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6-Hydroxy-1,3-dioxin-4-ones as Non-Peptidic HIV Protease Inhibitors

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Abstract—HIV protease inhibitors containing 6-hydroxy-1,3-dioxin-4-one ring system as a new scaffold have been prepared. Among them, compound **4d** showed potent HIV protease inhibitory activity ($IC_{50} = 0.01$ μM) and antiviral activity in cell culture ($EC_{50} = 0.96$ μM, SI = 65.69).

The alarming spread of the acquired immunodeficiency syndrome (AIDS) epidemic has stimulated the discovery of therapeutic agents to inhibit the replication of the causative virus, human immunodificiency virus (HIV).[1] The advanced understanding of viral cell cycle has made it possible to define the targets to interrupt the life cycle of virus. Among them, one such target is the virally encoded protease which is essential for viral maturation.[2] Although a number of compounds with potent activity have been reported as the protease inhibitors,[3,4] most of them are peptidomimetic compounds and therefore often possess pharmacological problems,[5] such as low oral bioavailability, rapid excretion, or synthetic difficulty of multi steps.

Since the discovery of phenprocoumon (**1**, Fig. 1) as a non-peptidic HIV protease inhibitor using a random screening approach,[6] various 4-hydroxypyrones have been synthesized by many research groups.[7–9] As a result, tipranavir (PNU-140690: **2**, Fig. 1) was identified to be a potent HIV protease inhibitor exhibiting low toxicity, acceptable drug delivery and distribution characteristics. It is currently undergoing clinical trials as a therapeutic agent for treatment of AIDS.[10]

During a continuous effort in our laboratory to develop new potent small molecules of the protease inhibitors, we designed 6-hydroxy-1,3-dioxin-4-one **4** as a possible scaffold of HIV-1 protease inhibitor based on the knowledge of X-ray crystal structure of the HIV protease complexed with 4-hydroxypyrone compound **3** (Fig. 2); the lactone carbonyl of pyrone ring forms hydrogen bonds with the backbone amide groups of isoleucine 50 and isoleucine 50′ on the flap of the enzyme, and the 4-hydroxy functionality forms hydrogen bonds with the carboxylic acids of the catalytic 25 and 25′ aspartic acid (Fig. 2).[11] We expected that a similar core binding mode would occur in 6-hydroxy-1,3-dioxin-4-one **4** as an isostere of 4-hydroxy-5,6-dihydropyrone and that additional hydrogen bonds might be possible via interaction of the oxygen atom at the 1 position of the dioxinone ring with HIV-1 protease residues (Fig. 2). Therefore, we wished to examine the influence of oxygen atom on the HIV protease inhibitory activity and antiviral activity in the cell culture.

With this in mind, we embarked on the synthesis of 6-hydroxy-1,3-dioxin-4-one derivatives (**4a**–**f**) for non-peptidic HIV protease inhibitor. Our synthetic effort was focused on the variation of the *m*-sulfonamide substituent of the phenyl ring at the C-5α position while the ethyl group in the C-5α position and C-2 side chains of 6-hydroxy-1,3-dioxin-4-one were fixed as shown in the structure of compounds **4a**∼**f** because these side chains in 4-hydroxypyrone are well known to fill five binding pockets (S_1, S_2, S_3, S_1', and S_2') of HIV protease (Scheme 1).[10]

As illustrated in Scheme 1, the reaction of 1-phenyl-3-hexanone (**5**) with malonic acid (18 equiv) in acetic anhydride in the presence of concd sulfuric acid afforded 1,3-dioxane-4,6-dione ring system **6** in 32%

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yield with the recovered 1-phenyl-3-hexanone (31%). Aluminum trichloride-catalyzed condensation of 1,3-dioxane-4,6-dione ring with *m*-nitrobenzaldehyde afforded a benzylidene intermediate, which was not isolated and directly reacted with triethylaluminum in the presence of copper(I) bromide–dimethyl sulfide to give the fully functionalized 6-hydroxy-1,3-dioxin-4-one **7** as a racemic mixture in 47% yield.[10] Reduction of the nitro group in compound **7** was accomplished using a catalytic hydrogenation in methanol to afford the free amine compound **8**, which was coupled with various arylsulfonyl chlorides in the presence of pyridine to provide the final sulfonamides **4a**–**f** in good yields.[12] Compound **4f** was obtained from **4e** by a catalytic hydrogenation on palladium–charcoal in 94% yield.

