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7-Oxo-24,25-dihydrolanosterol: a novel lanosterol 14α-demethylase P-450$_{14DM}$ inhibitor which blocks electron transfer to the oxyferro intermediate*

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7-Oxo-24,25-dihydrolanosterol (3β-hydroxy-8-lanosten-7-one, 7-oxo-DHL) was a potent competitive inhibitor for lanosterol 14α-demethylase (cytochrome P-450$_{14DM}$) of *Saccharomyces cerevisiae*. Affinity of 7-oxo-DHL for the enzyme was more than 50-times higher than those of the inherent substrates, lanosterol and 24,25-dihydrolanosterol. 7-Oxo-DHL accelated NADPH-dependent reduction of cytochrome P-450$_{14DM}$ in the reconstituted system consisting of the cytochrome and NADPH-cytochrome P-450 reductase. These observations indicated that 7-oxo-DHL interacted with the substrate site of cytochrome P-450$_{14DM}$. However, 7-oxo-DHL was not metabolized by the reconstituted system. Incubation of 7-oxo-DHL with the reconstituted system caused accumulation of oxyferro intermediate of cytochrome P-450$_{14DM}$. It can thus be concluded that 7-oxo-DHL interfered with electron transfer to the oxyferro intermediate of the cytochrome, though it stimulated reduction of the heme iron. So far as we know, 7-oxo-DHL is the first example of a cytochrome P-450 inhibitor which selectively interferes with the electron transfer to oxyferro intermediate. 7α-Hydroxy-24,25-dihydrolanosterol was also a competitive inhibitor of cytochrome P-450$_{14DM}$. However, this compound was metabolized by the reconstituted system and could not block the electron transfer to oxyferro intermediate. 11-Oxo-24,25-dihydrolanosterol, an isomer of 7-oxo-DHL, did not have such inhibitory effects. These lines of evidence suggest a possibility that the keto group at C-7 of lanost-8-ene skeleton may interact with a certain site of cytochrome P-450$_{14DM}$ which has an important role in the electron transfer to oxyferro intermediate.

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