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Design, synthesis, and biological evaluation of novel 4-hydroxypyrone derivatives as HIV-1 protease inhibitors

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Abstract—Twenty-four 4-hydroxypyrone derivatives were synthesized with a facile synthetic method to develop novel HIV protease inhibitors. Most of them were shown to display good antiviral activities in SIV-infected CEM cells. The introduction of α-naphthylmethyl group to C-6 of 5,6-dihydropyran-2-ones led to an effective antiviral compound that showed an EC_{50} value at 1.7 μM with a therapeutic index of 46.
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1. Introduction

HIV protease plays an important role in post-translational processing of the precursor polyproteins Gay and Gay/Pol, which is essential for maturation of the virus.[1] And now HIV-1 protease has become an attractive target for the design of inhibitors for effective antiviral therapy. Intense research into the therapeutic intervention of AIDS has brought to market several effective HIV protease inhibitors.[2,3] The clinical effectiveness of the HIV protease inhibitors in combination with reverse transcriptase inhibitors for the treatment of AIDS has been well established.[4] However, the currently marketed HIV protease inhibitors which are

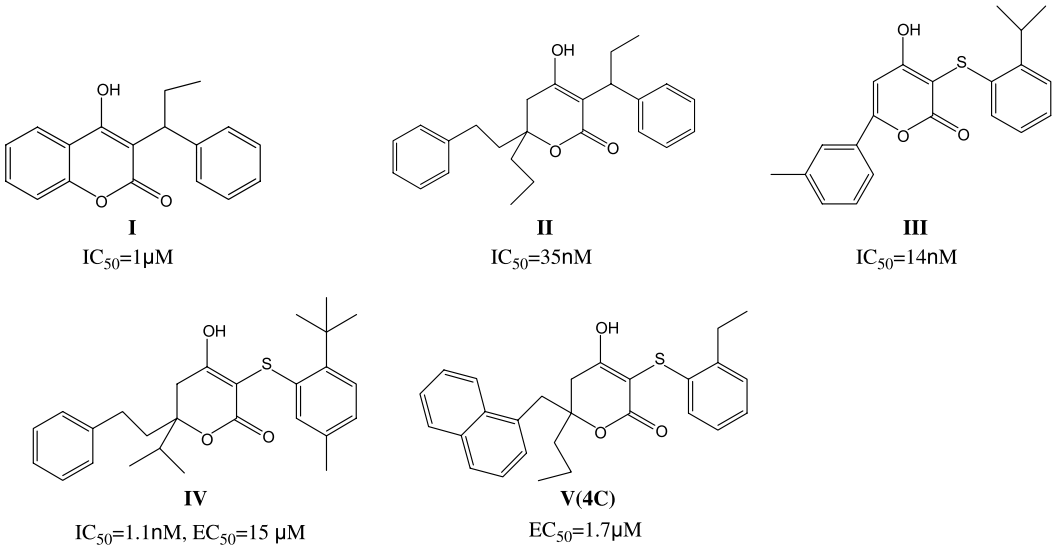

Figure 1. 4-Hydropyrone HIV protease inhibitors.

Keywords: 4-Hydroxypyrone; Antiviral activity; Protease inhibitor.
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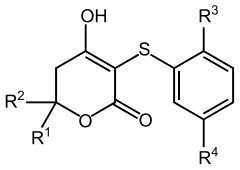
Table 1. The structures of 4-hydroxypyrones



