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Catechol-Substituted L-Chicoric Acid Analogues as HIV Integrase Inhibitors

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Abstract—HIV integrase catalyzes the integration of HIV DNA copy into the host cell DNA, which is essential for the production of progeny viruses. L-Chicoric acid and dicaffeoylquinic acids, isolated from plants, are well known potent inhibitors of HIV integrase. The common structural features of these inhibitors are caffeic acid derivatives connected to tartaric acid or quinic acid through ester bonds. In the present study, we have synthesized and tested the inhibitory activities of a new type of HIV IN inhibitors, which has catechol groups in place of caffeoyl groups in the structure of L-chicoric acid. Upon substitution of catechol groups at succinic acid, pyrrole-dicarboxylic acid, maleimide or maleic anhydride, the inhibitory activities ($IC_{50} = 3.8–23.6\,\mu M$) were retained or remarkably increased when compared to parent compound L-chicoric acid ($IC_{50} = 13.7\,\mu M$).

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.[1] Several biological processes in the life cycle of this virus have been targeted for anti-HIV therapy. Accordingly, a number of anti-HIV drugs targeting key enzymes for viral replication, HIV reverse transcriptase and HIV protease, has been approved in recent years for the treatment of HIV infected patients.[2] However, since the efficiency of these drugs is limited by the emergency of HIV mutants and adverse side effects further development of different type of drug is continuously required.

Another important step in the replication of HIV is integration of the viral DNA into the host cell DNA.[3] This step is catalyzed by the viral enzyme HIV integrase (IN). HIV IN catalyzes two distinct reactions, known as terminal cleavage at each 3′ end of the proviral DNA removing a pair of bases and strand transfer which results in the joining of each 3′ end to 5′-phosphates in the target 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.[4–6] Recently, HIV IN has also been recognized as a safe target against HIV because there are no similar enzymes involved in human cellular function.[7]

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 (**2**, DCQA) display potent inhibitory activity against HIV IN with moderate inhibitory activity on HIV replication (Fig. 1).[8–13] To further improve the anti-HIV effect, several analogues of L-chicoric acid (**1**) and DCQA have been synthesized. The common structural features of reported synthetic analogues are dicaffeoyl derivatives connected to aliphatic, alicyclic, or aromatic linker.[14,15] In our previous work, we also reported new types of caffeoyl-based HIV IN inhibitors, which have a glucose or five-membered heterocyclic ring as a basic skeleton.[16,17] However, almost precedent HIV IN inhibitors including our works have ester or amide bond which is expected to be susceptible to in vivo hydrolysis by plasma enzymes resulting in decreased bioavailability.[18] In this respect, the compounds having no ester or amide bonds between caffeoyl moiety and backbone might be potentially better HIV IN inhibitors with enhanced chemical and physiological stability if the inhibitory activities are retained.

Although the previous works showed that the caffeoyl group is required for the inhibitory activities against HIV IN,[14–17] it was envisioned that simplification of caffeoyl group into catechol group by removing acryloyl

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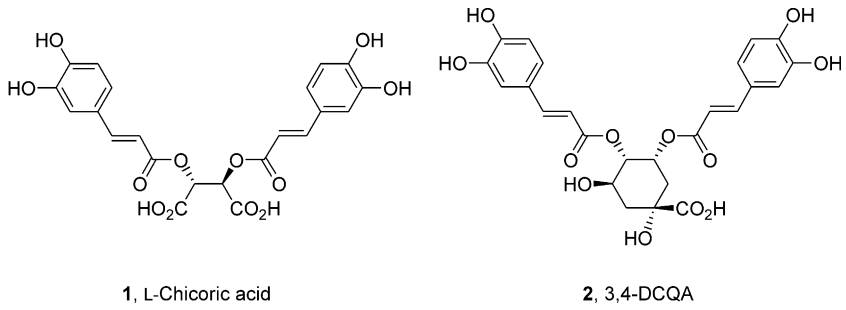


Figure 1.

part might also be effective for the inhibitory activity. Based upon these expectation, we prepared a new class of compounds (**3**–**5**), which have two catechol groups connected at succinic acid or pyrrole 2,5-dicarboxylic acid through carbon-carbon bond as shown in Figure 2. Additionally, we also synthesized catechol-substituted maleimide and maleic anhydride (**6**, **7**) to examine the effect of carboxylic acid group in this type of compounds on the inhibitory activity.

Catechol-substituted succinic acid derivatives (**3**, **4**) were synthesized straightforwardly by similar methods described in literatures as shown in Scheme 1.[19] Treatment of the dianions derived from 3,4-dimethoxyphenyl- or 3,4-dimethoxybenzylacetic acid with 2.2 equivalents of *n*-BuLi or lithium diisopropylamide (LDA) with 0.6 equivalent of iodine afforded **9a** and **9b** in 59 and 47% yields, respectively. Four methyl-protecting groups in **8a** and **8b** were removed with BBr_3 in CH_2Cl_2 to provide compounds **3** and **4** in 28 and 30% yields, respectively.

