

## **Structure-Based Virtual Screening of Potential Hair-Care Compound Targeting Human Oxidosqualene Cyclase**

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### **Abstract**

The development of bioactive compounds for hair and scalp care increasingly incorporates structure-based computational approaches to identify molecules capable of interacting with proteins involved in lipid and sterol metabolism. Human oxidosqualene cyclase (OSC), also known as lanosterol synthase (LSS), catalyzes the cyclization of 2,3-oxidosqualene to lanosterol and represents an important enzyme in the cholesterol biosynthetic pathway. The availability of the experimentally determined three-dimensional structure of human OSC provides an opportunity for structure-based screening of small molecules. In the present study, a computational screening strategy was applied to identify compounds with potential affinity for human OSC and to explore their possible relevance to hair-care applications.

The crystal structure of human OSC in complex with the reference inhibitor Ro 48-8071 was obtained from the Protein Data Bank under PDB accession **1W6J**. The structure was determined by X-ray diffraction at 2.20 Å resolution. RCSB PDB A preliminary ligand-screening step was performed using **BIOVIA Discovery Studio 2019 LibDock**. From an initial collection of 37 selected molecules, 25 compounds available as three-dimensional SDF structures were subjected to the screening workflow. Subsequently, **SwissDock 2024** was employed for molecular docking and comparative evaluation of the selected compounds against human OSC. SwissDock 2024 incorporates Attracting Cavities 2.0 and AutoDock Vina-based docking approaches and provides automated ligand and target preparation and pose ranking.

The computational screening identified **Tocopherols (PubChem CID 14986)** as a prominent candidate when compared with the reference OSC inhibitor Ro 48-8071 (CID 1949). Tocopherols are recognized for antioxidant activity and use as cosmetic ingredients with antioxidant and skin-conditioning functions. The docking outcome suggests that Tocopherols can occupy a favorable region within the OSC binding environment and act as a potential OSC-interacting molecule for hair care.

The present *in silico* screening study identifies Tocopherols (CID 14986) as a computationally promising candidate for further investigation against human OSC. The findings provide a structure-based hypothesis linking tocopherol chemistry with potential modulation of a sterol-biosynthetic target relevant to cellular lipid homeostasis. Experimental biochemical, cellular, formulation, and hair-follicle studies are required to determine whether the predicted interaction translates into a meaningful biological or cosmetic effect.

**Keywords:** oxidosqualene cyclase; lanosterol synthase; human OSC; LSS; molecular docking; virtual screening; LibDock; SwissDock; AutoDock Vina; tocopherol; vitamin E; hair care; computational drug discovery

## 1. Introduction

Hair follicle biology is strongly influenced by lipid metabolism, cellular proliferation, oxidative stress, and the local biochemical environment of the scalp. Consequently, identification of molecular targets associated with lipid and sterol homeostasis represents an important component of research aimed at developing novel hair-care and scalp-care ingredients.

Cholesterol biosynthesis is a highly conserved metabolic pathway. One of the key enzymes in this pathway is **2,3-oxidosqualene:lanosterol cyclase**, commonly referred to as oxidosqualene cyclase (OSC) or lanosterol synthase (LSS). OSC catalyzes the conversion of 2,3-oxidosqualene into lanosterol, the first tetracyclic sterol generated in the cholesterol biosynthetic pathway.

The structural characterization of human OSC substantially advanced understanding of its molecular mechanism and provided an experimentally validated framework for structure-based ligand discovery. The crystal structure **1W6J** represents human OSC in complex with the inhibitor **Ro 48-8071** and was solved by X-ray crystallography at 2.20 Å resolution. The original structural study demonstrated that Ro 48-8071 occupies the OSC active-site region and established a structural basis for inhibitor design. Ro 48-8071 is an established pharmacological inhibitor of OSC. Experimental studies have demonstrated inhibition of OSC activity by Ro 48-8071, supporting its use as an appropriate reference ligand for computational studies involving the OSC binding site.