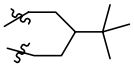
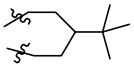
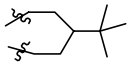
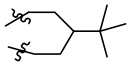
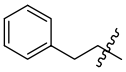
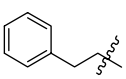
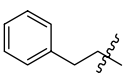
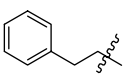
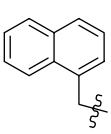
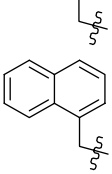
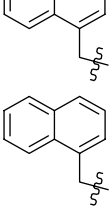
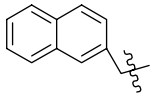
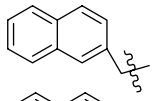
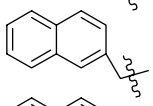
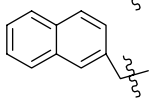
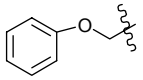
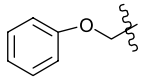
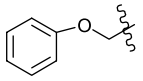
Entry	R^1	R^2	R^3	R^4
1A	R^1=R^2=		H	H
1B	R^1=R^2=		CH_3	H
1C	R^1=R^2=		C_2H_5	H
1D	R^1=R^2=		CH_3	CH_3
2A	R^1=R^2=		H	H
2B	R^1=R^2=		CH_3	H
2C	R^1=R^2=		C_2H_5	H
2D	R^1=R^2=		CH_3	CH_3
3A			H	H
3B			CH_3	H
3C			C_2H_5	H
3D			CH_3	CH_3
4A			H	H
4B			CH_3	H
4C			C_2H_5	H
4D			CH_3	CH_3

Table 1 (*continued*)

Entry	R^1	R^2	R^3	R^4
5A			H	H
5B			CH_3	H
5C			C_2H_5	H
5D			CH_3	CH_3
6A			H	H
6B			CH_3	H
6C			C_2H_5	H
6D			CH_3	CH_3

peptidomimetics have serious problems associated with low bioavailability and high toxicity.[5,6] Additionally, the emergence of HIV-1 resistant strains necessitates continued research for novel inhibitors of viral replications.[7,8]

Since the 4-hydroxycoumarin phenprocoumon **I** (Fig. 1) was previously identified as a non-peptidic protease inhibitor from a broad screening program,[9] many 4-hydroxypyrones have been synthesized by different research groups.[10,11] Suvit Thaisrivongs[10] and co-workers have synthesized a series of 5,6-dihydro-4-hydroxy-pyran-2-ones containing two substituents at C-6. The X-ray crystal structure of compound **II** (Fig. 1) bound to HIV-1 protease displayed that its side chains filled four binding pockets (S_1, S_2, S'_1, S'_2) of the HIV-1 protease. So pyrones **II** showed very good enzyme inhibitory activity (k_i = 35 nM), but exhibited low antiviral activity in the HIV-$1_{IIIB\text{-infected}}$ MT_4 cells.

The 4-hydroxy-3-thiosubstituted-pyran-2-one **III** (Fig. 1) is similar in structure to the carbon branched compounds of Upjohn,[12] but is generally more potent and does not have a chiral center at position 3. Great efforts[11,13] were focused on adding thiosubstitutes to C-3 of 5,6-dihydro-4-hydroxy-pyran-2-ones. As a result, compound **IV**[11] (Fig. 1) was identified to be a potent HIV protease inhibitor with a very low IC_{50} value of 1.1 nM. But it also showed low antiviral activity (EC_{50} = 15 μM). Thus, we became interested in preparing 5,6-dihydro-4-hydroxy-3-thiosubstituted-pyrones. We modified the known 5,6-dihydropyrones at C-3 with thiosubstitutes to get compounds **1A–D**, **3A–D**, **6A–D**

and changed different groups at C-6 to get compounds **2A–D**, **4A–D**, **5A–D** (Table 1).

The structures of these compounds were confirmed by EI-MS and ^{1}H NMR.[14] Most of them were shown to display good antiviral activities in SIV-infected CEM cells. Compound **4C** (Fig. 1) was the most potent in this study, with an EC_{50} value at 1.7 μM and a therapeutic index of 46.

