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Anti-AIDS agents 72. Bioisosteres (7-carbon-DCKs) of the potent anti-HIV lead DCK

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Abstract—Three 9,10-di-*O*-(−)-camphanoyl-7,8,9,10-tetrahydro-benzo[*h*]chromen-2-one (7-carbon-DCK) analogs (**3a**–**c**) were synthesized and evaluated for inhibition of HIV-1 replication in H9 lymphocytes. All three new carbon bioisosteres of the anti-HIV lead DCK showed anti-HIV activity. Compound **3a** had an EC_{50} value of 0.068 μM, which was comparable to that of DCK in the same assay. The preliminary results indicated that 7-carbon-DCK analogs merit attention as potential HIV-1 inhibitors for further development into clinical trials candidates.

3′,4′-Di-*O*-(−)-camphanoyl-(+)-*cis*-khellactone (DCK, **1**) demonstrated extremely potent inhibitory activity against HIV-1 replication in H9 lymphocytic cells with an EC_{50} value of 2.56×10^{-4} μM and a therapeutic index (TI) of 1.37×10^{5} in our prior research.[1] In subsequent structural modification studies, numerous DCK derivatives were synthesized and at least 20 DCK analogs have shown promising inhibitory activity against HIV-1 replication in H9 lymphocytes.[2] Among them, 3-methyl, 4-methyl, and 5-methyl substituted DCKs were much more potent than DCK and AZT in the same assay with EC_{50} and TI values ranging from 5.25×10^{-5} to 2.39×10^{-7} μM and 2.15×10^{6} to 3.97×10^{8}, respectively.[3] In addition, a preliminary mechanistic study showed that 3-hydroxymethyl-4-methyl DCK inhibits HIV reverse transcriptase (RT) via a different mechanism of action from those of current clinical anti-HIV/AIDS drugs.[4] It was also found that DCK analogs are strongly synergistic with approved drugs such as AZT and act at a point in the virus life cycle immediately following the target for AZT and nevirapine.[4] In our recent research on structural modification of 4-methyl DCK (**2**), the ring oxygen atom in the A or C ring of DCK was replaced by a sulfur atom, and these sulfur-containing analogs also exhibited potent inhibitory effects on HIV-1 replication in H9 lymphocytes.[5,6] Moreover, *gem*-dimethyl substitution at the 8-position was found to be preferable to larger alkyl substituents or hydrogen atoms.[7] In a continuing effort to identify the pharmacophores in this class of potent anti-HIV agents, we designed a new series of DCK analogs, namely 7-carbon-DCK derivatives (**3a**–**c**). In these compounds, a methylene group replaces the oxygen in the C ring of DCK. Thus, these analogs are bioisosteres of DCK, and the effect of the 7-oxygen atom on the anti-HIV activity of DCK-type compounds can be further explored. In addition, to help determine the possible impact of the 8,8-dimethyl groups, both unsubstituted (**3a** and **3b**) and dimethylated (**3c**) analogs were prepared. Herein, we report the synthesis of compounds **3a**–**c** and their preliminary anti-HIV bioassay results (Fig. 1).

The synthesis of **3a** and **3b** was accomplished by a seven-step sequence, as illustrated in Scheme 1. The key intermediates 7,8-dihydro-benzo[*h*]chromen-2-one (**10a**) and its 4-methyl analog (**10b**) were prepared according to the procedure reported in our prior work.[8] Sharpless asymmetric dihydroxylation (AD) of **10a** and **10b** afforded dihydroxy derivatives **11a** and **11b** in moderate yield (45–49%).[9] Finally, 7-carbon-DCK analogs **3a** and **3b**

