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Synthesis and HIV-1 Integrase Inhibitory Activities of Caffeoylglucosides

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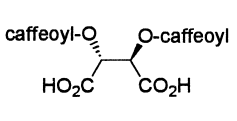
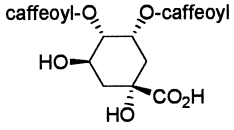
Abstract—Caffeoylglucosides, which have a glucose ring as a central linker, were synthesized from methyl D-glucosides, and their anti-HIV-1 activities were tested. Among them, four dicaffeoylglucosides (IC_{50} = 29.1–35.1 μM), **6a**, **6b**, **9b** and **10b**, showed HIV-1 integrase inhibitory activity as potent as L-chicoric acid.

Human immunodeficiency virus (HIV) is the probable causative agent of acquired immune deficiency syndrome (AIDS), which is one of the world's most serious health problems. Several biological processes in the life cycle of this virus have been targeted for anti-HIV therapy. Integrase (IN) catalyzes the integration of HIV DNA copy into the host cell DNA. Such integration is essential for the production of progeny viruses, and therefore therapeutic agents that can inhibit this process should be effective anti-HIV agents.[1–3] For the past few years, extensive efforts have been made resulting in a large number of HIV IN inhibitors. Recent studies showed that L-chicoric acid (**1**) and dicaffeoylquinic acids (DCQAs, for example, compound **2**) display potent activity against HIV IN and can inhibit HIV replication with moderate anti-HIV activity.[4–9] To further improve the anti-HIV effect in tissue culture, several analogues of L-chicoric acid (**1**) and DCQAs have been synthesized. The common structural features of reported synthetic analogues are caffeic acid esters separated by aliphatic, alicyclic, or aromatic linker.[10,11]

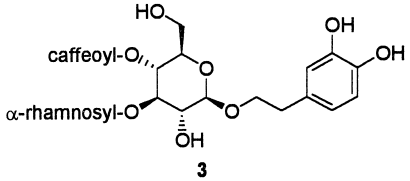
In an effort to identify new HIV-1 IN inhibitors from medicinal plants, we have recently isolated several HIV-1 IN inhibitory phenylpropanoid glycosides from the extract of *Clerodendron trichotomum*.[12] Among isolated compounds, phenylpropanoid glycoside **3**, which contains a β-D-glucopyranoside as a basic skeleton with an L-rhamnopyranosyl and a caffeoyl substituent, showed potent inhibitory activity against HIV-1 IN (IC_{50} = 7.8 μM). We envisioned that the compound **3** has a structural similarity to DCQAs since two substituents were separated by a glucose linker instead of a quinic acid ring of DCQAs. Furthermore, there is no report on the synthesis of caffeic acid esters separated by a sugar ring as a central linker. In the present studies, we synthesized and



1, L-Chicoric Acid

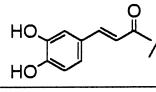


2, 4,5-DCQA



3

caffeoyl :