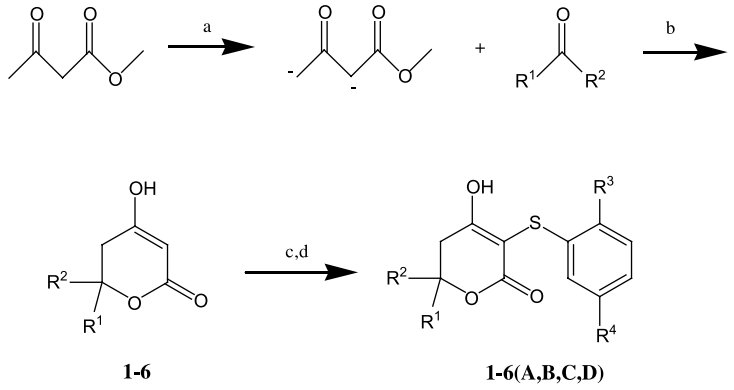
1.1. Chemistry

The title compounds for this study were synthesized using the methods shown in Scheme 1.[13] The dihydropyrone cores (**1–6**) were prepared from the requisite ketones and the dianion of methyl acetoacetate. The synthesis of the dihydropyrone targets involved preparation of the 3-bromodihydropyrone derivatives with NBS in the dark and then displacement of the bromide by the appropriately substituted thiophenol.

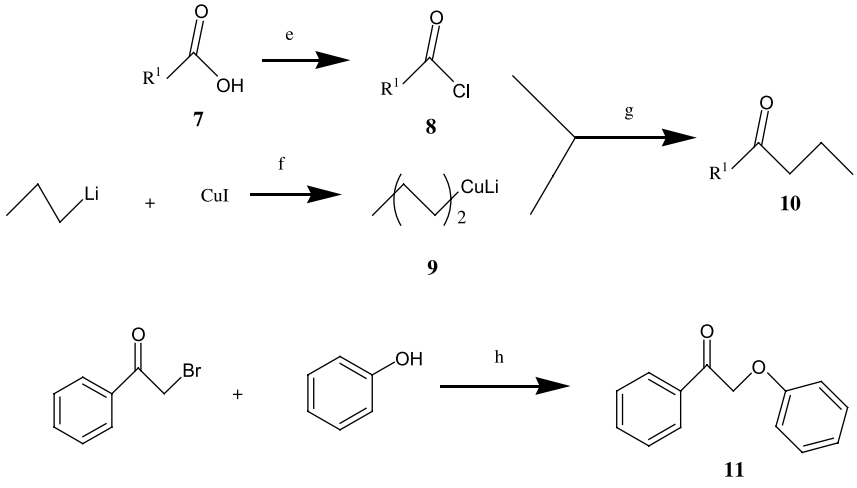
The synthetic pathway for the necessary ketones is shown in Scheme 2. Acyl chloride (**8**) was prepared by reaction of the corresponding acid (**7**) with thionyl chloride in the presence of a single drop DMF,[15] and then reacted with the compound (**9**), lithium di-*n*-propylcuprate(I), to get the appropriate ketone (**10**) possessing a *n*-propyl group.[16] α-Phenoxyacetophenone (**11**) was synthesized from α-bromoacetophenone and phenol in the presence of potassium carbonate.[17]

2. Results and discussion

It is reported in the literature[10] that 4-hydroxypyrones with a spirocycle at C-6 exhibited some inhibitory activity of HIV protease. The compound with the six-membered ring was the most potent ($IC_{50} \approx 1$ μM). The crystallographic structure of the HIV protease complexed with the pyrone possessing the six-membered ring demonstrated that the cyclohexyl ring at C-6 folded into the S_2' pocket of the HIV protease. We modified the pyrone at C-3 with thiosubstitutes, which resulted in achiral compounds **1A–D** (Table 1). They showed good antiviral activities in SIV-infected CEM cells[18] and low cytotoxicity ($TC_{50} > 100$ μM) except for compound **1A**. To discover whether adding a large group to C-8 of the spiro ring system could fill the S_2' pocket of the



Scheme 1. Reagents and conditions: (a) (1) NaH, (2) *n*-BuLi, dry THF, followed by ketone addition, 0 °C; (b) (1) NaOH, CH_3OH, (2) H+, 50–70% (for two steps); (c) NBS, dry *t*-BuOH, reflux; (d) Corresponding thiophenol, piperidine, CH_2Cl_2, 50–65% (for two steps).