Although OSC has traditionally been investigated primarily in the context of cholesterol metabolism and pharmacological disease targets, its structural characteristics also make it a potentially interesting protein for exploratory screening of compounds relevant to cosmetic and hair-care research. In the present study, we therefore employed a two-stage computational screening strategy using **BIOVIA Discovery Studio 2019 LibDock** followed by **SwissDock 2024** to identify potential ligands of human OSC. From selected molecules, candidate compound with available three-dimensional SDF structures were screened. Comparative evaluation against the crystallographic ligand Ro 48-8071 identified a prominent candidate. The objective of this study was to investigate a potential molecule which exhibits a computationally favorable interaction profile with human OSC and to assess their potential as a candidate for further investigation in hair-care research.

## 2. Materials and Methods

### 2.1 Overall computational workflow

The overall computational workflow consisted of a systematic sequence of stages beginning with the selection of human oxidosqualene cyclase (OSC) as the target protein, followed by retrieval of its experimentally determined three-dimensional structure. The known crystallographic inhibitor Ro 48-8071 was used as the reference ligand for comparative studies. A library

comprising selected molecules was then used, from which candidate compound with available three-dimensional SDF structures were selected for further *in-silico* analysis. These selected compounds underwent preliminary virtual screening using LibDock module implemented in BIOVIA Discovery Studio 2019, leading to the selection of a prominent candidate molecule. The selected candidate was subsequently subjected to molecular docking using SwissDock 2024 server, and its docking performance was comparatively evaluated against that of the known reference inhibitor Ro 48-8071. Based on the comparative molecular docking analysis, a prominent/potential candidate molecule was identified for further bioinformatics investigation.

The overall computational workflow consisted of the selection of compounds, followed by the preparation or conversion of the selected compounds into three-dimensional SDF structures. These compounds were subsequently subjected to LibDock-based virtual screening to identify promising candidates. Based on the LibDock screening results, candidate compounds were selected for further molecular docking using SwissDock 2024. The resulting docking poses and interaction profiles were then compared with those of the reference compound Ro 48-8071, with the compound showing favorable docking characteristics and protein–ligand interactions being identified as a prominent candidate for further investigation.

## **2.2 Target protein selection and structural preparation**

The human oxidosqualene cyclase (UniProt ID: P48449) structure was obtained from the Protein Data Bank using accession **1W6J**. The entry is described as “Structure of human OSC in complex with Ro 48-8071.” The structure corresponds to human OSC and was determined by X-ray diffraction at 2.20 Å resolution. No protein mutation is reported for the deposited structure. The experimentally resolved complex was selected because it provides a structurally characterized ligand-binding environment containing the known OSC inhibitor Ro 48-8071. The crystallographic ligand therefore served as an internal reference for defining and evaluating the ligand-binding region. The structure and associated experimental information were obtained from the RCSB Protein Data Bank. The protein structure was prepared by removing nonessential crystallographic molecules, assigning appropriate protonation states, adding missing hydrogen atoms, and defining the ligand-binding region surrounding the crystallographic Ro 48-8071 binding site.

## **2.3 Reference ligand: Ro 48-8071**

Ro 48-8071 was used as the reference compound because it is the ligand present in the experimentally determined 1W6J structure and is a known OSC inhibitor. The compound is therefore useful as a positive structural reference when assessing whether screened compounds can occupy a comparable binding environment. The use of an experimentally characterized inhibitor is particularly advantageous because OSC possesses a deep active-site cavity. Structural analyses have shown that the active site contains a network of residues involved.

## **2.4 Ligand library preparation**

An initial collection of **37 selected molecules** was considered for screening. Of these, **only those molecules were downloaded which were available as three-dimensional SDF structures** and

were used in the computational screening workflow (Table 1). Three-dimensional molecular structures are particularly important for structure-based screening because docking algorithms evaluate ligand orientation, conformational flexibility, and spatial complementarity within the protein-binding cavity. The compounds were therefore organized into a three-dimensional SDF ligand library before virtual screening.