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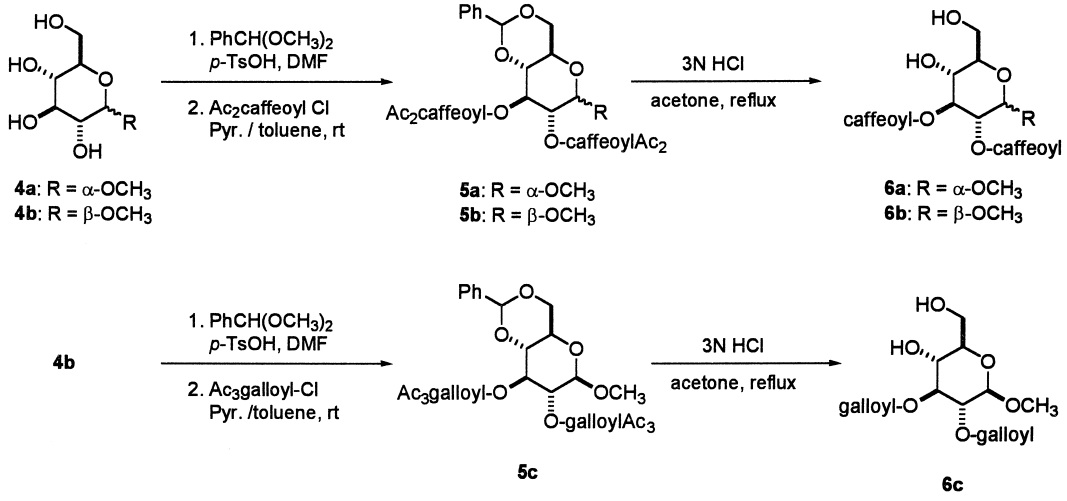
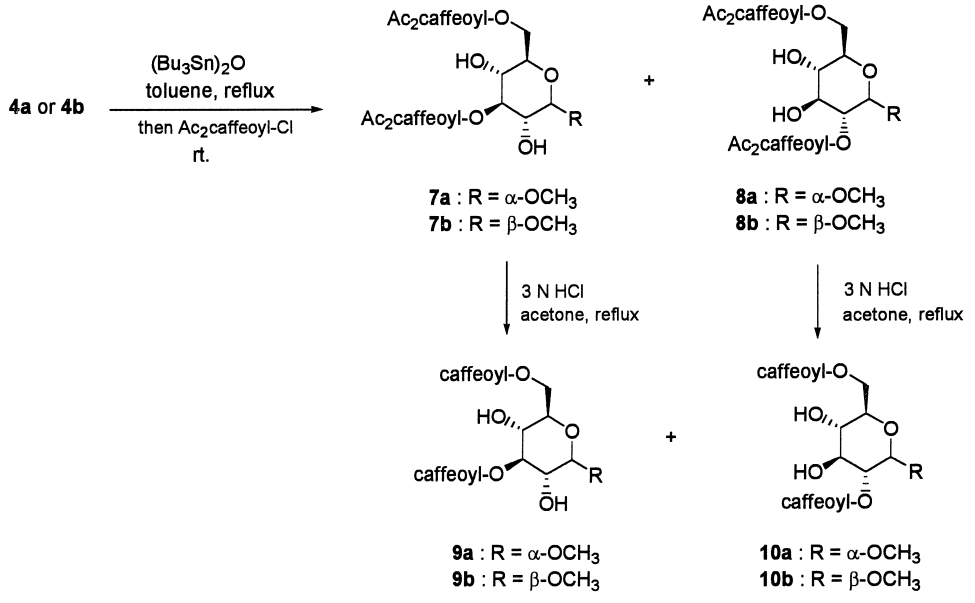
tested a new class of compounds with HIV-1 IN inhibitory activities, which have a glucose ring as a central linker. To simplify the structure of parent compound **3** and examine the effect of the glycosidic bond on the activity, methyl α-D-glucoside (**4a**) and methyl β-D-glucoside (**4b**) were used as starting materials instead of 3,4-dihydroxyphe-nylethyl glucosides.

The 4- and 6-hydroxyl groups of **4a** and **4b** were benzylideneated with benzaldehyde dimethyl acetal in DMF containing catalytic *p*-toluenesulfonic acid by heating to 80 °C under reduced pressure (Scheme 1).[13] The residual 2- and 3-hydroxyl groups were acylated with diacetylcaf-feoyl chloride (Ac_2caffeoyl-Cl) to give **5a** and **5b**. The benzylidene and acetyl protecting groups were removed concomitantly in refluxing acetone containing aqueous HCl to provide **6a** and **6b**, respectively.[11,14] 2,3-Digalloyl glucoside **6c** was also synthesized from **4b** by using triacetylgalloyl chloride (Ac_3galloyl-Cl) in a similar procedure as above since digalloyl-substituted tartaric acid derivatives were found to be potent inhibitors of HIV-1 IN.[11]

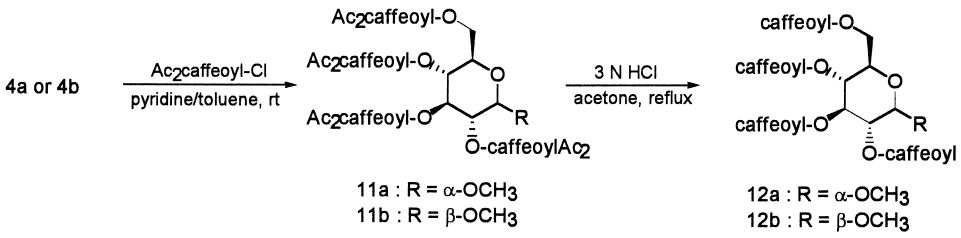
In order to investigate the influence of the position of caffeoyl groups on the HIV-1 IN inhibitory activity, 2,6- and 3,6-dicaffeoylglucosides (**9**, **10**) were synthesized (Scheme 2). The selective acylation of caffeoyl groups at 2- and 6-positions was carried out after conversion to the tributyltin ethers. Treatment of methyl α-D-glucoside (**4a**) with dibutyltin oxide in refluxing toluene followed by addition of Ac_2caffeoyl-Cl at room temperature afforded 2,6-Ac_2caffeoylglucoside **7a** and 3,6-Ac_2caffeoylglucoside **8a** in 16:1 ratio. On the other hand, acylation of methyl β-D-glucoside (**4b**) by the same procedure was not regioselective resulting in the formation of **7b** and **8b** in 1.7:1 ratio.[15] The acetyl protecting groups were removed by refluxing in acetone containing aqueous HCl to provide 2,6- and 3,6-caffeoylglucosides (**9a–b**, **10a–b**).[16]



