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Anti-AIDS agents. Part 58: Synthesis and anti-HIV activity of 1-thia-di-*O*-(−)-camphanoyl-(+)-*cis*-khellactone (1-thia-DCK) analogues ☆

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Abstract—Two 1-thia-DCK analogues (**9a** and **9b**) were synthesized and evaluated for inhibition of HIV-1 replication in H9 lymphocytes. Compound **9a** showed excellent anti-HIV activity with an EC_{50} value of 0.00012 μM and therapeutic index of 1,408,000. Compound **9b** was less active with EC_{50} and TI values of 3.11 μM and 62.3, respectively. The bioassay results indicated that thia-DCK analogues merit attention as potential HIV-1 inhibitors.

The anti-HIV drugs used clinically cannot completely eliminate HIV in the human body, show side effects and toxicity, and are subject to drug resistance by mutated virus. Thus, it is necessary to further explore novel anti-HIV agents with new mechanisms of action.

Suksdorfin (**1**, Fig. 1), isolated from the fruit of *Lomatium suksdorfii*, is a khellactone with interesting biological properties, especially anti-HIV activity.[2] Modification of **1** has already provided 3′,4′-di-*O*-(−)-camphanoyl-(+)-*cis*-khellactone (DCK) (**2**, Fig. 1), which showed 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}.[3] In further structural research, numerous DCK derivatives were synthesized and evaluated for activity in an in vitro anti-HIV assay. Among them, 3-methyl, 4-methyl, and 5-methyl DCK 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.[4] A preliminary mechanistic study showed that DCK and its analogues did not inhibit HIV-RT, integrase, or protease and, thus, might inhibit HIV-1 replication by a novel mechanism. Currently, their mechanism of action is still under investigation.

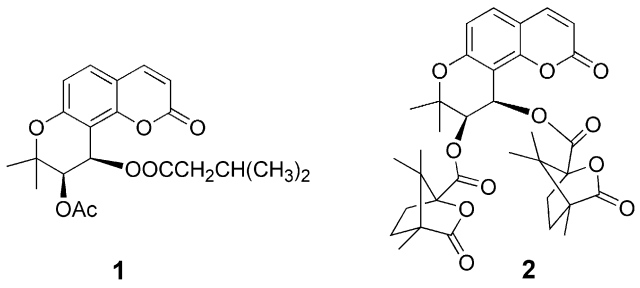

Figure 1. Structures of **1** and **2**.

Based on the concept of bioisosterism, we designed a new series of analogues by replacing the ring oxygen atom of DCK with a sulfur atom. Such novel thia-DCK analogues with new core structures would provide more insight into the SAR of this molecular scaffold. We have previously synthesized 7-thia-DCK analogues, which showed potent inhibitory effects on HIV-1 replication in

☆ For part 57, see Ref. 1.

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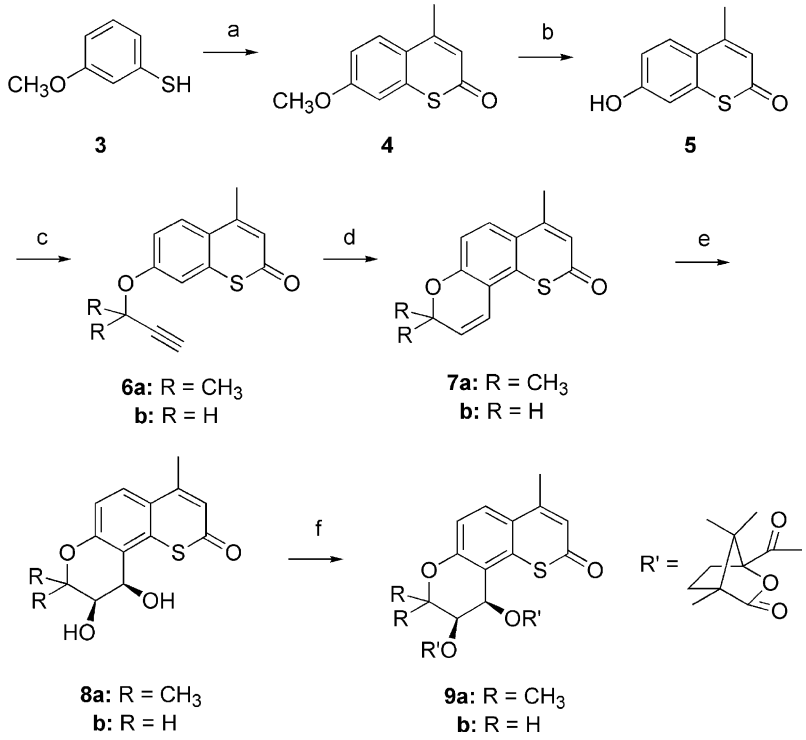

Scheme 1. Synthesis of 1-thia-DCK analogues. Reagents and conditions: (a) dioxinone, xylene/PPA 140 °C; (b) HCl/Py, 170 °C; (c) 3-chloro-3-methylbut-1-yne (R = CH_3) or 3-bromoprop-1-yne (R = H), K_2CO_3, KI in acetone reflux; (d) diethylaniline, reflux; (e) $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, $(DHQ)_2$–PHAL, K_2CO_3; (f) camphanic chloride, DMAP/CH_2Cl_2.