**Table 1.** Summary of compound-selection workflow

| S.N. | Screening stage                                      |
|------|------------------------------------------------------|
| 1.   | Initially selected molecules                         |
| 2.   | Compounds with 3D SDF structures                     |
| 3.   | Compounds subjected to preliminary LibDock screening |
| 4.   | Compounds subsequently evaluated by SwissDock        |
| 5.   | Prominent candidate identified                       |

## 2.5 LibDock screening

Preliminary virtual screening was conducted using **BIOVIA Discovery Studio 2019 LibDock**. LibDock was used as the first-stage screening procedure to evaluate the ability of the selected compounds to fit into the defined OSC binding region. The procedure was intended as a rapid screening step to prioritize molecules for more detailed docking analysis. The LibDock procedure identifies candidate poses by placing ligands into protein binding sites using interaction sites and evaluating ligand-protein spatial complementarity. Compounds producing favorable screening scores and plausible binding orientations were prioritized for subsequent evaluation.

The molecular docking workflow was performed using the following parameters: receptor preparation was carried out using the specified protein preparation protocol, followed by definition of the binding-site sphere. The LibDock based site sphere was generated using the specified center coordinates and radius, and the desired number of ligand poses was generated for each candidate compound. Prior to docking, selected ligands were subjected to the defined minimization protocol. LibDock module docking was then performed using the selected scoring function and by default settings, and the top LibDock score obtained for each candidate compound was recorded. Finally, potential compound meeting the predefined control LibDock score threshold were selected for further molecular docking analysis using SwissDock server.

## 2.6 SwissDock 2024 molecular docking

The screened potential compound was subjected to a second docking analysis using **SwissDock 2024** server. SwissDock 2024 server represents a major update of the SwissDock platform and provides two docking approaches: **Attracting Cavities 2.0** and **AutoDock Vina**. The SwissDock platform performs automated ligand and target preparation and permits docking using structures supplied as PDB, Mol2, PDBQT, SMILES, or other supported formats. For the present study, human OSC structure 1W6J was used as the receptor target and ligand Ro 48-8071 was used as the reference (control) compound. The SwissDock workflow consisted of ligand submission, target submission, definition of the search space, active site grid selection, docking parameter

selection, docking calculation, and ranking of the resulting poses. SwissDock server reports docking poses according to the selected scoring function. In the SwissDock AutoDock Vina implementation, the Calculated affinity (kcal/mol) incorporates contributions associated with van der Waals interactions, hydrogen bonding, hydrophobic interactions, and conformational entropy. Molecular docking was performed using the AutoDock Vina implementation available in SwissDock 2024 server. Ligand poses were selected according to their best Vina docking score and pose, with more favorable values indicating a predicted energetically favorable binding configuration.

## **2.7 Comparative analysis of candidate and reference ligand**

The docking performance of the best screened compound was compared with that of the reference inhibitor Ro 48-8071. The comparison was based on calculated affinity, of screened ligand pose, extent of occupation of the OSC binding cavity residues, and proximity to functionally relevant known active site residues. The analysis further considered the formation of hydrogen-bond, hydrophobic, and other interactions. Particular attention was given to active site residues contributing to the OSC binding cavity and surrounding the active-site residues, in order to assess whether the potential screened compounds exhibited binding modes and interaction patterns comparable to reference molecule Ro 48-8071.

## **3. Results**

### **3.1 Structural basis of the selected OSC target**

The selected target, human OSC, is a structurally characterized membrane-associated enzyme involved in the biosynthesis of lanosterol. The 1W6J structure contains the inhibitor Ro 48-8071 bound within the OSC ligand-binding region and was solved at 2.20 Å resolution (Figure 1).