Scheme 1.



Scheme 2.



Scheme 3.

Table 1. HIV-1 integrase inhibitory activities of caffeoylglucosides[18]

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
6a	29.1	**10b**	30.5
6b	31.8	**12a**	>118.7
6c	5.4	**12b**	89.6
9a	82.4	**3**	7.8
9b	35.1	Curcumin[a]	57.5
10a	70.0	L-Chicoric acid[b]	24.9

[a]Curcumin was purchased from Aldrich®.
[b]L-Chicoric acid was prepared by a known method.[10]

In order to examine the influence of a number of caffeoyl groups on the activity, fully caffeoylated glucosides **12a** and **12b** were also synthesized in a similar manner (Scheme 3).[17]

The caffeoylglucosides were tested for inhibitory activity against HIV-1 IN (Table 1). The activities of curcumin, L-chicoric acid and a phenylpropanoid glycoside **3**, isolated from the extract of *Clerodendron trichotomum* were included for comparisons. The inhibitory activities of 2,3-dicaffeoylglucosides (**6a**, **6b**) and 3,6- and 2,6-dicaffeoylglucosides (**9b**, **10b**), derived from methyl β-D-glucoside were more potent than that of curcumin and comparable to L-chicoric acid. However, all caffeoylglucosides were less active than the parent compound **3** implicating the important role of L-rhamnopyranosyl or 3,4-dihydroxyphenylethyl group in the binding with HIV-1 IN. β-Methyl glucosides, except **6b**, have more enhanced HIV-1 IN inhibitory activity than their α-anomers, respectively. Interestingly, upon substitution of digalloyl groups at the 2- and 3-positions of glucose (**6c**) instead of caffeoyl groups, the inhibitory activity was remarkably increased. More substitutions than two caffeoyl groups decreased the IN inhibitory activity (**12a**, **12b**). However, more studies on the caffeoylglucosides would be needed since none of the caffeoylglucosides synthesized in this study could inhibit the replication of HIV-1 at nontoxic concentration (data not shown).

In conclusion, we have synthesized and tested the inhibitory activities of new types of HIV-1 IN inhibitors which have a glucose ring as a basic skeleton. This work is the first example of the synthesis of caffeic acid esters separated by a sugar ring as a central linker for the development of HIV-1 integrase inhibitors.

