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Anti-AIDS agents 87. New bio-isosteric dicamphanoyl-dihydropyranochromone (DCP) and dicamphanoyl-khellactone (DCK) analogues with potent anti-HIV activity

Hong-Shan Liu [a], Shi-Qing Xu [a], Ming Cheng [a], Ying Chen [a,*], Peng Xia [a], Keduo Qian [b], Yi Xia [b], Zheng-Yu Yang [b], Chin-Ho Chen [c], Susan L. Morris-Natschke [b], Kuo-Hsiung Lee [b,d,*]

[a] Department of Medicinal Chemistry, School of Pharmacy, Fudan University, Shanghai 201203, China
[b] Natural Products Research Laboratories, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599-7568, USA
[c] Duke University Medical Center, Durham, NC 27710, USA
[d] Chinese Medicine Research and Development Center, China Medical University and Hospital, Taichung, Taiwan

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ABSTRACT

Six 3′*R*,4′*R*-di-*O*-(*S*)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-*f*]chromone (DCP) and two 3′*R*,4′*R*-di-*O*-(*S*)-camphanoyl-(+)-*cis*-khellactone (DCK) derivatives were designed, synthesized, and evaluated for inhibition of HIV-1_{NL4-3} replication in TZM-bl cells. 2-Ethyl-2′-monomethyl-1′-oxa- and -1′-thia-DCP (**5a**, **6a**), as well as 2-ethyl-1′-thia-DCP (**7a**) exhibited potent anti-HIV activity with EC_{50} values of 30, 38 and 54 nM and therapeutic indexes of 152.6, 48.0 and 100.0, respectively, which were better than or comparable to those of the lead compound 2-ethyl-DCP in the same assay. 4-Methyl-1′-thia-DCK (**8a**) also showed significant inhibitory activity with an EC_{50} of 128 nM and TI of 237.9.

In our previous research, 3′*R*,4′*R*-di-*O*-(*S*)-camphanoyl-(+)-*cis*-khellactone (DCK, **1**, Fig. 1) demonstrated extremely potent inhibitory activity against HIV-1 replication in H9 lymphocytic cells.[1] Subsequently, hundreds of DCK and some of its ring-A positional isomer DCP (3′*R*,4′*R*-di-*O*-(*S*)-camphanoyl-2′,2′-dimethyl-dihydropyrano[2,3-*f*]chromone, **2**, Fig. 1) derivatives have been designed, synthesized and screened for anti-HIV activity in H9 lymphocytes, MT-2 cell lines, and MT-4 cell lines.[2–8] 4-Methyl-DCK (**3**, Fig. 1) and 2-ethyl-DCP (**4**, Fig. 1) showed the most promising anti-HIV results in these two series. Structure–activity relationship (SAR) studies found that DCP derivatives exhibited better anti-HIV activity than the corresponding DCKs;[8] 2′-α-monomethyl-4-methyl DCK derivatives were more potent than 2′-*gem*-dimethyl DCKs;[9] bio-isosteric analogues with a sulfur rather than oxygen in the ring-C of DCK exhibited remarkable inhibitory effects on HIV-1 replication;[9,10] and a 3′,4′-dicamphanoyl moiety is indispensable for anti-HIV activity.[11] Considering these SAR research results, we have now designed and synthesized 2′-monomethyl-DCP (**5**, 1′-oxa; **6**, 1′-thia), 2-ethyl-1′-thia-DCP (**7**), and 4-methyl-1′-thia-DCK (**8**) analogues to further explore the pharmacophores of the 2′-position and the bio-isosteric effect at the 1′-position. This paper reports their synthesis and anti-HIV bioassay data.