Scheme 2. Reagents and conditions: (e) $SOCl_2$, DMF, EtoAc; (f) dry ether, −40 °C; (g) −78 °C; (h) K_2CO_3, acetone.

HIV protease more closely and result in enhanced antiviral activity, we synthesized compounds **2A–D** (Table 1). Contrary to our expectation, all four compounds displayed lower antiviral activities but higher toxicity. These results showed that the S'_2 pocket of the HIV protease probably could not accommodate such a large group.

To further explore the interaction between the pyrone derivatives and the HIV proteases, molecular modeling studies were conducted. All the compounds except **1A–D**, **2A–D** in Table 1 were docked in the binding site of HIV protease structure using AutoDock3.0[19] program to get predicted binding free energy. The results demonstrated that all the compounds in the naphthylmethyl series (**4A–D**, **5A–D**) had lower predicted binding free energy than that of compounds in the phenylethyl series (**3A–D**). We synthesized them all and got the EC_{50} values in a cell culture assay using SIV-infected CEM cells (Table 2).

Table 2. The antiviral activities (EC_{50}) and toxicities (TC_{50}) of 4-hydroxypyrones

Entry[a]	Mp (°)	EC_{50} (M)[b]	TC_{50} (M)[c]	TI[d]
1A	155–157	12.3	52	4
1B	123–125	3.3	>100	>30
1C	135–136	3.9	>100	>26
1D	146–147	3.6	>100	>28
2A	174–176	>5.0	5.0	1
2B	132–133	6.7	56.1	8
2C	55–57	8.1	20.1	3
2D	82–83	8.3	>100	>12
3A	Syrup	4.6	>100	>22
3B	Syrup	3.7	>100	>27
3C	Syrup	4.1	>100	>24
3D	37–38	4.3	>100	>23
4A	49–51	4.3	54	13
4B	33–34	3.8	>100	>26
4C	152–153	1.7	78.9	46
4D	127–128	4.6	49.7	11
5A	39–40	3.2	32.1	10
5B	32–34	2.0	34.8	17
5C	43–45	1.8	61.5	34
5D	42–44	4.0	40.1	10
6A	55–57	13.0	31.8	2
6B	157–158	8.2	>100	>12
6C	54–55	5.6	45.3	8
6D	47–48	9.2	47.3	5

[a] All compounds are racemic mixtures except for achiral molecules **1A–D**, **2A–D**.
[b] EC_{50} is the effective concentration at which 50% of the CEM cells are protected from SIV infection and is the average of at least two runs.[18]
[c] TC_{50} is the concentration that elicits cytotoxicity in 50% of uninfected CEM cells.
[d] TI, therapeutic index = TC_{50}/EC_{50}.

Among the 6-phenylethyl series, all the inhibitors showed similar antiviral activities in the range from 3.7 to 4.6 μM, though the alkyl group on thiophenol of C-3 varied, for example, methyl(**3B**), ethyl(**3C**), dimethyl(**3D**), and they showed low toxicity (TC_{50} > 100 μM). 5,6-Dihydropyran-2-ones containing a 6-position naphthylmethyl group (**4A–D**, **5A–D**), showed a different structure–activity relationship compared to the 6-phenylethyl series. Thus, as the bulk of the alkyl group at the α-position of thiophenol was increased, the antiviral activities were enhanced except for the compounds possessing a dimethyl on thiophenol (**4D**, **5D**). Moreover, the toxicity was increased compared with the phenylethyl series, especially for the β-naphthylmethyl series. The most potent inhibitor in the naphthylmethyl series (**4C**) showed EC_{50} of 1.7 μM with a therapeutic index of 46, which exhibited 2-fold enhancement in antiviral activities compared to the most potent one in the phenylethyl series (compound **3B**, EC_{50} = 3.7 μM). These results showed that the naphthylmethyl group at C-6 could possibly occupy the S_2 pocket of the HIV protease more closely than the phenylethyl group, although the phenylethyl group was more flexible and theoretically it should be conventional to fill the S_2 pocket of the HIV protease.

