H), 3.41 (s, 3H), 3.33 (s, 3H), 3.23 (dd, 1H, *J* = 10.2, 2.7 Hz), 1.07 (s, 9H), 0.98 (s, 9H); ^{13}C NMR δ 160.3, 150.9, 149.9, 99.1, 80.4, 77.4, 69.4, 69.0, 65.9, 60.5, 42.2, 28.9, 28.2, 27.2, (2C), 26.7 (2C), 22.5, 19.8, 14.0. MS (ES) (*m*/*z*) (rel. intensity) 473 (M + H) (100), 495 (M + Na) (13). Anal. calcd For $C_{20}H_{32}N_2O_7SSi$: C, 50.82; H, 6.83; N, 5.93. Found: C, 50.53; H, 6.51; N, 5.67.

Cycloaddition with 4,6-*O*-isopropylidene-D-glucal. To a solution of 4,6-*O*-isopropylidene-D-glucal **23** (0.2 g, 1.1 mmol) and barbiturate-*S*-phthalimide **11** (0.85 g, 1.3 mmol) in dry DMF (3 mL), 2,6-lutidine (0.13 mL, 1.1 mmol) and molecular sieves (0.3 g) was added. The mixture was stirred at rt for 3 days, then worked-up as previously described to afford crude product (0.5 g). Column chromatography (SiO_2; 50–80% ethyl acetate in petroleum ether) afforded 4,6-*O*-isopropylidene-2-thio-1-*O*,2-*S*-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-4,5-pyrimidinediyl)-α-D-glucopyranose **(24)** as an oil (0.1 g, 0.26 mmol, 23%): $[\alpha]_D$ +2.3° (*c* 0.8, $CHCl_3$). IR (neat) 3440, 2993, 2945, 1703, 1633, 1485, 1378, 1204, and 1129 cm^{-1}. ^1H NMR δ 5.87 (δ, 1H, *J* = 3.3 Hz), 3.99–3.95 (m, 1H), 3.89–3.67 (m, 4H), 3.43 (s, 3H), 3.40–3.38 (m, 1H), 3.33 (s, 3H), 3.23 (dd, 1H, *J* = 9.9, 3.0 Hz), 1.56 (s, 3H), 1.44 (s, 3H); ^{13}C NMR δ 160.6, 151.6, 150.0, 100.3, 99.6, 79.6, 73.9, 66.8, 66.7, 61.7, 43.5, 29.2, 28.8, 28.4, 18.9. MS (DEP/PCI) (*m*/*z*) (rel. intensity) 129 (65), 146 (81), 187 (81), 204 (100), 372 (M) (36), 390 ($M + NH_4^+$) (50). Anal. calcd For $C_{15}H_{20}O_7SN_2$: C, 48.39; H, 5.38. Found: C, 48.24; H, 5.77.

Cycloaddition with 3,4,6-tri-*O*-acetyl-D-galactal. To a solution of tri-*O*-acetyl-D-galactal **25** (0.31g, 1.2 mmol) and barbiturate-*S*-phthalimide **11** (0.46g, 1.4 mmol) in dry DMF (3 mL) containing 3 Å molecular sieves (0.15 g), 2,6-lutidine (0.13 mL, 1.2 mmol) was added as a single portion. The mixture was stirred at rt for 4 days, then worked-up as described to afford crude product (0.4 g). Column chromatography (SiO_2; 40–70% ethyl acetate in petroleum ether) afforded 3,4-6-tri-*O*-acetyl-2-thio-1-*O*,2-*S*-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-4,5-pyrimidinediyl)-α-D-galactopyranose **(26)** (0.19 g, 33%) as a white powder: mp 160–161 °C (ether:hexanes); $[\alpha]_D$ +128° (*c* 1.6, $CHCl_3$). IR (thin film) 1748, 1700, 1647, 1540, 1508, 1371, 1230, 1144, and 1026 cm^{-1}. ^1H NMR δ 5.93 (d, 1H, *J* = 2.7 Hz), 5.45 (br d, 1H, *J* = 3 Hz), 4.98 (dd, 1H, *J* = 11.7, 3.0 Hz), 4.41 (apparent t, 1H, *J* = 6.4 Hz), 4.17 (apparent d, 2H, *J* = 6.6 Hz), 3.65 (dd, 1H, *J* = 11.7, 2.7), 3.40 (s, 3H), 3.33 (s, 3H), 2.17 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H); ^{13}C NMR δ 170.2, 169.8, 169.7, 150.1, 149.9, 98.9, 77.4,