Acknowledgements

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14. The yields were not optimized. **5a**; 66% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44 (d, 1H, J=16.0 Hz), 7.41 (d, 1H, J=16.0 Hz), 7.28–7.00 (m, 11H), 6.18 (d, 1H, J=16.0 Hz), 6.15 (d, 1H, J=16.0 Hz), 5.62 (t, 1H, J=9.7 Hz), 5.36 (s, 1H), 4.91 (dd, 1H, J=9.8, 3.7 Hz), 4.86 (d, 1H, J=3.7 Hz), 4.16 (dd, 1H, J=10.1, 4.7 Hz), 3.83 (td, 1H, J=9.8, 4.7 Hz), 3.64 (t, 1H, J=10.2 Hz), 3.59 (t, 1H, J=9.6 Hz), 3.26 (s, 3H), 2.11–2.09 (m, 12H). **5b**; 58% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63 (d, 1H, J=16.0 Hz), 7.60 (d, 1H, J=16.0 Hz), 7.47–7.19 (m, 11H), 6.36 (d, 1H, J=16.0 Hz), 6.35 (d, 1H, J=15.9 Hz), 5.57 (t, 1H, J=9.5 Hz), 5.57 (s, 1H), 5.25 (t, 1H, J=9.3 Hz), 4.63 (d, 1H, J=7.8 Hz), 4.45 (dd, 1H, J=10.4, 4.8 Hz), 3.92–3.80 (m, 2H), 3.64 (td, 1H, J=9.5, 4.8 Hz), 3.57 (s, 3H), 2.33–2.30 (m, 12H). **6a**; 38% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.55 (d, 1H, J=15.9 Hz), 7.52 (d, 1H, J=15.9 Hz), 7.00 (s, 1H), 6.99 (s, 1H), 6.90 (d, 1H, J=8.2 Hz), 6.89 (d, 1H, J=8.2 Hz), 6.74 (2d, 1H each, J=8.2 Hz), 6.25 (d, 1H, J=15.9 Hz), 6.17 (d, 1H, J=15.8 Hz), 5.53 (m, 1H), 4.98 (d, 1H, J=3.5 Hz), 4.90 (1H, overlapped with HDO signal), 3.89–3.62 (m, 4H), 3.44 (s, 3H). **6b**; 10% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.53 (d, 1H, J=15.8 Hz), 7.51 (d, 1H, J=15.9 Hz), 7.01 (2s, 2H), 9.91 (d, 2H, J=7.9 Hz), 6.10 (2d, 2H, J=8.1 Hz), 6.24 (d, 1H, J=15.8 Hz), 6.19 (d, 1H, J=15.9 Hz), 5.28

(t, 1H, J = 9.5 Hz), 4.98 (dd, 1H, J = 9.8, 8.0 Hz), 4.62 (d, 1H, J = 8.0 Hz), 4.06–3.66 (m, 4H), 3.54 (s, 3H). **5c**; 16% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (s, 2H), 7.74 (s, 2H), 7.43–7.40 (m, 2H), 7.37–7.32 (m, 3H), 5.71 (t, 1H, J = 9.5 Hz), 5.54 (s, 1H), 5.37 (dd, 1H, J = 8.9, 8.2 Hz), 4.65 (d, 1H, J = 7.8 Hz), 4.44 (dd, 1H, J = 10.5, 4.8 Hz), 3.91–3.84 (m, 2H), 3.65 (td, 1H, J = 9.5, 4.8 Hz), 3.52 (s, 3H), 2.29–2.27 (m, 18H). **6c**; 44% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 6.89 (s, 2H), 6.85 (s, 2H), 5.32 (t, 1H, J = 8.7 Hz), 4.98 (dd, 1H, J = 9.7, 8.0 Hz), 4.54 (d, 1H, J = 8.0 Hz), 3.84 (dd, 1H, J = 11.9, 1.7 Hz), 3.68 (dd, 1H, J = 11.9, 5.3 Hz), 3.65 (d, 1H, J = 9.5 Hz), 3.43–3.41 (bs, 4H).

