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Anti-AIDS agents 84. Synthesis and anti-human immunodeficiency virus (HIV) activity of 2′-monomethyl-4-methyl- and 1′-thia-4-methyl-(3′*R*,4′*R*)-3′,4′-di-*O*-(*S*)-camphanoyl-(+)-*cis*-khellactone (DCK) analogs ☆

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ABSTRACT

In a continuing investigation into the pharmacophores and structure–activity relationship (SAR) of (3′*R*,4′*R*)-3′,4′-di-*O*-(*S*)-camphanoyl-(+)-*cis*-khellactone (DCK) as a potent anti-HIV agent, 2′-monomethyl substituted 1′-oxa, 1′-thia, 1′-sulfoxide, and 1′-sulfone analogs were synthesized and evaluated for inhibition of HIV-1 replication in H9 lymphocytes. Among them, 2′*S*-monomethyl-4-methyl DCK (**5a**)[‡] and 2′*S*-monomethyl-1′-thia-4-methyl DCK (**7a**) exhibited potent anti-HIV activity with EC_{50} values of 40.2 and 39.1 nM and remarkable therapeutic indexes of 705 and 1000, respectively, which were better than those of the lead compound DCK in the same assay. In contrast, the corresponding isomeric 2′*R*-monomethyl-4-methyl DCK (**6**) and 2′*R*-monomethyl-1′-thia-4-methyl DCK (**8**) showed much weaker inhibitory activity against HIV-1 replication. Therefore, the bioassay results suggest that the spatial orientation of the 2′-methyl group in DCK analogs can have important effects on anti-HIV activity of this compound class.

1. Introduction

Since first reported in the 1980s, acquired immunodeficiency syndrome (AIDS) has spread rapidly through the human population and become one of the most devastating diseases facing mankind.[1,2] This disease is caused by infection with the human immunodeficiency virus (HIV) and results in life-threatening opportunistic infections and malignancies. The increasing incidence of HIV drug resistance together with many serious side effects and long-term complications in patients diminish the action of current anti-HIV drugs. Consequently, the development of new anti-HIV agents continues to focus on novel structures or new action mechanisms.

In our previous research, 3′,4′-di-*O*-(−)-camphanoyl-(+)-*cis*-khellactone (DCK, **1**, Fig. 1) demonstrated extremely potent inhibitory activity against HIV-1 replication in H9 lymphocytic cells.[3] In subsequent structural modification studies, numerous DCK derivatives were synthesized and more than 20 DCK analogs have shown promising inhibitory activity against HIV-1 replication in H9 lymphocytes, MT-2 cell lines, and MT-4 cell lines, respectively.[4] Among them, 3-methyl, 4-methyl, and 5-methyl substituted DCKs were much more potent than DCK and zidovudine (AZT) in the same assay.[5] Initial structure–activity relationships (SAR) have been established for this compound type.[4] In addition, a preliminary mechanistic study showed that DCK is a unique inhibitor of HIV-1 reverse transcriptase (RT). It did not significantly affect RNA-dependent DNA polymerase activity when poly-rA or poly-rC was used as template, while it did affect DNA-dependent DNA polymerase activity of HIV-1 RT when poly-dA or poly-dC was used

Abbreviations: DCK, (3′*R*,4′*R*)-3′,4′-di-*O*-(*S*)-camphanoyl-(+)-*cis*-khellactone; SAR, structure–activity relationships; AIDS, acquired immunodeficiency syndrome; HIV-1, human immunodeficiency virus type 1; AZT, zidovudine; RT, reverse transcriptase; DMF, dimethyl formamide; AD, asymmetric dihydroxylation; DMAP, 4-(dimethylamino)pyridine; $(DHQ)_2PHAL$, hydroquinine 1,4-phthalazinediyl diether; MCPBA, 3-chloroperoxybenzoic acid.

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