H9 lymphocytes.[5] In this paper, we would like further to report the synthesis and anti-HIV bioassay results of another class of thio-analogues, 1-thia-4-methyl-8-DCK derivatives. Further structural modifications and biological screening are ongoing.

As shown in Scheme 1, 7-methoxy-4-methylbenzo[*e*]thiin-2-one (**4**) was synthesized via the reaction of 3-methoxybenzene-1-thiol (**3**) with dioxinone.[6] Demethylation of (**4**) with pyridine/HCl at 170 °C gave 7-hydroxy-4-methylbenzo[e]thiin-2-one (**5**) in 97% yield. The reaction of **5** with 3-chloro-3-methylbut-1-yne and 3-bromoprop-1-yne in the presence of K_2CO_3 and KI in refluxing acetone afforded the propargyl ethers **6a** and **6b**, respectively. The cyclization of **6a** and **6b** in *N*,*N*-dimethylaniline at reflux temperature followed by asymmetric dihydroxylation[7] and acylation with camphanic chloride gave the desired 1-thia-DCK analogues (**9a** and **9b**).[8]

Table 1 shows that 1-thia-DCK analogue **9a** exhibited extremely potent inhibitory activity against HIV-1 replication with an EC_{50} value of 0.00012 μM and a TI value of 1,408,000. In the same assay, the EC_{50}/TI values of AZT, DCK, and 4-methyl DCK were 0.045 μM/52,400; 0.000256 μM/137,000; and 1.83×10^{-6} μM/$> 6.89 \times 10^{7}$, respectively.[4] Thus, although less active than 4-methyl DCK, compound **9a** was significantly more potent than AZT and somewhat more potent than DCK with EC_{50} values ca. 375-fold and 2-fold lower than those of AZT and DCK in the same assay. The activity of compound **9b**, which does not have *gem*-methyl moieties at the 8-position, was reduced dramatically; its EC_{50} value was 3.11 μM. This result suggests that the 8-position might be crucial for potency against HIV replication.

Table 1. Anti-HIV activity of 1-thia-DCK analogues in acutely infected H9 lymphocytes

Compound	IC_{50} (μM)[a]	EC_{50} (M)[b]	TI[c]
7a	339[d]	NA[e]	—
7b	478[d]	7.67	62.3
8a	302	NA[e]	—
8b	340	30.5	11.1
9a	169	0.00012	1,408,000
9b	194	3.11	62.3
DCK	35[f]	0.000256	137,000
AZT	1875	0.045	41,700

[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] Maximum IC_{50} value possible for this assay due to DMSO, which is used to solubilize the agents tested.
[e] NA = not active (did not suppress infected cell growth).
[f] Data for DCK were previously cited in Ref. 9.

Generally, camphanoyl moieties are very important for anti-HIV activity of these khellactone. Compounds **7a**,**b** and **8a**,**b** were much less potent than the camphanoyl derivatives. This finding was consistent with the SAR found for compounds in the DCK series.

In conclusion, these bioassay results indicated that 1-thia-DCK analogues are another class of potential novel anti-HIV agents. To further assess the anti-HIV

activity of 1-thia-DCK analogues, further modifications are under investigation.