For the synthesis of catechol-substituted pyrrole-dicarboxylic acid **5**, 3-(3,4-dimethoxyphenyl)pyruvic acid (**10**) was transformed to pyrrole-dicarboxylic acid **11** in 55% yield by iodine-mediated coupling reaction followed by condensation of resulting dimer with ammonia and $TiCl_4$ (Scheme 2).[20] The methyl-protecting groups in **11** were removed again with BBr_3 to provide pyrrole-dicarboxylic acid **5** in 31% yield. The compound **11** was also utilized in the synthesis of catechol-substituted maleimide and maleic anhydride (**6**, **7**). On oxidation of pyrrole-dicarboxylic acid **11** with sodium hypochlorite and quenching with sodium hydrogensulfite maleimide derivative **12** was obtained in 78% yield. Removal of methyl groups in **12** provided catechol-substituted maleimide **6** in 82% yield. Catechol-substituted maleic anhydride **7** could also be obtained from maleimide **12** by hydrolysis followed by deprotection of *O*-methyl groups of the resulting anhydride **12** in 81% combined yield.[21]

The resulting catechol-substituted compounds **3**–**7** were assayed on inhibition of HIV IN (Table 1).[22] To compare the inhibitory activity, L-chicoric acid (**1**) was prepared by using a known procedure[23] and the activity data was included as a reference in Table 1. Every compound showed good to excellent HIV IN inhibitory activities with IC_{50} values in the range of 3.8–23.6 μM. As expected, *O*-methylated compounds (**9a**, **9b**, **11**–**13**) showed complete lack of inhibitory activities ($IC_{50} > 150$ μM) to indicate the importance of catechol group on the activity. The inhibitory activities of succinic acid derivatives (**3**, **4**) were comparable or somewhat inferior to L-chicoric acid ($IC_{50} = 13.7$ μM). On the other hand, catechol-substituted pyrrole-dicarboxylic acid **5** exhibited about 2-fold more potent inhibitory activity than L-chicoric acid. Furthermore, catechol-

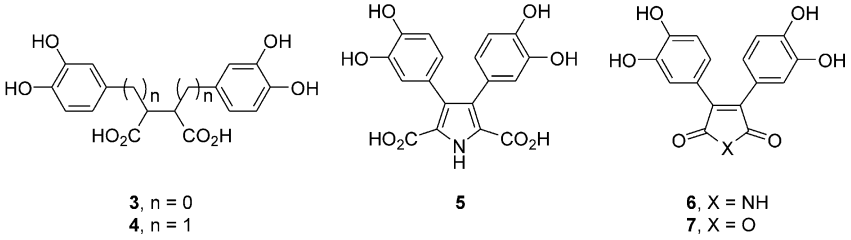
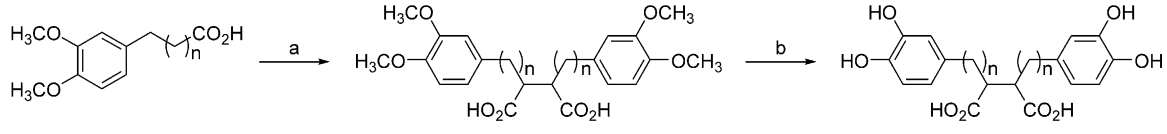
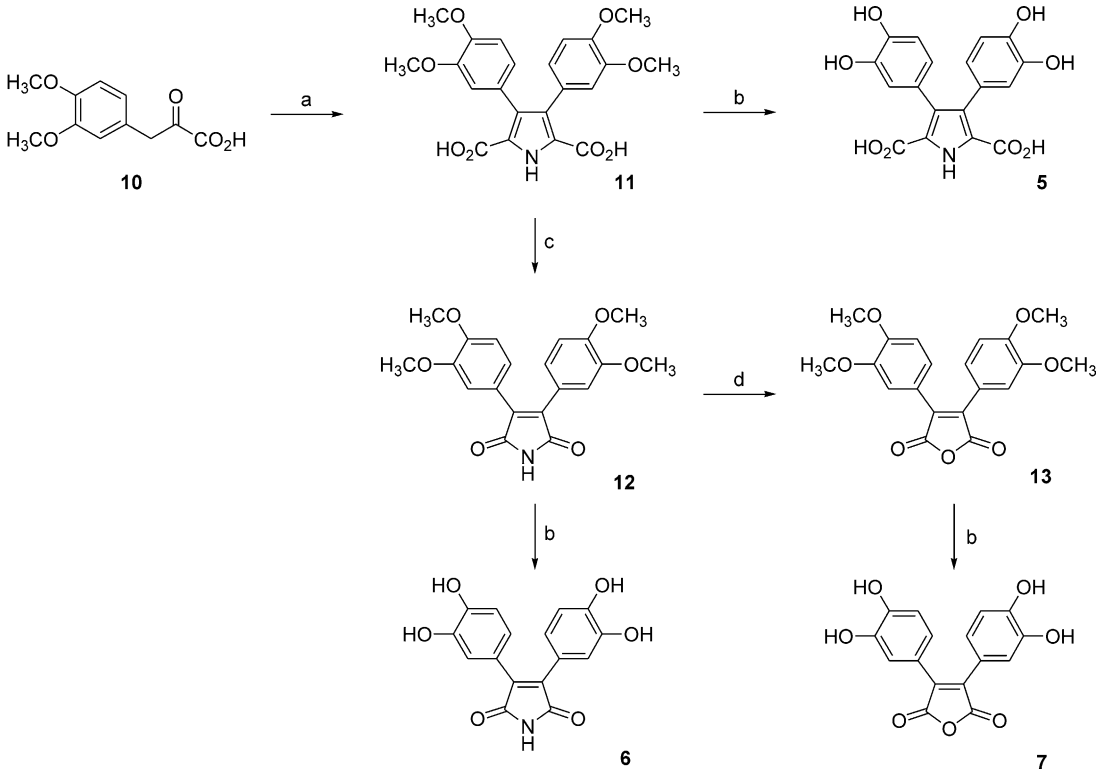