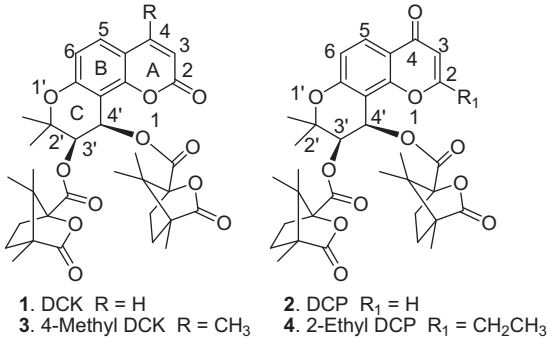

Figure 1. Structures of previously synthesized DCK and DCP analogues (**1**–**4**).

The synthetic routes to **5a**, **5b**, **6a** and **6b** are shown in Scheme 1. The intermediate 2-ethyl-7-mercapto-4*H*-chromen-4-one (**12**) was obtained by reacting 2-ethyl-7-hydroxy-4*H*-chromen-4-one (**9**) with dimethylthiocarbamoyl chloride in EtOH in

* Corresponding authors. Tel.: +86 21 51980116 (Y.C.); tel.: +1 919 962 0066; fax: +1 919 966 3893 (K.H.L.)
E-mail addresses: yingchen71@fudan.edu.cn (Y. Chen), khlee@unc.edu (K.-H. Lee).

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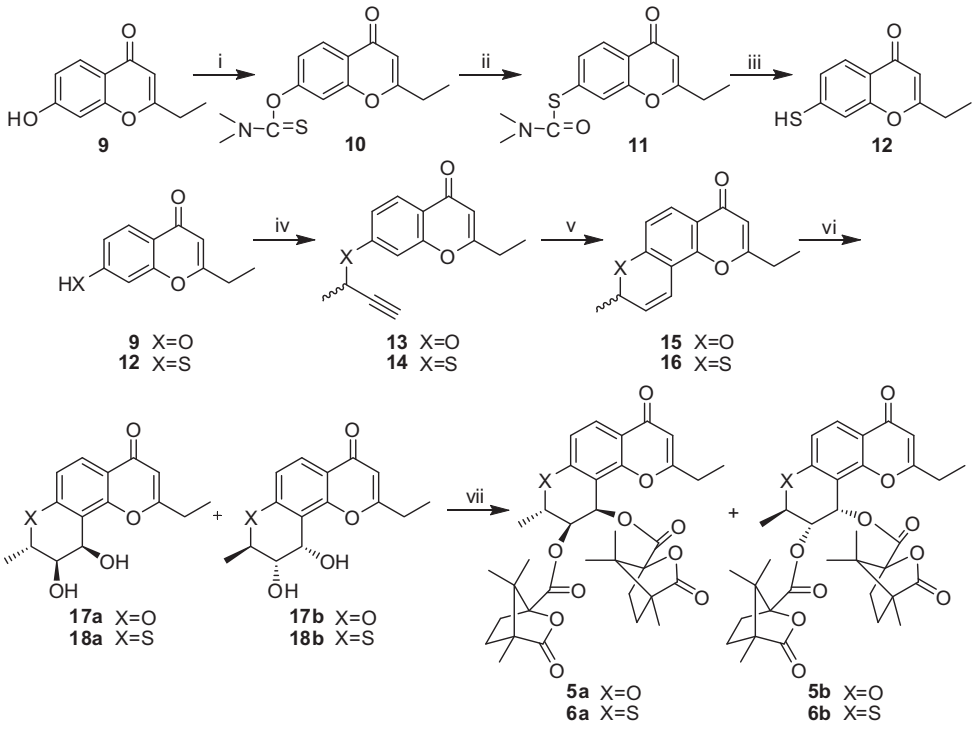
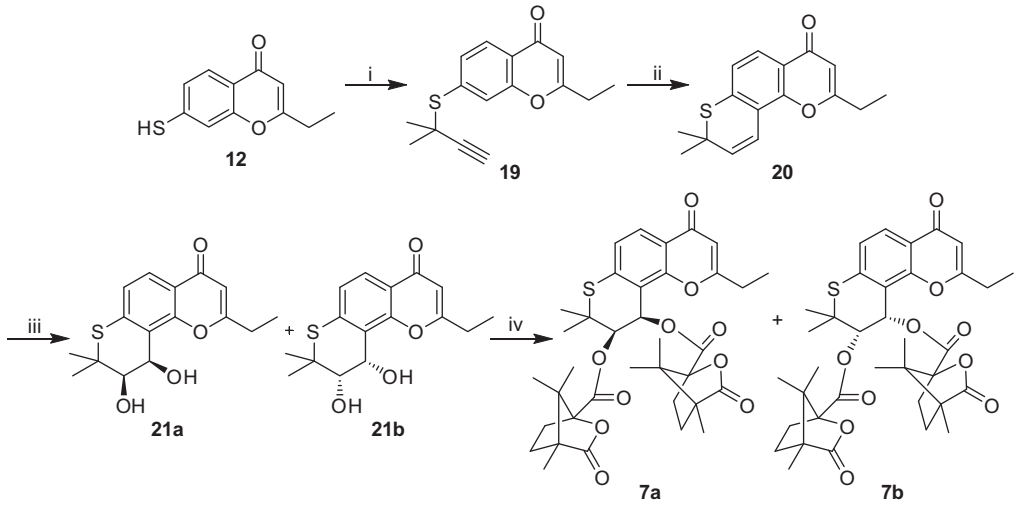