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16. The yields were not optimized. **7a**; 2% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74 (d, 2H, J = 15.9 Hz), 7.71–7.42 (m, 4H), 7.29 (d, 1H, J = 8.3 Hz), 7.27 (d, 1H, J = 8.3 Hz), 6.51 (d, 2H, J = 16.1 Hz), 5.27 (t, 1H, J = 9.5 Hz), 4.91 (d, 1H, J = 3.8 Hz), 4.72 (dd, 1H, J = 12.2, 4.3 Hz), 4.49 (dd, 1H, J = 12.2, 2.0 Hz), 3.95 (ddd, 1H, J = 9.9, 4.0, 2.0 Hz), 3.77 (bs, 1H), 3.66 (t, 1H, J = 9.5 Hz), 3.54 (s, 3H), 3.23 (bs, 1H, OH), 2.39–2.36 (m, 13H) . **7b**; 14% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70 (d, 1H, J = 15.9 Hz), 7.67 (d, 1H, J = 16.0 Hz), 7.43–7.37 (m, 4H), 7.24–7.17 (m, 2H), 6.47 (d, 1H, J = 16.1 Hz), 6.45 (d, 1H, J = 16.0 Hz), 5.09 (t, 1H, J = 9.0 Hz), 4.61 (d, 1H, J = 11.7 Hz), 4.49 (d, 1H, J = 12.0 Hz), 4.34 (d, 1H, J = 7.7Hz), 3.81 (s, 1H), 3.72–3.46 (m, 6H), 3.08 (d, 1H, J = 2.8 Hz), 2.32–2.29 (m, 12H) . **8a**; 34% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (d, 1H, J = 16.0 Hz), 7.70 (d, 1H, J = 16.0 Hz), 7.47–7.38 (m, 4H), 7.26 (d, 1H, J = 8.4 Hz), 7.24 (d, 1H, J = 8.3 Hz), 6.49 (d, 1H, J = 15.9 Hz), 6.48 (d, 1H, J = 16.0 Hz), 5.03 (d, 1H, J = 3.7 Hz), 4.87 (dd, 1H, J = 10.0, 3.7 Hz), 4.75 (dd, 1H, J = 12.2, 3.9 Hz), 4.39 (d, 1H, J = 12.2 Hz), 4.10 (t, 1H, J = 9.4 Hz), 3.87 (d, 1H, J = 9.6 Hz), 3.52 (t, 1H, J = 9.3 Hz), 3.43 (s, 3H), 3.25 (bs, 1H, OH), 2.69 (bs, 1H, OH), 2.33–2.32 (2s, 12H) . **8b**; 8% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68 (d, 1H, J = 16.0 Hz), 7.67 (d, 1H, J = 16.0 Hz), 7.44–7.34 (m, 4H), 7.25–7.21 (m, 2H), 6.46 (d, 1H, J = 16.0 Hz), 6.44 (d, 1H, J = 16.0 Hz), 4.95 (dd, 1H, J = 9.3, 8.0 Hz), 4.60–4.48 (m, 2H), 4.44 (d, 1H, J = 8.0 Hz), 3.71–3.56 (m, 3H), 3.51 (s, 3H), 2.32–2.30 (m, 12H) . **9a**; 42% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.77 (d, 1H, J = 15.9 Hz), 7.75 (d, 1H, J = 15.9 Hz), 7.23–7.19 (m, 2H), 7.15–7.07 (m, 2H), 6.97–6.92 (m, 2H), 6.51 (d, 1H, J = 15.9 Hz), 6.47 (d, 1H, J = 15.9 Hz), 5.46 (t, 1H, J = 9.5 Hz), 4.92 (d, 1H, J = 3.7 Hz), 4.67 (dd, 1H, J = 11.9, 2.1 Hz), 4.52 (dd, 1H, J = 11.9, 5.7 Hz), 4.07 (ddd, 1H, J = 9.9, 5.6, 2.1 Hz), 3.79 (m, 2H), 3.64 (s, 3H), 3.23 (bs, 1H, OH), 2.39–2.36 (m, 13H) . **9b**; 87% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.71 (d, 1H, J = 15.9 Hz), 7.70 (d, 1H, J = 15.9 Hz), 7.17 (s, 1H), 7.16 (s, 1H), 7.10–7.05 (m, 2H), 6.89 (d, 1H, J = 8.1 Hz), 6.88 (d, 1H, J = 8.1 Hz), 6.45 (d, 1H, J = 15.9 Hz), 6.43 (d, 1H, J = 15.9 Hz), 5.19 (t, 1H, J = 9.2 Hz), 4.62 (t, 1H, J = 12.0 Hz), 4.46 (dd, 1H, J = 12.0, 5.0 Hz), 4.45 (d, 1H, J = 7.8 Hz), 3.79–3.61 (m, 5H), 3.51 (dd, 1H, J = 9.5, 7.8 Hz) . **10a**; 32% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.63 (d, 1H, J = 15.9 Hz), 7.60 (d, 1H, J = 15.9 Hz), 7.07 (d, 1H, J = 2.1 Hz), 7.06 (d, 1H, J = 2.2 Hz), 6.98 (d, 1H, J = 8.1 Hz), 6.80 (d, 1H, J = 8.2 Hz), 6.33 (d, 1H, J = 15.9 Hz), 6.32 (d, 1H, J = 15.9 Hz), 4.94 (d, 1H, J = 3.7 Hz), 4.74 (dd, 1H, J = 10.0, 3.7 Hz), 4.53 (dd, 1H, J = 11.9, 2.1 Hz), 4.37 (dd, 1H, J = 11.8, 5.7 Hz), 3.92 (t, 1H, J = 9.4 Hz), 3.78 (m, 1H), 3.49 (t, 1H, J = 9.3 Hz), 3.42 (s, 3H) . **10b**; 59% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.55 (d, 1H, J = 15.9 Hz), 7.53 (d, 1H, J = 15.9 Hz), 7.01 (s, 2H), 6.92 (d, 2H, J = 8.4 Hz), 6.74 (d, 2H, J = 8.1 Hz), 6.28 (d, 1H, J = 15.9 Hz), 6.26 (d, 1H, J = 15.9 Hz), 4.79 (dd, 1H, J = 9.3, 8.2 Hz), 4.48 (d, 1H, J = 10.4 Hz), 4.43 (d, 1H, J = 8.0 Hz), 4.33 (m, 1H), 3.61–3.55 (m, 2H), 3.50–3.42 (m, 4H) .