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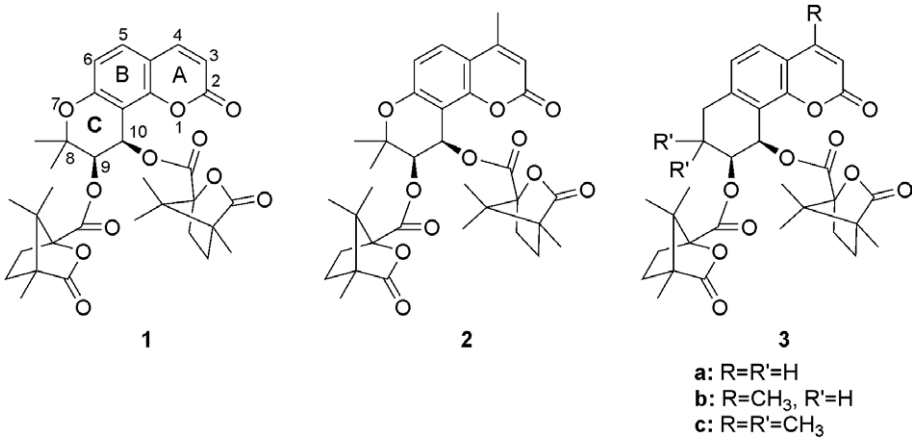
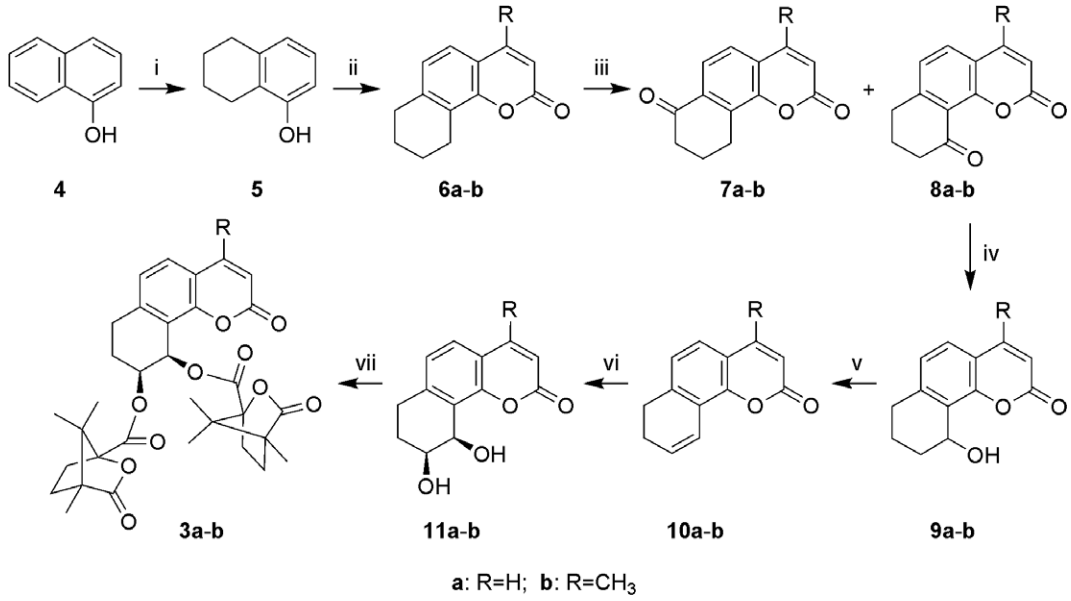


Figure 1. Structures of DCK (**1**), 4-methyl DCK (**2**), and 7-carbon-DCK analogs (**3a**–**c**).