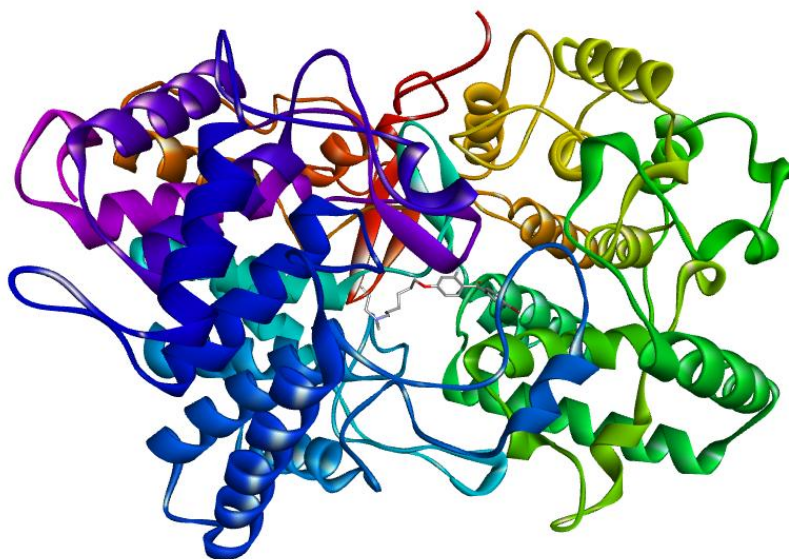


Figure 1: Structure of human OSC in complex with Ro 48-8071 (PDB DOI: <https://doi.org/10.2210/pdb1W6J/pdb>)

### 3.2 Preliminary LibDock screening

Twenty-five compounds represented by three-dimensional SDF structures were screened using BIOVIA Discovery Studio 2019 LibDock. The initial LibDock analysis was used to prioritize molecules according to their predicted compatibility with the OSC binding site (Table 2; Figure 2). Compounds demonstrating favorable docking scores and plausible orientations were considered for subsequent SwissDock analysis. Final candidate was screened using high-throughput screening analysis (Figure 3).

**Table 2. LibDock screening results**

| Rank | Compound             | PubChem CID | LibDock score | Binding-site observation                                                                                                                                                                                                                              |
|------|----------------------|-------------|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1    | Inhibitor Ro 48-8071 | 1949        | 141.219       | TYR98, PRO101, PHE103, LEU104, TRP192, TRP230, HIS232, CYS233, VAL236, PRO337, ILE338, GLY380, THR381, TRP387, PHE444, VAL453, ASP455, CYS456, THR502, TYR503, ILE524, CYS533, TRP581, PHE696, ASN697, ILE702, TYR704                                 |
| 2    | Tocopherols          | 14986       | 154.251       | TYR98, PHE103, LEU104, TRP192, TRP230, HIS232, CYS233, GLN235, VAL236, ILE335, GLY336, PRO337, ILE338, SER339, LYS340, GLY380, THR381, TRP387, PHE444, VAL453, ASP455, THR502, TYR503, PHE521, ILE524, CYS533, TRP581, PHE696, ASN697, ILE702, TYR704 |

