Molecular Modeling of Human Lanosterol 14α-Demethylase Complexes with Substrates and Their Derivatives

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Abstract—Lanosterol 14α-demethylase (CYP51A1) is a key enzyme in sterol biosynthesis. In humans, this enzyme is involved in the cholesterol biosynthesis pathway. The majority of antifungal drugs are aimed at the inhibition of CYP51 in fungi. To elucidate the molecular mechanisms of highly specific protein–ligand recognition, we have developed a full-atomic model of human CYP51A1 and performed docking of natural substrates and their derivatives to the active site of the enzyme. The parameters of the binding enthalpy of substrates, intermediates, and final products of the reaction of 14α-demethylation were estimated using the MMPB(GB)SA algorithm. Dynamic properties and conformational changes of the protein globule upon binding of the ligand near the active site have been investigated by the molecular dynamics method. Our studies reveal that hydroxylated intermediate reaction products have a greater affinity than the initial substrates, which facilitates the multistage reaction without accumulation of intermediate products. The contribution to the free energy of steroid ligand binding of 30 amino acids forming the substrate-binding region of CYP51A1, as well as the influence of their substitutions to alanine on the stability of the protein molecule, has been clarified using alanine scanning modeling. We demonstrate that the most serious weakening of the binding is observed in the case of substitutions Y137A, F145A, V149A, I383A, and R388A. The results of molecular modeling are in agreement with the data obtained by analysis of primary sequences of representatives of the CYP51 family.

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