77.0, 69.7, 66.7, 65.5, 61.2, 36.1, 29.1, 28.4, 20.6, 20.5 (2C). MS (ES) (*m*/*z*) (rel. intensity) 459 (M + H) (100), 481 (M + Na) (70). Anal. calcd for $C_{18}H_{22}O_{10}SN_2$: C, 46.99; H, 5.16; N, 6.08. Found: C, 47.12; H, 5.03, N, 5.84.

Cycloaddition reaction with 3,4-di-*O*-acetyl-L-rhamnal. To a solution of 3,4-di-*O*-acetyl-L-rhamnal **27** (0.17 g, 0.78 mmol), and barbiturate-*S*-phthalimide **11** (0.33 g, 0.85 mmol) in dry DMF (3 mL) containing 3 Å molecular sieves (0.2 g), 2,6-lutidine (0.09 mL, 0.78 mmol) was added as a single portion. The mixture was stirred at rt for 1 week, then worked up to afford a crude product (0.28 g). Column chromatography (SiO_2; 33–66% ethyl acetate in petroleum ether) afforded 3,4-di-*O*-acetyl-2-thio-1-*O*,2-S-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-4,5-pyrimidinediyl)-α-D-rhamnopyranose **(28)** (0.04 g, 8.25×10^{-5} mol, 11%) as a white powder: mp 186–188 °C; $[\alpha]_D$ –30.1° (*c* 0.7, $CHCl_3$). IR (neat) 2936, 1751, 1690, 1636, 1507, 1472, 1457, 1374, 1232, 1140, 1046, and 1009 cm^{-1}. ^1H NMR δ 5.81 (d, 1H, *J* = 3.0 Hz), 5.09 (dd, 1H, *J* = 10.8, 9.3 Hz), 4.88 (apparent t, *J* = 9.6 Hz), 4.13–4.04 (m, 1H), 3.40 (s, 3H), 3.36 (dd, 1H, *J* = 7.8, 3.0 Hz), 3.32 (s, 3H), 2.05 (s, 3H), 1.28 (d, 1H, *J* = 6.3 Hz); ^{13}C NMR δ 169.7, 169.5, 160.0, 150.5, 150.0, 134.1, 123.4, 98.4, 73.8, 69.0, 67.7, 40.5, 29.2, 28.4, 20.7, 17.5. MS (ES) (*m*/*z*) (rel. intensity) 299 (100), 423 (M + Na) (37). HRMS (FAB+) calcd for $C_{16}H_{21}N_2O_8S$: 401.102000. Found: 401.101863.