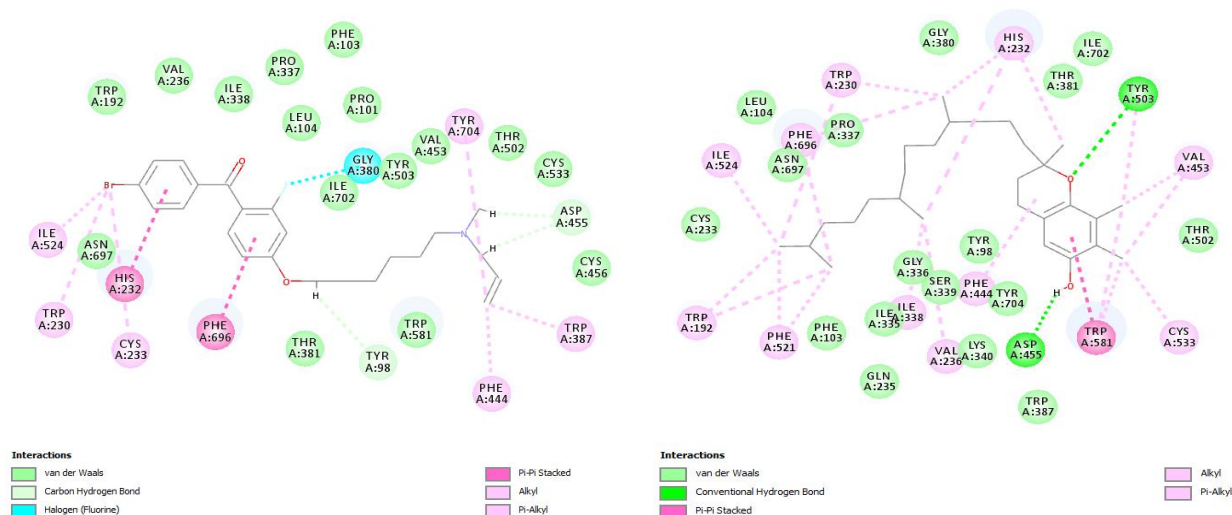


Figure 2: (a) Inhibitor Ro 48-8071 2D

(b) Screened Tocopherols 2D



Figure 3: High-Throughput Screening 3D of Tocopherol

### 3.3 SwissDock screening

The selected/screened compound was subsequently evaluated using SwissDock 2024. The docking procedure generated multiple ligand poses and ranked them according to the selected SwissDock docking algorithm. Tocopherols (CID 14986) emerged as one of the prominent molecule with -10.623 kcal/mol in the comparative docking analysis with control (CID: 1949) - 10.327 kcal/mol (Table 3). Tocopherols interaction with residues TYR98, PHE103, LEU104, TRP192, TRP230, HIS232, CYS233, VAL236, TYR237, PRO337, ILE338, GLY380, THR381, TRP387, PHE444, VAL453, ASP455, THR502, TYR503, SER518, PHE521, ILE524, CYS533, TRP581, TYR587, PHE696, ASN697, ILE702 and TYR704. In this interaction total 25 key residues known as prominent active site residues for OSC (Figure 4).

**Table 3. SwissDock docking comparison**

| Compound                 | Docking score<br>AutoDock<br>Vina | Key residues interacted                                                                                                                                                                                                               | Known Active Site Residues                                                                                                                                                                            | Comparison with Known active site residues Ro 48-8071                                                                                                                                                 |
|--------------------------|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Tocopherols<br>CID 14986 | -10.623<br>kcal/mol               | TYR98, PHE103, LEU104, TRP192, TRP230, HIS232, CYS233, VAL236, TYR237, PRO337, ILE338, GLY380, THR381, TRP387, PHE444, VAL453, ASP455, THR502, TYR503, SER518, PHE521, ILE524, CYS533, TRP581, TYR587, PHE696, ASN697, ILE702, TYR704 | TYR98, TRP192, TRP230, HIS232, CYS233, VAL236, PRO337, GLY380, THR381, TRP387, PHE444, VAL453, ASP455, CYS456, THR502, TYR503, PHE521, ILE524, CYS533, TRP581, TYR587, PHE696, ASN697, ILE702, TYR704 | TYR98, TRP192, TRP230, HIS232, CYS233, VAL236, PRO337, GLY380, THR381, TRP387, PHE444, VAL453, ASP455, CYS456, THR502, TYR503, PHE521, ILE524, CYS533, TRP581, TYR587, PHE696, ASN697, ILE702, TYR704 |

