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Anti-HIV Agents. Part 55:† 3′*R*,4′*R*-Di-(*O*)-(−)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-*f*]chromone (DCP), a Novel Anti-HIV Agent

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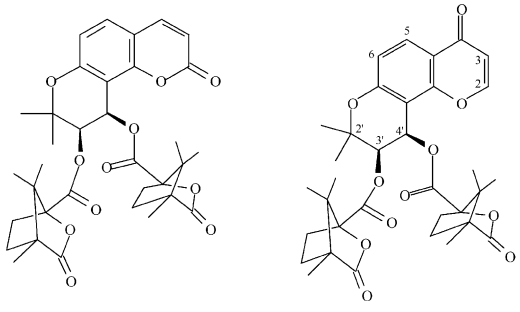
Abstract—3′*R*,4′*R*-Di-*O*-(−)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-*f*]chromone (DCP) (**2**) was designed and synthesized on the basis of a structure–activity relationship study of 3′*R*,4′*R*-di-*O*-(−)-camphanoyl-(+)-*cis*-khellactone DCK (**1**) and its analogues. DCP (**2**), a pyranochromone, and DCK (**1**), a pyranocoumarin, have different skeletons. Compound **2** showed potent in vitro inhibition of HIV-1 replication in H9 lymphocyte cells with an EC_{50} of 6.78×10^{-4} μM and TI of 14,500. These values are comparable with those for DCK (**1**) and better than those of AZT in the same assay.

Our previous papers reported the discovery of 3′,4′-di-*O*-(*S*)-camphanoyl-(+)-*cis*-khellactone (DCK, **1**) as a potent anti-HIV agent. It has a remarkable EC_{50} value of 2.56×10^{-4} μM and a therapeutic index (TI) of 1.37×10^{5} in HIV-1 infected H9 lymphocytes, and was more potent than AZT in the same assay.[1,2] Although their molecular target has not been identified, at least 20 DCK analogues have shown promising inhibitory activity against HIV-1 replication in H9 lymphocytes.[3] However, to conduct a QSAR study of DCK-type compounds, structural variety is needed. Thus, we replaced the coumarin nucleus in DCK with a chromone system in 3′*R*,4′*R*-di-*O*-(−)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-*f*]chromone (DCP) (**2**). This article reports the synthesis of **2** and its bioassay data in H9 lymphocytes (Fig. 1).

Our previous SAR study of DCK analogues showed that the aromaticity and planarity of the coumarin nucleus and the absolute configurations of the 3′ and 4′ position in the pyrano ring are key factors for the anti-HIV activity.[2–5] In this paper, we wanted to determine the importance of the position of the A ring carbonyl group; therefore, we changed the coumarin skeleton to a planar aromatic chromone. Coumarin and chromone are both benzopyranones, but they differ in the positions of the carbonyl group and double bond in their pyranone (A) ring.



1 **2**

Figure 1. Structures of DCK (**1**) and DCP (**2**).

The synthesis of DCP (**2**) was accomplished by a 5-step sequence, as illustrated in Scheme 1. 7-Hydroxychromone (**4**) was prepared in a 65% yield by treating 2′,4′-dihydroxyacetophone (**3**) with triethyl orthoformate and 70% perchloric acid, followed by aqueous hydrolysis of the intermediate perchlorate salt.[6] Compound **4** was then converted in two steps to 2′,2′-dimethyldihydropyrano[2,3-*f*]chromone (**6**) in a 30% yield.[4] The

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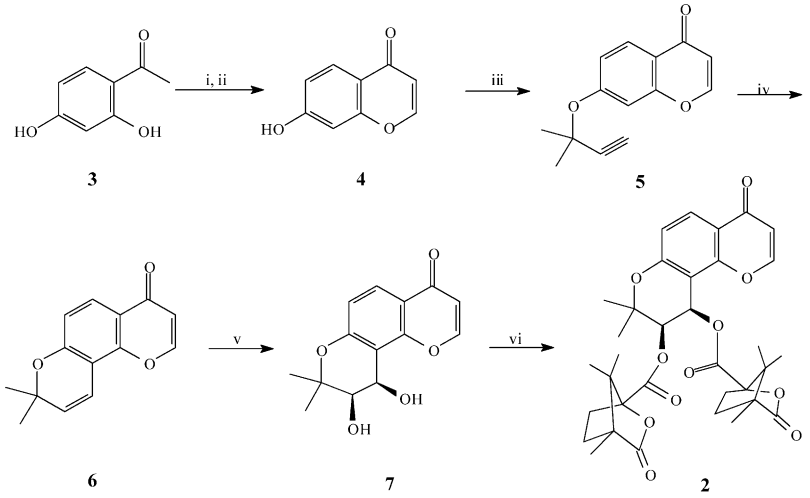