17. The yields were not optimized. **11a**; 31% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69 (d, 1H, J = 15.9 Hz), 7.64 (d, 1H, J = 15.8 Hz), 7.61 (d, 1H, J = 16.0 Hz), 7.56 (d, 1H, J = 15.9 Hz), 7.43–7.16 (m, 12H), 6.46 (d, 1H, J = 16.0 Hz), 6.38 (d, 1H, J = 16.1 Hz), 6.32 (d, 1H, J = 16.1 Hz), 6.28 (d, 1H, J = 16.0 Hz), 5.84 (t, 1H, J = 9.8 Hz), 5.39 (t, 1H, J = 9.8 Hz), 5.17 (dd, 1H, J = 10.0, 3.7 Hz), 5.12 (d, 1H, J = 3.5 Hz), 4.45–4.34 (m, 2H), 4.25–4.21 (m, 1H), 3.51 (s, 3H), 2.33–2.28 (m, 24H) . **11b**; 20% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 (d, 1H, J = 15.7 Hz), 7.53 (d, 1H, J = 14.6 Hz), 7.51 (d, 1H, J = 15.7 Hz), 7.46 (d, 1H, J = 14.5 Hz), 7.32–7.22 (m, 8H), 7.14–7.08 (m, 4H), 6.35 (d, 1H, J = 16.0 Hz), 6.26 (d, 1H, J = 15.9 Hz), 6.22 (d, 1H, J = 15.9 Hz), 6.17 (d, 1H, J = 15.9 Hz), 5.48 (t, 1H, J = 9.6 Hz), 5.31 (t, 1H, J = 9.7 Hz), 5.20 (dd, 1H, J = 9.6, 7.9 Hz), 4.54 (d, 1H, J = 7.9 Hz), 4.37 (dd, 1H, J = 12.4, 3.0 Hz), 4.31 (dd, 1H, J = 12.3, 5.0 Hz), 3.88 (m, 1H), 3.35 (s, 3H), 2.24–2.10 (m, 24H). **12a**; 65% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.60 (d, 1H, J = 15.7 Hz), 7.56 (d, 2H, J = 15.5 Hz), 7.51 (d, 1H, J = 15.7 Hz), 7.05–7.01 (m, 3H), 6.97–6.85 (m, 5H), 6.77–6.71 (m, 4H), 6.29 (d, 1H, J = 15.9 Hz), 6.22 (d, 2H, J = 16.2 Hz), 6.16 (d, 1H, J = 16.0 Hz), 5.78 (t, 1H, J = 9.7 Hz), 5.36 (t, 1H, J = 9.7 Hz), 5.14–5.11 (m, 2H), 4.37–4.36 (m, 2H), 4.15–4.08 (m, 1H), 3.52 (s, 3H) . **12b**; 32% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.40 (d, 1H, J = 15.6 Hz), 7.35 (d, 2H, J = 15.5 Hz), 7.29 (d, 1H, J = 15.9 Hz), 6.86–6.65 (m, 8H), 6.58–6.52 (m, 4H), 6.10 (d, 1H, J = 15.9 Hz), 6.03 (d, 1H, J = 15.8 Hz), 6.02 (d, 1H, J = 15.9 Hz), 5.94 (d, 1H, J = 15.9 Hz), 5.41 (t, 1H, J = 9.5 Hz), 5.15 (t, 1H, J = 9.7 Hz), 4.98 (dd, 1H, J = 9.7, 8.1 Hz), 4.53 (d, 1H, J = 9.2 Hz), 4.19 (d, 2H, J = 3.5 Hz), 3.89 (m, 1H), 3.35 (s, 3H) .

18. The enzyme inhibition assay of compounds against HIV-1 integrase was carried out as described previously. Oh, J.-W.; Shin, C.-G. *Mol. Cells* **1996**, *6*, 96.