Cycloaddition reaction with 6,6′-di-*O*-(*tert*-butyldiphenylsilyl)-3,2′,3′,4′-tetra-*O*-acetyl-D-lactal. To a solution of lactal **29** (0.09 g, 9.5×10^{-5} mol) and barbiturate-S-phthalimide **11** (0.08 g, 0.2 mmol) in dry DMF (1 mL) containing powdered 3 Å molecular sieves (0.15 g), 2,6-lutidine (0.016 mL, 0.1 mmol) was added. The mixture was stirred at rt for 2 days, then worked up as previously described to afford crude product (0.13 g). Column chromatography (SiO_2; 1:1:1 hexanes/Et_2O/CH_2Cl_2) afforded 6,6′-di-*O*-(*tert*-butyldiphenyl)-3,2′,3′,4′-tetra-*O*-acetyl-2-thio-1-*O*,2-S-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-4,5-pyrimidinediyl)-α-D-lactopyranose **(30)** (0.04 g, 3.5×10^{-5}mol, 37%) as a white powder: mp 144–149 °C; $[\alpha]_D$ +32.8° (*c* 0.9, $CHCl_3$). IR (thin film) 3015, 2932, 2858, 1751, 1706, 1684, 1659, 1559, 1472, 1456, 1368, 1218, 1112, and 1009 cm^{-1}. ^1H NMR δ 7.73–7.68 (m, 5H), 7.62–7.57 (m, 5H), 7.48–7.35 (m, 10H), 5.84 (d, 1H, *J* = 3.0 Hz), 5.52 (d, 1H, *J* = 3.0 Hz), 5.06 (dd, 1H, *J* = 11.1, 9.6 Hz), 5.00–4.89 (m, H), 4.70 (d, 1H, *J* = 7.5 Hz), 4.15 (apparent t, 1H, *J* = 9.6 Hz), 3.99–3.89 (m, 1H), 3.83 (d, 1H, *J* = 9.9 Hz), 3.73–3.66 (m, 1H), 3.57–3.50 (m, 1H), 3.36 (s, 3H), 3.32 (s, 3H), 3.25 (dd, 1H, *J* = 11.4, 3.6 Hz), 2.01 (s, 3H), 1.98 (s, 3H), 1.81 (s, 3H), 1.79 (s, 3H), 1.10 (s, 9H), 1.04 (s, 9H); ^{13}C NMR δ170.6, 170.4, 169.9, 169.5, 160.8, 150.9, 150.7, 100.7, 99.5, 81.4, 77.9, 77.6, 75.4, 74.7, 73.7, 72.1, 70.4, 68.1, 67.4, 61.6, 61.5, 41.2, 29.9, 29.1, 27.7 (3C), 27.5 (3C), 21.4 (2C), 20.2, 19.8. MS (ES) (*m*/*z*) (rel. intensity) 149 (64); 205 (77), 279 (46), 301 (49), 391 (44), 535 (72), 975 (100), 1161 (M + Na) (7). Anal. calcd for $C_{58}H_{68}O_{16}N_2Si_2S$: C, 61.16; H, 5.98; N, 2.46. Found: C, 60.90; H, 6.37; N, 2.24.

Tri-*O*-acetyl-D-galactal free amido barbiturate cycloadduct. To a solution of tri-*O*-acetyl-D-galactal **25** (0.12 g, 0.42 mmol) and bis-phthalimidosulfenylated barbiturate **36** (0.31 g, 0.47 mmol) in dry DMF (3 mL) was added 2,6-lutidine (0.05 mL, 0.42 mmol). The reaction mixture was stirred at rt for 3 days, then was worked up as previously described. Column chromatography (SiO_2; 50% ethyl acetate in petroleum ether) afforded 3,4,6-tri-*O*-acetyl-2-thio-1-*O*,2-*S*-(1,2,3,6-tetrahydro-2,6-dioxo-4,5-pyrimidinediyl)-α-D-galactopyranose **(37)** (0.14 g, 0.24 mmol, 57%) as a brown oil: $[\alpha]_D$ +20.3° (*c* 1.4; CH_3OH). IR (neat) 3374, 2924, 1744, 1566, 1413, 1370, 1233 and 1046 cm^{-1}. ^1H NMR (CD_3OD) δ 6.07 (d, 1H, *J* = 3 Hz); 5.45 (br d, 1H, *J* = 2.1 Hz), 5.14 (dd, 1H, *J* = 11.7, 3.0 Hz), 4.56 (apparent t, 1H, *J* = 6.6 Hz), 4.17 (d, 2H, *J* = 6.3 Hz), 3.76 (dd, 1H, *J* = 11.7, 3.0 Hz), 2.17 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H); ^{13}C NMR δ 172.0, 171.7, 171.3, 164.5, 155.1, 155.0, 100.4, 80.2, 70.9, 68.8, 66.8, 62.9, 37.7, 20.7, 20.6 (2C). MS (ES) (*m*/*z*) (rel. intensity) 459 (M + K) (8), 430 (M+) (22), 429 (M-H) (100); HRMS (FAB+) calcd For $C_{16}H_{18}N_2O_{10}S$: 431.075900. Found 431.076042.