Scheme 1. Synthesis of DCP (**2**): (i) 70% perchloric acid, triethyl orthoformate, 40 min; (ii) H_2O, reflux, 5 min; (iii) K_2CO_3, KI, 3-chloro-3-methyl-1-butyne, DMF, 80 °C, 18–24 h; (iv) Diethylaniline, reflux, 4 h; (v) $K_3Fe(CN)_6$, $K_2Os_2O_2(OH)_4$, K_2CO_3, $(DHQ)_2PYR$ in *t*-butanol/H_2O 1:1, 0 °C, 24 h; (vi) camphanoyl chloride, pyridine/CH_2Cl_2, rt, 1–2 days.

Table 1. Anti-HIV activities of DCP (**2**) in acutely infected H9 lymphocytes

Compd	IC_{50}, μM[a]	EC_{50}, μM[b]	T.I.[c]
DCK (**1**)	35	2.56×10^{-4}	136,719
DCP (**2**)	9.83	6.78×10^{-4}	14,500
AZT	500	0.045	11,200

[a]Concentration that inhibits uninfected H9 cell growth by 50%.
[b]Concentration that inhibits viral replication by 50%.
[c]In vitro therapeutic index ($TI = IC_{50}/EC_{50}$).

dihydroxy pyranochromone (**7**) was prepared in a 40% yield, as in the asymmetric synthesis of DCK, by Sharpless asymmetric dihydroxylation (AD) of **6** with $K_3Fe(CN)_6$ as oxidant in conjunction with catalytic amounts of $K_2OsO_2(OH)_4$ and $(DHQ)_2$-PYR as a chiral catalyst.[7–9] Compound **7** was then reacted with (−)-(*S*)-camphanoyl chloride at room temperature for 48 h, monitored by TLC, to produce DCP (**2**) in a 71% yield.[10] The % ee of the AD reaction was more than 90%.

DCP (**2**) was tested against HIV-1 replication in acutely infected H9 lymphocytes. The anti-HIV data, along with those of AZT and DCK included in the same assay for comparison, are shown in Table 1. DCP (**2**) showed potent activity with a remarkable EC_{50} of 6.78×10^{-4} μM and TI of 14,500. These values are comparable with those of DCK and better than those of AZT in the same assay.[11]

This modification study indicated that the coumarin nucleus can be replaced by a similar skeleton without loss of activity; therefore, the carbonyl group can be in position 4 of the nucleus. Additional modification and SAR studies are in progress with an aim to continually improve pharmacological properties.

Acknowledgements

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10. 3′*R*,4′*R*-di-(*O*)-(−)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-*f*]chromone (**2**): mp 90–92 °C; $[\alpha]_D$ −95.3° (*c* 0.17, $CHCl_3$); ESI–MS: 645 $(M+Na)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (1H, d, $J=9.0$, Hz, H-5), 7.69 (1H, d, $J=6.3$, H-2), 6.94 (1H, d, $J=9.0$, H-6), 6.72 (1H, d, $J=4.8$, H-4′), 6.32 (1H, d, $J=6.3$, H-3), 5.37 (1H, d, $J=4.8$, H-3′), 2.46, 2.20, 1.90, 1.74 (each 2H, m, camphanoyl CH_2), 1.52, 1.47 (each 3H, s, 2′-CH_3), 1.11, 1.10, 1.08, 1.02, 0.99, 0.89 (each 3H, s, camphanoyl CH_3). Anal. $(C_{34}H_{38}O_{11}\cdot1\frac{1}{2}H_2O)$, C, H.
11. HIV growth inhibition assay in H9 lymphocytes was performed by Panacos, Inc. and has been described previously.[5]