Molecular modeling studies showed that compound **4C**, which was docked in the HIV protease binding sites (S_1, S_2, S'_1, S'_2 pockets) using program AutoDock3.0, was overlaid with Tipranavir,[20] a nonpeptidic inhibitor, in its bound conformation in the X-ray crystal structure (Fig. 2).

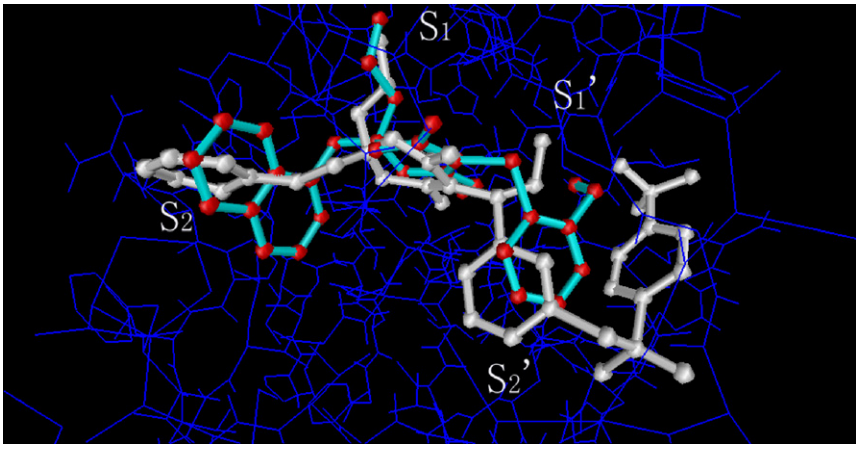


Figure 2. Compound **4C** docked in the HIV protease binding sites (S_1, S_2, S'_1, S'_2 pockets) using program AutoDock3.0 was overlaid with Tipranavir, a nonpeptidic inhibitor, in its bound conformation in the X-ray crystal structure. The protein was from the docking experiment and was colored blue. Compound **4C** was colored red and green and Tipranavir was colored white.

In conclusion, we have synthesized 24 compounds of 4-hydroxy-pyran-2-one derivatives as new HIV-1 protease inhibitors. Most of them were shown to display good antiviral activities in SIV-infected CEM cells. The introduction of α-naphthylmethyl group to C-6 of 5,6-dihydropyran-2-ones leads to an effective antiviral compound **4C** (EC_{50} = 1.7 μM, TI = 46), which can be easily synthesized from the corresponding ketone in 4 steps with about 40% yield.

