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Study, Design and Development of Inhibitors for Oxidosqualene Cyclase

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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 anticholesteraemic 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 oxidosqulene 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.

1. INTRODUCTION

Cholesterol has gained a bad reputation in recent years. It is absolutely essential in our lives: it is needed to keep our membranes fluid and it is the raw material used to build a host of important molecules such as vitamin D and steroid hormones. However, elevated levels of cholesterol (for instance from a fat-rich diet) have been linked to the formation of atherosclerosis and heart disease. Today, doctors suggest that a combination of a healthy low-fat diet and exercise will keep these two faces of cholesterol in balance.[11]

The membrane-bound enzyme oxidosqualene cyclase (OSC, PDB ID: 1W6K) from *Homo sapiens*, commonly known as lanosterol synthase, plays a main role in forming the steroid scaffold in sterol biosynthesis. More specifically, lanosterol synthase catalyzes the cyclization of (3S)-2,3-oxidosqualene to lanosterol in the reaction that forms the sterol nucleus. The critical task of OSC is to properly fold the open triterpene oxidosqualene to generate the four-membered steroid ring. Despite its structurally critical role, lanosterol synthase is not a regulatory enzyme in sterol biosynthesis, but rather indirectly plays a role in lipid regulatory processes. The crucial importance of oxidosqualene cyclase in cholesterol biosynthesis represents a target for the discovery of novel OSC inhibitors that function as anticholesteraemic drugs

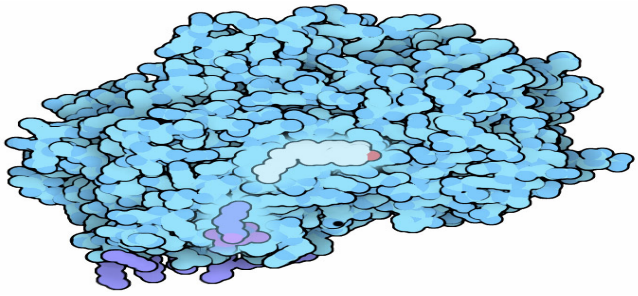


Fig. 1: BOOLEAN FORM OF OXIDOSQUALENE CYCLASE

2. STRUCTURE

The structure of oxidosqualene cyclase was deduced through x-ray crystallographic results of OSC with both the inhibitor Ro 48-8071 and its product lanosterol. These findings show that the secondary structure of lanosterol synthase consists of alpha helices, beta sheets, and random coils. Human OSC is a monomer that consists of two α-α barrel domains that are connected by loops and three smaller β-structures. The two domains of the single subunit form a dumbbell shape. Domain 1 is an α_6-α_6 barrel of two concentric rings of parallel α

helices. Domain 2 is inserted into domain 1 and contains an evolved form of the α_6-α_6 barrel that is found in domain 1. The amino ends of the inner α helices of both barrels point toward the molecular center. This consists of long loops from both domains that form a β structure and enclose the active site cavity. The amino-terminal region of OSC is positively charged and thus polar. It fills the space between the two domains and is thought to stabilize their relative orientations. There are five signature QW-sequence motifs that are located toward the carboxy terminus and reside outside the two main α-α barrel domains. These QW motifs connect surface α helices and are thought to stabilize OSC by tightening the protein structure. This avoids structural damage that can occur from absorbing the reaction energy during the highly exergonic cyclization.

The molecular weight of lanosterol synthase is 83,294.72 Da and the isoelectric point (pI) is 6.16. The primary structure of this enzyme has 732 amino acids with several natural variations or mutations. These natural variations can be seen in amino acids 175 (Arg to Gln), 310 (His to Arg), 614 (Arg to Trp), 642 (Leu to Val), and 688 (Pro to Leu). The main catalytic amino acids are the acidic Asp 455 residue and the basic His 232 residue. The secondary structure of oxidosqualene cyclase consists of about 50% α helices, about 7% β strands, about 1% β turns, and about 42% random coils. OSC does not have a prosthetic group or any associations with metal ions.

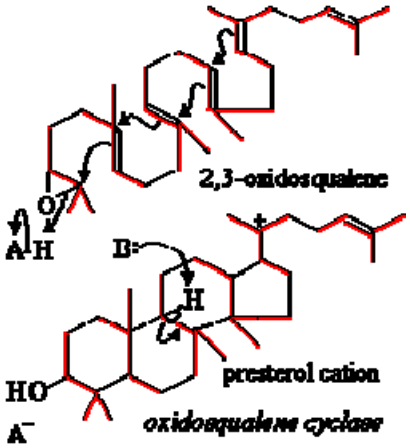


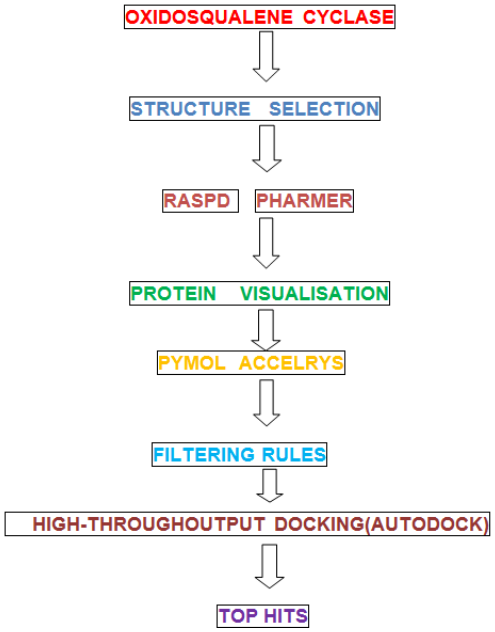
Fig. 2: STRUCTURAL VIEW OF OXIDOSQUALENE CYCLASE[30]

3. DISEASE ASSOCIATED WITH OXIDOSQUALENE CYCLASE

(HYPERCHOLESTEROLEMIA)

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.

4. FLOWCHART OF OVERALL METHODOLOGY:



5. CONCLUSION AND FUTURE WORK:

Thus based on the analysis **ZINC67912796** is chosen as the most favorable molecule which can be used as a ligand with Oxidosqualene cyclase.

Table 1: Showing all the physical parameters of ZINC67912796

pH range	xlogP	Apolar desolvation (kcal/mol)	Polar desolvation (kcal/mol)	H-bond donors	H-bond acceptors	Net charge	tPSA (Å²)	Molecular weight (g/mol)	Rotatable bonds	DL
Reference (pH 7)	1.07	0.23	-43.6	5	10	-1	177	525.615	5	↓

6. LIPINSKI'S RULE OF FIVE STATES:

1. There are not more than 5 H-bond donors (expressed as the sum of OHs and NHs).
2. The molecular weight (MW) is below 500.
3. The Log P (Log P) is less than 5.
4. There are less than 10 H-bond acceptors (expressed as the sum of Ns and Os).

With reference to the Lipinski's rule of 5 we can conclude:

1. H-bonds donor are less than 5 i.e. 5
2. H-bond acceptors are less than 10 i.e. 10
3. Molecular mass is less than 500 Daltons i.e. 431.661 Daltons
4. Octanol-water partition coefficient log *P* is less than 5 i.e. 1.07.

Also according to the variants of Lipinski's rule

1. Rotatable bonds are less than 10 i.e. 5
2. Polar Surface area is equal or more than 140 i.e. 177Å^2

The final result will come out by the in-vitro testing of the molecule