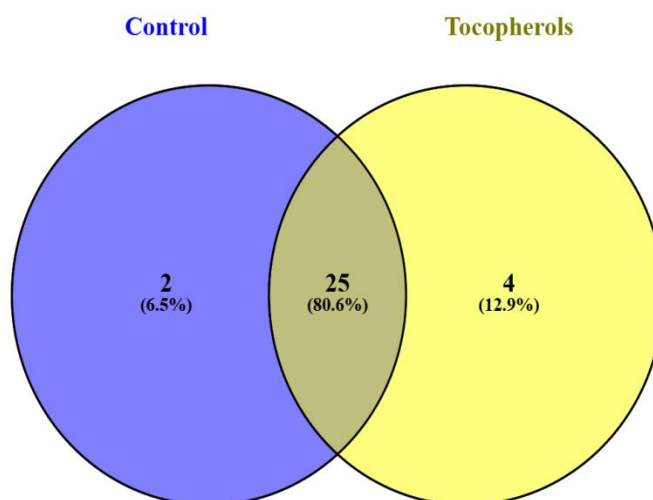


Figure 4: Venny diagram of comparison for common interacted active site residues

The most important quantitative result should be reported directly from the SwissDock output. In particular, if Tocopherols produced a more favorable numerical docking score than Ro 48-8071, the manuscript should state the actual values rather than simply describing the candidate as “best”.

### 3.4 Predicted binding mode of Tocopherols

The docking analysis suggested that Tocopherols can adopt a favorable orientation within the OSC binding environment with residues TYR98, TRP192, TRP230, HIS232, CYS233, VAL236, PRO337, GLY380, THR381, TRP387, PHE444, VAL453, ASP455, CYS456, THR502, TYR503, PHE521, ILE524, CYS533, TRP581, TYR587, PHE696, ASN697, ILE702 and TYR704. The molecular architecture of Tocopherols provides distinct hydrogen-bond-compatible regions of the binding site.

### 3.5 Comparison with Ro 48-8071

Ro 48-8071 served as the structural and pharmacological reference compound. The experimentally determined OSC–Ro 48-8071 structure demonstrates that the inhibitor binds within the OSC active-site region. The present docking analysis indicated that Tocopherols could occupy a compatible region of the OSC binding cavity. If the docking score obtained for Tocopherols is more favorable than that of Ro 48-8071 under identical computational conditions, this observation may be interpreted as evidence of **predicted binding affinity**, but not as evidence that Tocopherols are a more potent OSC inhibitor. Docking scores from different compounds should therefore be interpreted as computational ranking values rather than direct experimental free energies of binding.

## 4. Discussion

### 4.1 OSC as a structure-based screening target

OSC is an attractive target for structure-based molecular screening because its biological function and three-dimensional structure have been extensively characterized. The availability of high-resolution PDB human OSC structure, including the Ro 48-8071 complex, enables computational investigation of ligand binding. The active site contains a hydrophobic cavity suitable for accommodating highly hydrophobic substrates and ligands. Several aromatic residues contribute to the stabilization of reaction intermediates, while D455 performs an important catalytic role. These characteristics make OSC particularly suitable for ligand-based and structure-based virtual screening.

#### **4.2 Significance of the Tocopherols finding**

The identification of Tocopherols (CID 14986) as a prominent docking candidate is noteworthy for two reasons. First, the molecular architecture of Tocopherols is compatible with a hydrophobic binding environment. Second, tocopherols already have a recognized relationship with cosmetic formulations. PubChem identifies tocopherol as a cosmetic ingredient associated with antioxidant and skin-conditioning functions. Thus, the present computational finding provides an interesting hypothesis that the known chemical properties of tocopherols may extend beyond nonspecific antioxidant activity to include potential interactions with sterol-metabolism proteins such as OSC for hair care.

