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Anti-AIDS agents 79. Design, synthesis, molecular modeling and structure–activity relationships of novel dicamphanoyl-2′,2′-dimethyldihydropyranochromone (DCP) analogs as potent anti-HIV agents

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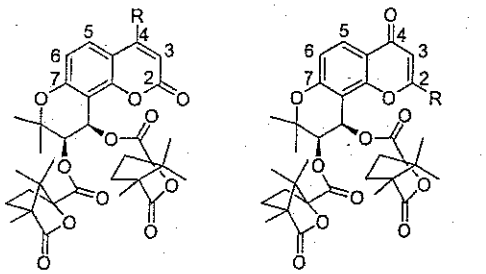
ABSTRACT

In a continued study, 23 3′*R*,4′*R*-di-*O*-(−)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-*f*]chromone (DCP) derivatives (**5–27**) were synthesized, and screened for anti-HIV activity against both a non-drug-resistant NL4-3 strain and multiple reverse transcriptase (RT) inhibitor-resistant (RTMDR-1) strain, using 2-EDCP (**4**) and 2-MDCP (**35**) as controls. New DCP analogs **5**, **9**, **14**, and **22** exhibited potent anti-HIV activity against HIV_{NL4-3} with EC_{50} and therapeutic index (TI) values ranging from 0.036 μM to 0.14 μM and from 110 to 420, respectively. Compounds **5** and **9** also exhibited good activity against RTMDR-1 (EC_{50} 0.049 and 0.054 μM; TI 310 and 200, respectively), and were twofold more potent than the leads **4** and **35** (EC_{50} 0.11 and 0.19 μM; TI 60 and 58, respectively). Evaluation of water solubility showed that **5** and **22** were 5–10 times more water soluble than **4**. Quantitative structure–activity relationship (QSAR) modeling results were first performed on this compound type, and the models should aid in design of future anti-HIV DCP analogs and potential clinical drug candidates.

1. Introduction

Although over 30 formulations are now approved by the US FDA to treat AIDS, drug resistance problems have dramatically reduced the efficacy of these current anti-HIV agents.[1] Therefore, research to find new anti-HIV agents with either higher potency or novel mechanisms has attracted great attention to overcome this problem.[2]

In our prior studies, 3′*R*,4′*R*-di-*O*-(−)-camphanoyl-(+)-*cis*-khellactone (DCK, **1**) and 4-methyl DCK (4-MDCK, **2**) showed high potency against HIV-1_{IIIB} replication in H9 lymphocytes. The EC_{50} and therapeutic index (TI) values were reported as 0.049 μM and 328 for DCK, and, 0.0059 μM and 6660 for 4-MDCK, respectively (Fig. 1).[3,4] More specifically, preliminary mechanism of action-related studies indicated that 4-MDCK inhibited the activity of HIV-RT through inhibition of DNA-dependent DNA polymerase activity, in contrast to currently available NNRTIs that block HIV-RT by inhibiting RNA-dependent DNA polymerization.[5] However, DCK had reduced activity against the multi-RT inhibitor resistant (RTMDR-1) strain. In the course of our continuing exploration of DCK analogs as potent anti-HIV agents,



1 DCK, R = H
2 4-Me-DCK, R = CH_3
3 DCP, R = H
4 2-Ethyl-DCP, R = CH_2CH_3

Figure 1. DCK and DCP analogs.

4*H*-chrom-4-one derivatives (DCPs) were designed and synthesized as DCK positional isomers (Fig. 1).[6,7] Compared with DCKs, DCP analogs not only retained high activity against wild-type HIV, but also showed potency against RTMDR-1 HIV.[7] Among the previously reported DCP derivatives, 2-ethyl DCP (2-EDCP, **4**) exhibited the best anti-HIV activity against both wild-type and drug-resistant strains with EC_{50} values of 0.070 and 0.11 μM and TI values of 94 and 60, respectively. The uniqueness of DCP analogs opens a new avenue for us to discover a distinct class of potent, effective anti-HIV drugs for AIDS therapy.

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