The resulting 6-hydroxy-1,3-dioxin-4-one derivatives **4a**–**f** have been assayed on inhibition of HIV protease. Shown in Table 1 are IC_{50} values on HIV-1 protease and CC_{50} and EC_{50} values in a cell culture assay using HIV-I_{IIIB} infected MT-4 cells. For the purpose of comparison of biological activity, we prepared a racemic form of **2** (***rac*-2**) as a reference by using a known procedure.[10]

In general, all compounds **4a**–**f** showed good HIV protease inhibitory activities with IC_{50} values in the 0.003–0.065 μM range, as compared to ***rac*-2** ($IC_{50} = 0.05$ μM). This result explains more efficient binding of 6-hydroxy-1,3-dioxin-4-one derivatives to the active site of HIV protease. With respect to cytotoxicity, all compounds except **4e** (5-nitopyridine; $CC_{50} = 14.79$ μM) were found

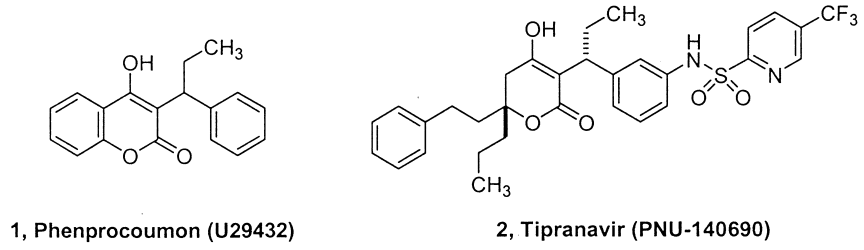


Figure 1. 4-Hydroxypyrone protease inhibitors.

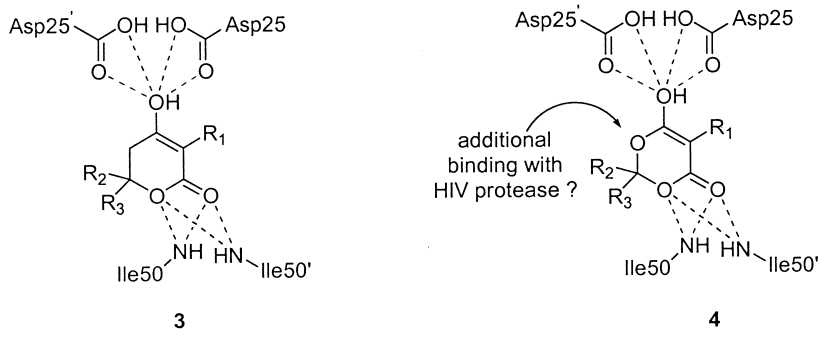
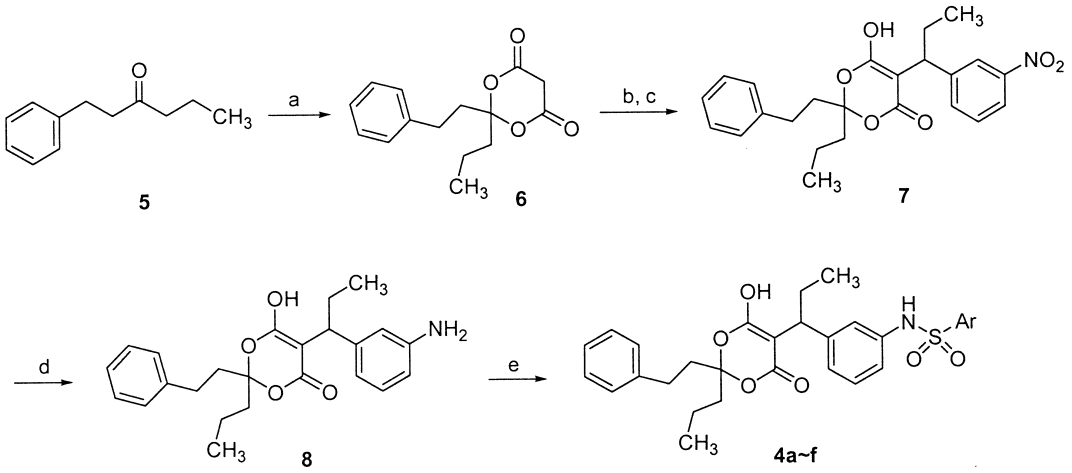


Figure 2. Potential 4-hydroxy-5,6-dihydropyrone (**3**) and 6-hydroxy-1,3-dioxin-4-one (**4**) core interactions.



Scheme 1. (a) Malonic acid (18 equiv), Ac_2O, concd H_2SO_4, 32%; (b) *m*-nitrobenzaldehyde, $AlCl_3$, THF; (c) Et_3Al, CuBr–Me_2S, THF, 47% (for two steps); (d) H_2, Pd/C, MeOH, 99%; (e) $ArSO_2Cl$, pyr., CH_2Cl_2.