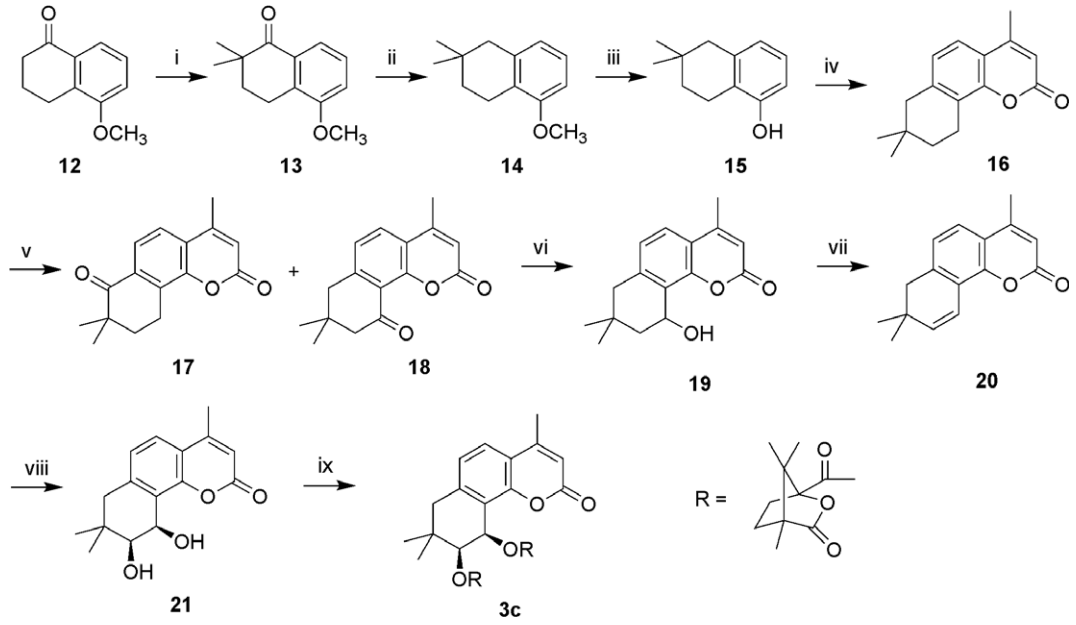


Scheme 1. Synthesis of **3a** and **3b**. Reagents and conditions: (i) Raney Ni-Al alloy, 1% aq KOH/water, 90 °C, 2 h; (ii) *L*-Malic acid, H_2SO_4, HOAc, 140 °C, 6 h (R = H); $CH_3COCH_2COOC_2H_5$, $POCl_3$, 100 °C, 18 h (R = CH_3); (iii) CrO_3, HOAc, rt, 3 days; (iv) $NaBH_4$, CH_3OH, 1 h; (v) 2% H_2SO_4, reflux, 6–16 h; (vi) AD-mix-α ($K_2OsO_4 \cdot 2H_2O$, $K_3Fe(CN)_6$, $(DHQ)_2PHAL$, K_2CO_3), *t*-butanol/H_2O 1:1, rt, 2–3 days; (vii) (*S*)-camphanic chloride, pyridine, DMAP, CH_2Cl_2, rt, 24 h.

were obtained in 62% and 82% yields, respectively, by acylation of **11a** and **11b** with (*S*)-(−)-camphanic chloride in CH_2Cl_2 at room temperature with pyridine as acid scavenger.

As shown in Scheme 2, the preparation of **3c** followed a slightly different synthetic route with 5-methoxy-1-tetralone (**12**) as starting material. Dimethylation of **12** with CH_3I in the presence of *t*-BuOK afforded 2,2-dimethyl-5-methoxy-1-tetralone (**13**) in 91% yield.[10] Reduction of dimethylated tetralone **13** with H_2 catalyzed with 10% Pd-C gave 1,2,3,4-tetrahydro-5-methoxy-2,2-dimethylnaphthalene (**14**) quantitatively.[11] Demethylation of **14** with BBr_3 resulted in the formation of phenol derivative **15** in 98% yield.[11] The remaining synthetic steps followed those detailed above for **3a** and **3b** from phenol **5**. The target compound **3c** was thus obtained in an overall yield of 5% via a six-step reaction sequence starting from **15**. Physical and spectral data for **3a–c** were consistent with their chemical structures.[12]

The anti-HIV activities of compounds **3a-c** were evaluated in H9 lymphocytes, with AZT as the reference compound. The bioassay data are shown in Table 1 and indicated that all three compounds inhibited HIV replication and had reasonable therapeutic index (TI) values. Compounds **3a** and **3b** had significant EC_{50} values of 0.068 and 0.083 μM, respectively. Thus, the presence of the C-4 methyl in these 7-carbon DCK analogs did not lead to increased potency, in contrast to results with DCK and 4-methyl DCK. Although an absence of *gem*-dimethylation was detrimental in the 7-oxy DCK series,[7] it was hard to make a definitive conclusion in the 7-carbon DCK series (comparison of **3c** with **3b**) due to solubility problems with **3c**. However, the 7-carbon analog **3b** was more potent and had a higher TI than the corre-



Scheme 2. Synthesis of **3c**. Reagents and conditions: (i) *t*-BuOK/THF, reflux, 5 h, CH_3I, 0.5 h; (ii) H_2, Pd-C, CH_3SO_3H, HOAc, $CH_3COOC_2H_5$, C_2H_5OH, rt, 36 h; (iii) BBr_3/CH_2Cl_2, −78 °C; (iv) $CH_3COCH_2COOC_2H_5$, $POCl_3$, benzene, reflux, 24 h, 66.0%; (v) CrO_3, HOAc, rt, 30 h (yield: **17** = 39.0%, **18** = 19.9%); (vi) $NaBH_4$, CH_3OH, 0.5 h (yield: 70.3%); (vii) 2% H_2SO_4, 120–130 °C, 5 h (yield: 95.0%); (viii) AD-mix-α ($K_2OsO_4 \cdot 2H_2O$, $K_3Fe(CN)_6$, $(DHQ)_2PHAL$, K_2CO_3), *t*-butanol/H_2O 1:1, $CH_3SO_2NH_2$, rt, 32 h (yield: 75.5%); (ix) (*S*)-camphanic chloride, Et_3N, DMAP, CH_2Cl_2, rt, 4 h (yield: 81.2%).