Figure 2.



Scheme 1. Reagents: (a) for **8a**, *n*-BuLi in THF, then I_2; for **8b**, LDA in THF, then I_2; (b) BBr_3 in CH_2Cl_2.



Scheme 2. Reagents: (a) (i) *n*-BuLi in THF, then I_2, (ii) NH_3, $TiCl_3$; (b) BBr_3 in CH_2Cl_2; (c) NaOCl, then $NaHSO_3$; (d) (i) KOH; (ii) HCl.

Table 1. HIV-1 Integrase inhibitory activities of catechol-substituted compounds (**3**–**7**)

Compd	IC_{50} (μM)[b]	Compd	IC_{50} (μM)
3[a]	23.6±5.4	**6**	15.5±5.5
4[a]	19.1±3.5	**7**	3.8±3.1
5	5.3±2.1	L-Chicoric acid[c]	13.7±3.4

[a]Compounds are racemic mixtures.
[b]All values are averages of at least three runs.
[c]L-Chicoric acid was prepared by known method.[24]

substituted malic anhydride **7** showed the most potent inhibitory activity with IC_{50} value of 3.8 μM. It is interesting to note that even after elimination of carboxylic acid groups as in compounds **6** and **7**, the inhibitory activities were retained or even remarkably increased implicating the different binding modes of these compounds to HIV IN. These data indicate that for HIV IN inhibitory activity catechol group can be substituted directly at succinic acid or other skeleton through carbon–carbon bond instead of caffeoyl ester group. However, more studies on the catechol-substituted compounds would be needed since none of the compounds synthesized could inhibit the replication of $HIV\text{-}1_{IIIB}$ infected MT-4 cells under nontoxic concentration (data not shown) in spite of their excellent HIV IN inhibitory activities.[22]

In conclusion, we have synthesized and tested the inhibitory activities of a new type of HIV IN inhibitors, which has catechol groups instead of caffeoyl groups in the structure of L-chicoric acid. Upon substitution of catechol groups at succinic acid, pyrrole-dicarboxylic acid, maleimide or maleic anhydride, the inhibitory activities were retained or remarkably increased when compared to parent compound L-chicoric acid. This work is the first example on the synthesis of catechol-substituted dicarboxylic acid, maleimide and maleic anhydride for the development of HIV IN inhibitors.

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21. Selected spectroscopic data. **3**: IR (KBr) 3444, 3252, 1718, 1604, 1526, 1444 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.53–6.48 (m, 4H), 6.34 (d, 2H, $J = 11.1$ Hz), 3.75 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 51.6, 53.1, 115.2, 115.5, 119.4, 126.6, 127.2, 144.8, 173.7, 174.6. **4**: IR (KBr) 3418, 3276, 1720, 1606, 1530 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.58 (d, 2H, $J = 7.8$ Hz), 6.5 (s, 2H), 6.35 (d, 2H, $J = 7.8$ Hz), 3.16 (m, 2H), 2.69–2.67 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 34.7, 48.9, 115.6, 116.6, 119.9, 131.9, 143.5, 145.1, 176.5. **5**: IR (KBr) 3388, 2934, 1608, 1546, 1356 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.69 (s, 1H), 6.54 (s, 2H), 6.42 (d, 2H, $J = 6.0$ Hz), 6.23 (d, 2H, $J = 6.0$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 170.0, 143.4, 142.9, 128.4, 127.5, 122.0, 119.2, 113.9. **6**: IR (KBr) 3423, 3347, 3288, 1713, 1612, 1482 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 6.93 (s, 2H), 6.89 (d, 2H, $J = 8.3$ Hz), 6.86 (d, 2H, $J = 8.3$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 106.9, 108.1, 115.4, 115.7, 116.7, 116.9, 120.0, 121.5, 121.8, 123.2, 127.6, 134.0, 145.0, 146.9, 147.5, 149.2, 171.6, 172.2. **7**: IR (KBr) 3594, 3364, 1816, 1744, 1600, 1520, 1440 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.96 (s, 2H), 6.88 (d, 2H, $J = 8.3$ Hz), 6.77 (d, 2H, $J = 8.3$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 115.5, 116.4, 118.7, 121.6, 135.0, 145.1, 148.0, 165.6.
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