Acknowledgments

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14. **1A**: MS(EI) *m/z* 290 (M^+). ^{1}H NMR ($CDCl_3$) 1.25–1.53 (m, 6H), 1.64–1.83 (m, 2H), 1.85–2.03 (m, 2H), 2.77 (s, 2H), 7.19–7.41 (m, 5H); **1B**: MS(EI) *m/z* 304 (M^+). ^{1}H NMR ($CDCl_3$) δ 1.28–1.78 (m, 10H), 2.44 (s, 2H), 3.88 (s, 3H), 7.22–7.25 (m, 4H); **1C**: MS(EI) *m/z* 318 (M^+). ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J* 7.5 Hz), 1.33–1.41 (m, 1H), 1.47–1.53 (m, 2H), 1.58–1.65 (m, 3H), 1.77–1.85 (m, 2H), 2.00–2.04 (m, 2H), 2.79 (s, 2H), 2.83–2.88 (m, 2H), 6.95–7.18 (m, 4H); **1D**: MS(EI) *m/z* 318 (M^+). ^{1}H NMR ($CDCl_3$) δ 1.36–1.66 (m, 6H), 1.68–1.86 (m, 2H), 2.04–2.09 (m, 2H), 2.23 (s, 3H), 2.40 (s, 3H), 2.8 (s, 2H), 6.75 (s, 1H), 6.90 (d, 1H, *J* 7.8 Hz), 7.04 (d, 1H, *J* 7.8 Hz); **2A**: MS(EI) *m/z* 346 (M^+). ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 9H), 1.20–1.82 (m, 7H), 2.08–2.22 (m, 2H), 2.69 (s, 1H), 2.87 (s, 1H), 7.11–7.31 (m, 5H); **2B**: MS(EI) *m/z* 360 (M^+). ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 9H), 1.24–1.28 (m, 2H), 1.51–1.55 (m, 4H), 1.99–2.03 (m, 3H), 2.38 (s, 2H), 3.88 (s, 3H), 7.20–7.31 (m, 4H); **2C**: MS(EI) *m/z* 374 (M^+). ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 9H), 1.30 (t, 3H, *J* 7.5 Hz), 1.10–1.81 (m, 7H), 2.12–2.16 (m, 2H), 2.70–2.90 (m, 4H), 6.94–7.27 (m, 4H); **2D**: MS(EI) *m/z* 374 (M^+). ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 9H), 1.10–1.80 (m, 9H), 2.15 (s, 3H), 2.24 (s, 3H), 2.73 (s, 1H), 2.90 (s, 1H), 6.75–7.04 (m, 3H); **3A**: MS(EI) *m/z* 368 (M^+). ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, *J* 7.2 Hz), 1.41–1.44 (m, 2H), 1.77–1.83 (m, 2H), 1.99–2.11 (m, 2H), 2.68–2.81 (m, 4H), 7.13–7.32 (m, 10H); **3B**: MS(EI) *m/z* 382 (M^+). ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, *J* 7.35 Hz), 1.32–1.38 (m, 2H), 1.64–1.71 (m, 2H), 1.91–1.98 (m, 2H), 2.49 (s, 2H), 2.63–2.71 (m, 2H), 3.86 (s, 3H), 7.15–7.32 (m, 9H); **3C**: MS(EI) *m/z* 396 (M^+). ^{1}H NMR ($CDCl_3$) δ 0.94–1.00 (m, 3H), 1.27–1.32 (m, 3H), 1.41–1.47 (m, 2H), 1.83–1.86 (m, 2H), 2.03–2.12 (m, 2H), 2.71–2.91 (m, 6H), 6.96–7.33 (m, 9H); **3D**: MS(EI) *m/z* 396 (M^+). ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, *J* 7.35 Hz), 1.44–1.58 (m, 2H), 1.83–1.93 (m, 2H), 2.07–2.17 (m, 5H), 2.42 (s, 3H), 2.72–2.86 (m, 4H), 6.76 (s, 1H), 6.90 (d, 1H, *J* 7.5 Hz), 7.04 (d, 1H, *J* 7.5 Hz), 7.17–7.33 (m, 5H); **4A**: MS(EI) *m/z* 404 (M^+). ^{1}H NMR ($CDCl_3$) δ 0.93–0.98 (m, 3H), 1.54–1.62 (m, 2H), 1.85–1.90 (m, 2H), 2.69–2.71 (m, 2H), 3.45–3.65 (m, 2H), 7.15–7.89 (m, 12H); **4B**: MS(EI) *m/z* 418 (M^+). ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3H, *J* 7.35 Hz), 1.49–1.54 (m, 2H),1.73–1.75 (m, 2H), 2.38 (s, 3H), 3.33–3.78 (m, 4H), 7.04–7.88 (m, 11H); **4C**: MS(EI) *m/z* 432 (M^+). ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, *J* 7.25 Hz), 1.26 (t, 3H, *J* 7.5 Hz), 1.54–1.66 (m, 2H), 1.83–1.93 (m, 2H), 2.65–2.84 (m, 4H), 3.47–3.64 (m, 2H), 6.90–7.87 (m, 11H); **4D**: MS(EI) *m/z* 432 (M^+). ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3H, *J* 7.25 Hz), 1.55–1.68 (m, 2H), 1.87–2.04 (m, 2H), 2.18 (s, 3H), 2.38 (s, 3H), 2.66–2.76 (m, 2H), 3.51–3.67 (m, 2H), 6.74–7.88 (m, 10H); **5A**: MS(EI) *m/z* 404 (M^+). ^{1}H NMR ($CDCl_3$) δ 0.93–0.98 (m, 3H), 1.56–1.60 (m, 2H), 1.76–1.81 (m, 2H), 2.69–3.33 (m, 4H), 7.21–7.89 (m, 12H); **5B**: MS(EI) *m/z* 418 (M^+). ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, *J* 7.2 Hz), 1.47–1.68 (m, 4H), 2.36–2.48 (m, 2H), 2.97–3.16 (m, 2H), 3.79 (s, 3H), 7.09–7.83 (m, 11H); **5C**: MS(EI) *m/z* 432 (M^+). ^{1}H NMR ($CDCl_3$) δ 0.95 −1.00 (m, 3H), 1.28–1.33 (m, 3H), 1.61–1.83 (m, 4H), 2.71–2.90 (m, 4H), 3.17–3.37 (m, 2H), 6.95–7.84 (m, 11H); **5D**: MS(EI) *m/z* 432 (M^+). ^{1}H NMR ($CDCl_3$) δ 0.95–1.00 (m, 3H), 1.62–1.85 (m, 4H), 2.20 (s, 3H), 2.41 (s, 3H), 2.77–2.84 (m, 2H), 3.24–3.38 (m, 2H), 6.80–7.84 (m, 10H); **6A**: MS(EI) *m/z* 404 (M^+). ^{1}H NMR ($CDCl_3$) δ 3.44 (d, 1H, *J* 17.7 Hz), 3.82 (d, 1H, *J* 17.7 Hz), 4.06 (d, 1H, *J* 9.9 Hz), 4.35 (d, 1H, *J* 10.2 Hz), 6.60–7.60 (m, 15H); **6B**: MS(EI) *m/z* 418 (M^+). ^{1}H NMR ($CDCl_3$) δ 3.11 (d, 1H, *J* 17.7 Hz), 3.51–3.57 (m, 3H), 3.76 (d, 1H, *J* 12.9 Hz), 3.98 (d, 1H, *J* 9.9 Hz), 4.25 (d, 1H, *J* 9.9 Hz), 6.87–7.55 (m, 14H); **6C**: MS(EI) *m/z* 432 (M^+). ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, *J* 7.5 Hz), 2.70–2.78 (m, 2H), 3.46 (d, 1H, *J* 17.4 Hz), 3.83 (d, 1H, *J* 17.7 Hz), 4.06 (d, 1H, *J* 9.9 Hz), 4.35 (d, 1H, *J* 9.9 Hz), 6.83–7.67 (m, 14H); **6D**: MS(EI) *m/z* 432 (M^+). ^{1}H

NMR ($CDCl_3$) δ 1.92 (s, 3H), 2.30 (s, 3H), 3.43 (d, 1H, *J* 17.7 Hz), 3.84 (d, 1H, *J* 17.7 Hz), 4.03 (d, 1H, *J* 10.2 Hz), 4.353 (d, 1H, *J* 10.2 Hz), 6.78–7.61 (m, 13H).

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18. Inhibition of SIV-induced syncytium in CEM174 cell cultures was measured in a 96-well microplate containing 2×10^5 CEM cells/ml infected with 100 $TCID_{50}$ of SIV per well and containing appropriate dilutions of the tested compounds. After 5 days of incubation at 37 °C in 5% CO_2 containing humidified air, CEM giant (syncytium) cell formation was examined microscopically (COIC). The EC_{50} was defined as the compound concentration required to protect cells against the cytopathogenicity of SIV by 50%.
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