Table 1. Yields and biological activity of 6-hydroxy-1,3-dioxin-4-one protease inhibitors **4a–f**

Compd[a]	Ar	Yields[b]	IC_{50} (μM)[c,d]	EC_{50} (μM)[c,e]	CC_{50} (μM)[c,e]	SI (CC_{50}/EC_{50})
4a		52	0.015	>66.53	66.53	< 1
4b		37	0.013	86.71	>178	>2.05
4c		50	0.003	11.37	76.96	6.77
4d		70	0.010	0.96	63.01	65.69
4e		51	0.065	>14.79	14.79	< 1
4f		94	0.013	>69.97	69.97	< 1
***rac*-2**[f]	—	—	0.050	0.70	18.60	26.57

[a]All compounds are racemic mixtures.
[b]Yields from compound **8**.
[c]All values are averages of at least two runs.
[d]HIV protease inhibitory activity.
[e]Antiviral activity in HIV-1_{IIIB} infected MT-4 cells.
[f]Racemic compound prepared by means of known procedure.[10]

to be less cytotoxic than compound ***rac*-2** (CC_{50} = 18.60 μM). However, they unexpectedly showed no antiviral activities in HIV-1_{IIIB} infected MT-4 cells under non-toxic concentration except (5-cyanopyridine)-sulfonamide- and (5-trifluoromethylpyridine) sulfonamide-substituted 6-hydroxy-1,3-dioxin-4-one derivatives (**4c**, **4d**). Compound **4d** exhibited good antiviral activity (EC_{50} = 0.96 μM) comparable to compound ***rac*-2** (EC_{50} = 0.7 μM), and showed a 2.5-fold lower cytotoxic effect (CC_{50} = 63.01 μM, SI = 65.69) than ***rac*-2** (SI = 26.57). This overall result implies that the compound **4d** would be a promising HIV-1 protease inhibitor because of potent enzyme inhibitory activity, antiviral activity, and lower cytotoxicity.

In conclusion, we have synthesized 6-hydroxy-1,3-dioxin-4-one derivatives **4a–f** as new HIV-1 protease inhibitors. The introduction of an oxygen atom in the dihydropyrone ring enhanced remarkably HIV protease inhibitory activity. Even though the antiviral activity was not improved, cytotoxicity was slightly lowered when compared to the parent dihydropyrone-based HIV protease inhibitor, ***rac*-2**.

Acknowledgements

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12. Selected ^{1}H NMR spectroscopic data. **4a**: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.85–7.65 (m, 3H), 7.63 (d, 1H, *J* = 8.6 Hz), 7.16–6.78 (m, 9H), 3.21 (m, 1H), 2.73 (m, 1H), 2.10–1.98 (m, 3H), 1.83–1.74 (m, 2H), 1.49–1.20 (m, 2H), 1.04 (m, 1H), 0.86–0.45 (m, 7H). **4b**: ^{1}H NMR (CD_3OD, 300 MHz) δ 8.59–8.48 (m, 1H), 7.89–7.78 (m, 2H), 7.47–7.16 (m, 1H), 7.15–6.77 (m, 9H), 3.38 (m, 1H), 2.55 (m, 1H), 2.10–1.87 (m, 4H), 1.74 (m, 1H), 1.46 (m, 1H), 1.30 (m, 1H), 0.94 (m, 1H), 0.85–0.45 (m, 7H). **4c**: ^{1}H NMR (CD_3OD, 300 MHz) δ 8.96–0.74 (m, 1H), 8.31–8.12 (m, 1H), 8.03–7.90 (m, 1H), 7.15–6.90 (m, 9H), 3.38 (m, 1H), 2.55 (m, 1H), 2.06–1.97 (m, 3H), 1.82–1.71 (m, 2H), 1.47 (m, 1H), 1.31 (m, 1H), 0.97 (m, 1H), 0.85–0.49 (m, 7H). **4d**: ^{1}H NMR (CD_3OD, 300 MHz) δ 8.95–8.82 (m, 1H), 8.28–8.12 (m, 1H), 8.07–7.97 (m, 1H), 7.15–6.80 (m, 9H), 3.21 (m, 1H), 2.52 (m, 1H), 2.10–1.90 (m, 3H), 1.80–1.68 (m, 2H), 1.45–1.41 (m, 2H), 1.00–0.90 (m, 1H), 0.83–0.45 (m, 7H). **4e**: ^{1}H NMR (CD_3OD, 300 MHz) δ 9.42–9.22 (m, 1H), 8.70–8.50 (m, 1H), 8.11–7.96 (m, 1H), 7.18–6.80 (m, 9H), 3.37 (m, 1H), 2.47 (m, 1H), 2.07–1.90 (m, 3H), 1.79–1.97 (m, 2H), 1.47 (m, 1H), 1.26 (m, 1H), 1.8 (m, 1H), 0.97–0.50 (m, 7H). **4f**: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.87–7.76 (m, 1H), 7.61–7.45 (m, 1H), 7.15–6.73 (m, 10H), 3.38 (m, 1H), 2.55 (m, 1H), 2.17–1.65 (m, 5H), 1.30–1.15 (m, 3H), 0.85–0.46 (m, 7H).