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References and notes

1. For Part 57, see: Sakurai, N.; Wu, J. H.; Sashida, Y.; Mimaki, Y.; Nikaido, T.; Koike, K.; Itokawa, H.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1329.
2. Lee, T. T.; Kashiwada, Y.; Huang, L.; Snider, J.; Cosentino, L. M.; Lee, K. H. *Bioorg. Med. Chem.* **1994**, *2*, 1051.
3. Huang, L.; Kashiwada, Y.; Cosentino, L. M.; Fan, S.; Chen, C. H.; McPhail, A. T.; Fujioka, T.; Mihashi, K.; Lee, H. K. *J. Med. Chem.* **1994**, *37*, 3947.
4. Xie, L.; Takeuchi, Y.; Cosentino, L. M.; Lee, K. H. *J. Med. Chem.* **1999**, *42*, 2662.
5. Chen, Y.; Zhang, Q.; Zhang, B.; Xia, P.; Xia, Y.; Yang, Z. Y.; Kilgore, N.; Wild, C.; Morris-Natschke, S. L.; Lee, K. H. *Bioorg. Med. Chem.*, in press.
6. Nakazumi, H.; Asada, A.; Kitao, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2046.
7. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768.
8. Physical and spectral data for final products and key intermediates.
4-Methyl-1-thia-seselin (**7a**): Yield 71.4%; mp 157–158 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 6H, 2′–$CH_3 \times 2$), 2.49 (s, 3H, 4-CH_3), 5.79 (d, 1H, $J = 10.1$ Hz, H-9), 6.40 (s, 1H, H-3), 6.62 (d, 1H, $J = 10.1$ Hz, H-10), 6.86 (d, 1H, $J = 8.9$ Hz, H-6), 7.65 (d, 1H, $J = 8.86$ Hz, H-5); MS m/z 258 (M^+).
4-Methyl-2′,2′-dihydro-1-thia-seselin (**7b**): Yield 78.6%; mp 168–171 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.53 (s, 3H, 4-CH_3), 4.94 (dd, 2H, 8-CH_2), 5.99 (dt, 1H, $J = 10.1$ Hz, H-9), 6.45 (s, 1H, H-3), 6.76 (dt, 1H, $J = 10.1$ Hz, H-10), 6.90 (d, 1H, $J = 8.8$ Hz, H-6), 7.68 (d, 1H, $J = 8.9$ Hz, H-5); MS m/z 230 (M^+).
(*3′R,4′R*)-*3′,4′-Dihydroxy-4-methyl-1-thia-seselin* (**8a**): Yield 32.3%; mp 184–185 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.45 (s, 6H, 8-$CH_3 \times 2$), 2.51 (s, 3H, 4-CH_3), 3.37 (d, 1H, 9-OH), 3.80 (d, 1H, 10-OH), 3.88 (dd, 1H, H-9), 5.01 (dd, 1H, H-10), 6.44 (s, 1H, H-3), 6.92 (d, 1H, $J = 9.0$ Hz, H-6), 7.75 (d, 1H, $J = 9.0$ Hz, H-5); MS m/z 292 (M^+); HRMS calcd for $C_{15}H_{16}O_4S$ 292.07693, found 292.07385.
(*3′S,4′R*)-*3′,4′-Dihydroxy-2′,2′-dihydro-4-methyl-1-thia-seselin* (**8b**): Yield 84.6%; mp 205–206 °C; ^{1}H NMR (DMSO-d_6 500 MHz) δ 2.50 (s, 3H, 4-CH_3), 3.88–3.93 (m, 1H, H-9), 3.98–4.04 (m, 2H, 8-CH_2), 4.68 (t, 1H, H-10), 5.26 (d, 1H, 9-OH), 5.47 (d, 1H, 10-OH), 6.47 (s, 1H, H-3), 6.97 (d, 1H, $J = 9.0$ Hz, H-6), 7.87 (d, 1H, $J = 9.0$ Hz, H-5); MS m/z 264 (M^+); HRMS calcd for $C_{13}H_{12}O_4S$ 264.04563, found 264.04373.
(*3′R,4′R*)-*4-Methyl-3′,4′-di-O-*(*S*)-*camphanoyl-*(+)-*cis-1-thia-khellactone* (**9a**): Yield 85.0%; mp 226–228 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95–1.20 (m, 18H, $CH_3 \times 6$ in camphanoyl), 1.45, 1.50 (s × 2, 6H, 8-$CH_3 \times 2$), 1.60–2.65 (m × 4, 8H, camphanoyl H), 2.52 (s, 3H, 4-CH_3), 5.39 (d, 1H, H-9), 6.40 (d, 1H, H-10), 6.42 (s, 1H, H-3), 6.97 (d, 1H, $J = 9.0$ Hz, H-6), 7.83 (d, 1H, $J = 9.1$ Hz, H-5); MS m/z 652 (M^+); HRMS calcd for $C_{35}H_{40}O_{10}S$ 652.23423, found 652.23834.
(*3′S,4′R*)-*4-Methyl-2′,2′-dihydro-3′,4′-di-O-*(*S*)-*camphanoyl-*(+)-*cis-1-thia-khellactone* (**9b**): Yield 57.8%; mp 221–222 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80–1.04 (m, 18H, $CH_3 \times 6$ in camphanoyl), 1.59–2.44 (m × 4, 8H, camphanoyl H), 2.42 (s, 3H, 4-CH_3), 4.15–4.34 (m, 2H, 8-CH_2), 5.41–5.50 (m, 1H, H-9), 6.34 (s, 1H, H-3), 6.43 (d, 1H, H-10), 6.92 (d, 1H, $J = 9.1$ Hz, H-6), 7.75 (d, 1H, $J = 9.1$ Hz, H-5); MS m/z 624 (M^+); HRMS calcd for $C_{33}H_{36}O_{10}S$ 624.20292, found 624. 20041.
9. Yang, Z. Y.; Xia, Y.; Xia, P.; Brossi, A.; Cosentino, L. M.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1003.