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Role of the Side Chain of Lanosterol in Substrate Recognition and Catalytic Activity of Lanosterol 14α-Demethylase (Cytochrome p-450$_{14DM}$) of yeasts*

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The 14α-demethylation of 24,25-dihydrolanosterol (DHL) derivatives having trimmed side chains, 27-nor-DHL, 26,27-dinor-DHL, 25,26,27-trinor-DHL, 24,25,26,27-tetranor-DHL, 23,24,25,26,27-pentanor-DHL and 22,23,24,25,26,27-hexanor-DHL, was studied with the reconstituted lanosterol 14α-demethylase system consisting of cytochrome P-450$_{14DM}$ and NADPH-cytochrome P-450 reductase both purified from yeast microsomes. The demethylase catalyzed the 14α-demethylation of the derivatives having the side chains longer than tetranor but the activities for the trinor- and tetranor-derivatives were lower. Kinetic analysis indicated that affinity of the trinor-derivative for the demethylase was considerably higher than that of DHL. The affinities of the 27-nor- and dinor-derivatives were increased by this order and were the intermediates of DHL and the trinor-derivative.

On the other hand, Vmax values of the demethylase for the DHL derivatives were decreased depending on their side-chain lengths, and the substrate-dependent reduction rate of cytochrome P-450$_{14DM}$ was also decreased in the same manner. Based on these observations, it was concluded that interaction of the side chain of lanosterol especially C-25, 26 and 27 with the substrate site of lanosterol 14α-demethylase was necessary for enhancing the catalytic activity of the enzyme. However, this interaction was considered not to be essential for substrate binding.

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