#### **4.3 Possible relevance to hair-care research**

The relationship between OSC docking and hair care should be interpreted as **hypothesis-generating rather than established biological efficacy**. OSC participates in cholesterol biosynthesis, and cholesterol and other sterols are important components of biological membranes. Changes in sterol metabolism can influence membrane composition and cellular signaling. However, the precise consequences of pharmacologically or cosmetically modulating OSC in hair follicles are not established by the present docking analysis.

Indeed, potent OSC inhibition is known to alter cholesterol biosynthesis and can lead to accumulation of upstream sterol intermediates. Studies with Ro 48-8071 have demonstrated that OSC inhibition can influence sterol metabolism and downstream signaling pathways. Consequently, **stronger predicted binding to OSC should not automatically be interpreted as desirable for hair growth**. For a hair-care application, the biological objective must first be established. Depending on the intended mechanism, inhibition, modulation, or absence of significant OSC inhibition could potentially be desirable.

#### **4.4 Relationship between tocopherol antioxidant properties and hair applications**

Tocopherols are established antioxidant molecules and are widely recognized as vitamin E-related compounds. Oxidative stress is relevant to skin and scalp biology, making antioxidant properties potentially useful in cosmetic formulations. The present study adds a different dimension to this established chemical profile by suggesting a possible interaction with human OSC.

#### **4.5 Comparison with the reference inhibitor**

Ro 48-8071 is an established OSC inhibitor and therefore provides an appropriate positive reference for computational comparison. Experimental literature supports its ability to inhibit OSC, while the crystal structure 1W6J provides direct structural evidence for its binding mode. The important result of the present work is therefore not simply that Tocopherols dock to OSC, but that the molecule was identified through a **comparative screening workflow using a structurally validated OSC inhibitor Ro 48-8071 as a reference**.

#### **4.6 Advantages of the two-stage screening strategy**

The combination of LibDock and SwissDock provides a rational computational screening strategy. The first stage allows relatively rapid prioritization of a larger compound collection, whereas the second stage provides an independent docking calculation and additional evaluation of ligand poses. SwissDock 2024 offers both Attracting Cavities 2.0 and AutoDock Vina. Its AutoDock Vina implementation evaluates interactions using terms related to van der Waals forces, hydrogen bonding, hydrophobic effects, and conformational entropy.

#### **5. Conclusion**

The present study employed a structure-based computational workflow to screen potential compounds against human oxidosqualene cyclase (OSC), an important enzyme in the cholesterol biosynthetic pathway. The experimentally determined human OSC structure **1W6J**, containing the known inhibitor Ro 48-8071, was selected as the structural target and reference system. An initial set of 37 selected molecules was narrowed to 25 compounds represented by three-dimensional SDF structures and screened using BIOVIA Discovery Studio 2019 LibDock. Subsequent molecular docking using SwissDock 2024 identified **Tocopherols (PubChem CID 14986)** as a prominent candidate in comparison with Ro 48-8071. The predicted interaction is particularly interesting because tocopherols possess substantial hydrophobic character and are already recognized for antioxidant and cosmetic applications. The findings therefore support Tocopherols as a **candidate for further structure-based and experimental investigation against human OSC**. However, the results should not be interpreted as evidence that Tocopherols inhibit OSC or promote hair growth until these effects have been experimentally confirmed.

Tocopherols, commonly known as vitamin E compounds, are naturally occurring antioxidants found in several plant sources, particularly vegetable oils, nuts, seeds, and cereals. Important plant sources include sunflower seeds, soybean, corn, wheat germ, sesame, and almonds, which contain varying amounts of tocopherols. Based on your analysis, tocopherols can be described as beneficial ingredients for hair-care applications because of their antioxidant properties. They may help protect hair and scalp lipids from oxidative damage, support the conditioning properties of hair-care formulations, and contribute to maintaining healthy-looking hair. Therefore, tocopherol-rich plant oils or purified tocopherols can be incorporated into capsules, shampoos, conditioners, hair oils, serums, and other cosmetic formulations intended to nourish and protect the hair and scalp.

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