

Oxidosqualene Cyclase: A Novel Inhibitor

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Abstract : Oxidosqualene cyclase is a membrane bound enzyme in which helps in the formation of steroid scaffold in higher organisms. In a highly selective cyclization reaction oxidosqualene cyclase forms LANOSTEROL with seven chiral centres starting from the linear substrate 2,3-oxidosqualene. In humans OSC in cholesterol biosynthesis it represents a target for the discovery of novel anticholesteremic drugs that could complement the widely used statins. The enzyme oxidosqualene: lanosterol cyclase (OSC) represents a novel target for the treatment of hypercholesterolemia. OSC catalyzes the cyclization of the linear 2,3-monoepoxysqualene to lanosterol, the initial four-ringed sterol intermediate in the cholesterol biosynthetic pathway. OSC also catalyzes the formation of 24(S), 25-epoxycholesterol, a ligand activator of the liver X receptor. Inhibition of OSC reduces cholesterol biosynthesis and selectively enhances 24(S),25-epoxycholesterol synthesis. Through this dual mechanism, OSC inhibition decreases plasma levels of low-density lipoprotein (LDL)-cholesterol and prevents cholesterol deposition within macrophages. The recent crystallization of OSC identifies the mechanism of action for this complex enzyme, setting the stage for the design of OSC inhibitors with improved pharmacological properties for cholesterol lowering and treatment of atherosclerosis. While studying and designing the inhibitor of oxidosqualene cyclase, I worked on the pdb id of 1w6k which was the most worked on pdb id and I used several methods, techniques and softwares to identify and validate the top most molecules which could be acting as an inhibitor for oxidosqualene cyclase. Thus, by partial blockage of this enzyme, both an inhibition of lanosterol and subsequently cholesterol formation as well as a concomitant effect on HMG-CoA reductase can be achieved. Both effects complement each other and lead to an effective control of cholesterol biosynthesis. It is therefore concluded that 2,3-oxidosqualene cyclase plays a crucial role in the regulation of intracellular cholesterol homeostasis. 2,3-Oxidosqualene cyclase inhibitors offer an attractive approach for novel lipid-lowering agents.

Keywords : anticholesteremic, crystallization, statins, homeostasis