Table 1. Anti-HIV data of compounds **3a**–**c** in acutely infected H9 lymphocytes

Compound	IC_{50}[a] (μM)	EC_{50}[b] (μM)	TI[c]
3a	57.2	0.068	841
3b	54.4	0.083	659
3c[d]	>39.4	<0.39	>100
DCK[e]	>16.1	0.049	>328
4-Me DCK[e]	>38.9	0.0059	>6600
AZT	500	0.0137	36,520

[a] Concentration that inhibits uninfected H9 cell growth by 50%.
[b] Concentration that inhibits viral replication by 50%.
[c] TI, therapeutic index IC_{50}/EC_{50}.
[d] More precise data could not be determined due to solubility problems.
[e] The data for DCK and 4-methyl DCK were cited from Ref. 8. EC_{50} and TI values for DCK and 4-methyl DCK were 2.56×10^{-4} μM, 1.83×10^{-6} μM, and 1.37×10^{5}, 6.89×10^{7}, respectively, in previous screenings, using a different methodology, and publications.[1]

sponding demethylated 7-oxy DCK derivative, 2′,2′-dihydro-4-methyl DCK (EC_{50} = 6.9 μM, TI > 6).[7] Compound **3b** was also more potent against HIV replication but was more cytotoxic than the analogous 7-thio analog (EC_{50} = 0.141 μM, TI = 1,110).[6]

Further structural modification and biological screening are in progress as these promising bioassay results demonstrate that 7-carbon-DCK analogs merit attention as potential HIV-1 inhibitors.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.05.026.

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12. Physical and spectral data for **3a**–**c**:
9,10-Di-O-(−)*-camphanoyl-7,8,9,10-tetrahydro-benzo* [*h*] *chromen-2-one* (***3a***). Mp 120–122 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94–1.13 (m, 18H, camphanoyl CH_3), 1.61–2.56 (m, 10H, 8-H, camphanoyl CH_2), 3.07–3.17 (m, 2H, 7-H), 5.31–5.40 (m, 1H, 9-H), 6.38 (d, J = 9.3 Hz, 1H, 3-H), 6.82 (d, J = 2.7 Hz, 1H, 10-H), 7.12 (d, J = 8.1 Hz, 1H, 6-H), 7.44 (d, J = 8.1 Hz, 1H, 5-H), 7.67 (d, J = 9.6 Hz, 1H, 4-H). ESI-MS *m*/*z* (%): 615.25 (M+Na$^+$, 100). HR-MS: calcd for $C_{33}H_{36}O_{10}Na^+$ 615.2201, found 615.2191.
9,10-Di-O-(−)*-camphanoyl-4-methyl-7,8,9,10-tetrahydro-benzo* [*h*] *chromen-2-one* (***3b***). Mp 159–161 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96–1.12 (m, 18H, camphanoyl CH_3), 1.61–2.56 (m, 10H, 8-H, camphanoyl CH_2), 2.42 (s, 3H, 4-CH_3), 3.00–3.20 (m, 2H, 7-H), 5.31–5.38 (m, 1H, 9-H), 6.24 (s, 1H, 3-H), 6.83 (d, J = 2.7 Hz, 1H, 10-H), 7.12 (d, J = 8.1 Hz, 1H, 6-H), 7.55 (d, J = 8.1 Hz, 1H, 5-H). ESI-MS *m*/*z* (%): 606.30 (M$^+$, 19). HR-MS: calcd for $C_{34}H_{38}O_{10}Na^+$ 629.2357, found 629.2367.
9,10-Di-O-(−)*-camphanoyl-4,8,8-trimethyl-7,8,9,10-tetra-hydro-benzo* [*h*] *chromen-2-one* (***3c***). Mp 148–150 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92–1.30 (m, 24H, camphanoyl CH_3, 8-CH_3), 1.61–1.76 (m, 2H, camphanoyl CH_2), 1.86–1.98 (m, 2H, camphanoyl CH_2), 2.11–2.28 (m, 2H, camphanoyl CH_2), 2.45 (s, 3H, 4-CH_3), 2.50–2.61 (m, 2H, camphanoyl CH_2), 2.82–3.02 (m, 2H, 7-H), 5.35 (d, J = 5.1 Hz, 1H, 9-H), 6.25 (s, 1H, 3-H), 6.76 (d, J = 5.1 Hz, 1H, 10-H), 7.11 (d, J = 8.4 Hz, 1H, 6-H), 7.59 (d, J = 8.1 Hz, 1H, 5-H). ESI-MS *m*/*z* (%): 657.30 (M+Na$^+$, 100). HR-MS: calcd for $C_{36}H_{42}O_{10}Na^+$ 657.2670, found 657.2690.