Scheme 1. Reagents and conditions: (i) Dimethylthiocarbamoyl chloride, EtOH, K_2CO_3, rt; (ii) 240 °C, N_2; (iii) KOH, CH_3OH, N_2, reflux; (iv) 3-chloro-1-butyne, K_2CO_3, KI in DMF or acetone, rt; (v) *N*,*N*-diethylaniline, reflux; (vi) $K_2OsO_2(OH)_4$, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3 in *t*-butanol/H_2O (v/v = 1:1), ice bath; (vii) (*S*)-camphanic chloride, DMAP in CH_2Cl_2, rt.

the presence of anhydrous potassium carbonate, followed by a rearrangement at 240 °C, then hydrolysis with methanolic KOH and acidification with HCl. Compounds **9** and **12** were treated with 3-chloro-1-butyne in dimethyl formamide (DMF) or acetone in the presence of anhydrous potassium carbonate and potassium iodide at room temperature to produce the propargyl ethers **13** and **14**, followed by thermal rearrangement in refluxing *N*,*N*-diethylaniline to form intermediates **15** and **16**. Sharpless dihydroxylation (AD) of **15** and **16** afforded dihydroxy derivatives **17a**/**17b** and **18a**/**18b**, respectively, as diastereoisomeric mixtures. Target compounds **5a** and **5b** were obtained by acylation of **17a** and **17b** with (*S*)-(−)-camphanic chloride in CH_2Cl_2 at room temperature with 4-dimethylaminopyridine (DMAP) as acid scavenger. Compounds **6a** and **6b** were synthesized by the same procedure from **18a** and **18b**. The pure diastereoisomers **5a**, **5b**, **6a**, and **6b** were obtained by separation with column chromatography on silica gel [petroleum ether/ethyl acetate, 3:1 (v/v)].

The preparation of **7a** and **7b** is illustrated in Scheme 2. 2-Ethyl-7-mercapto-4*H*-chromen-4-one (**12**) was treated with 3-chloro-3-methyl-1-butyne in EtOH/H_2O (v/v = 1:1) in the presence of potassium hydroxide at room temperature to produce the propargyl ether **19**, followed by thermal rearrangement in refluxing *N*,*N*-diethylaniline to form intermediate **20**. Sharpless AD of **20** afforded dihydroxy derivatives **21a** and **21b**. Target compounds



Scheme 2. Reagents and conditions: (i) 3-Chloro-3-methyl-1-butyne, KOH, N_2, EtOH/H_2O (v/v = 1:1), rt; (ii) *N*,*N*-diethylaniline, reflux; (iii) $K_2OsO_2(OH)_4$, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3 in *t*-butanol/H_2O (v/v = 1:1), ice bath; (iv) (*S*)-camphanic chloride, DMAP in CH_2Cl_2, rt.