Di-*O*-acetyl-L-rhamnal free amido barbiturate cycloadduct. To a solution of rhamnal **27** (0.11 g, 0.52 mmol) and bis-phthalimidosulfenylated barbiturate **36** (0.34 g, 0.52 mmol) in dry DMF (3 mL) was added 2,6-lutidine (0.06 mL, 0.52 mmol). The mixture was stirred at rt for 5 days then was worked up as previously described. Column chromatography (SiO_2; 50% ethyl acetate in petroleum ether) afforded the 3,4-di-*O*-acetyl-2-thio-1-*O*,2-*S*-(1,2,3,6-tetrahydro-2,6-dioxo-4,5-pyrimidinediyl)-β-L-rhamnopyranose **(38)** (0.07 g, 0.18 mmol, 35%) as a white film: $[\alpha]_D$−23.4° (*c* 0.8; $CHCl_3$). IR (thin film) 3160, 1714, 1682, 1651, 1622, 1514, 1434, 1378. 1294, 1232, 1152, 1131, 1099 and 1045 cm^{-1}. ^1H NMR (CD_3OD) δ 5.94 (d, 1H, *J* = 3 Hz), 5.14–5.04 (m, 1H), 4.95–4.87 (m, 1H), 4.11 (qd, 1H, *J* = 9, 6 Hz), 3.64 (dd, 1H, *J* = 9, 3 Hz), 2.05 (s, 3H), 2.02 (s, 3H), 1.24 (d, 1H, *J* = 6 Hz); ^{13}C NMR (CD_3OD) δ 171,7, 171.3, 164.5, 155.1, 151.3, 100.1, 80.5, 75.2, 70.2, 69.0, 41.5, 20.7 (2C), 17.8; HRMS (FAB+) calcd for $C_{14}H_{16}N_2O_8S$: 373.070400. Found: 373.070563.

1,3-Dimethyl-barbituric acid α-D-glucopyranose cycloadduct (34). To a solution of bis silyl cycloadduct **21** (0.27 g, 0.57 mmol) in dry THF at 5 °C, TBAF (1.14 mL; 1.14 mmol) was added as a single portion. The mixture was stirred for 2.5 h, then TMSCl (0.07 mL, 0.57 mmol) was added. After stirring for an additional 15 min, the mixture was concentrated in vacuo. Preparative TLC (RP, C18) using 20:1 CH_3CN/H_2O afforded 2-thio-1-*O*,2-*S*-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-4,5-pyrimidinediyl)-α-D-glucopyranose **(34)** (0.12 g, 0.36 mmol, 63%) as a beige oil: $[\alpha]_D$ +16.4° (*c* 2.3; CH_3OH). IR (thin film) 3389, 2961, 1727, 1674, 1574, 1470, 1416, 1366, 1273 and 1072 cm^{-1}. ^1H NMR (CD_3CN) δ 5.71 (d, 1H, *J* = 3 Hz), 3.64–3.60 (m, 1H), 3.36 (dd, 1H, *J* = 7.5, 2.1 Hz), 3.15 (s, 3H), 3.07 (s, 3H), 3.03–2.99 (m, 1H), 2.04 (br s, 2H), 1.12 (br s, 1H); ^{13}C NMR δ 162.1, 153.2, 151.7, 101.2, 77.0, 72.2, 70.6, 62.4, 43.9, 30.0, 29.1, 28.5.

Antiviral and cytotoxicity assays

Anti-HIV-1 activity of the compounds was determined in human PBM cells as described previously.[18] Stock solutions (20–40 mM) of the compounds were prepared in sterile DMSO and then diluted to the desired concentration in growth medium. Cells were infected with the prototype HIV-1_{LAI} at a multiplicity of infection of 0.01. Virus obtained from the cell supernatant was quantitated on day 6 after infection by a reverse transcriptase assay using $(rA)_n \cdot (dT)_{12-18}$ as template-primer. The DMSO present in the diluted solution ($<0.1\%$) had no effect on the virus yield. The anti-HSV-1 assays were performed in Vero cells by a plaque assay using strain F, as described previously.[19]

The toxicity of the compounds was assessed in human peripheral blood mononuclear (PBM), Vero (African Green monkey kidney) and CEM cells, as described previously.[18] After incubation, actively metabolizing cells were quantified using the CellTiter 96 Cell Proliferation Assay (MTT, Promega, Madison, WI, USA), as described by the manufacturer. The antiviral EC_{50}, EC_{90} and cytotoxicity IC_{50} were obtained from the concentration-response curve using the median effective method described previously.[20]

Supporting information available

^1H and ^{13}C spectra for all compounds. NOESY spectra for compounds **13** and **14** (32 pages).

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