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Research Article

Elucidating the Potential Compounds Targeting OPNL1W Through Virtual Screening for the Treatment of Color Blindness

Kashaf Shahid[1], Azhar Iqbal[2], Ayesha Zafar[3], Sidrah Hafeez[3], Ayesha Afzal[4], Muhammad Jahangir Shafi[5], Ayman Rashid[4], , Keziah Shaheen[3], Rabbia Allah Rakha[6], Muhammad Mumtaz Tahir[7], Noel Shamaun[6,*], Hassan Bin Waseem[4,*]

[1]Department of Bioinformatics, Faculty of Life Sciences, University of Okara, Okara, 56300, Punjab, Pakistan
[2]Department of Biotechnology, Faculty of Life Sciences, University of Okara, Okara, 56300, Punjab Pakistan
[3]Faculty of Pharmacy, Hamdard University, Islamabad Campus, Pakistan
[4]Department of Bioinformatics, Institute of Biochemistry, Biotechnology and Bioinformatics, The Islamia University of Bahawalpur, Bahawalpur, Pakistan
[5]Department of Biotechnology, Institute of Biochemistry, Biotechnology and Bioinformatics, The Islamia University of Bahawalpur, Bahawalpur, Pakistan
[6]Department of Biological Sciences, Forman Christian College (A Chartered University), Lahore, Pakistan
[7]Medical Research Institute, Southwest University, Chongqing 400715, China
***Correspondence:** NS: microbioresearcher70@gmail.com , HBW: expertbioinfo@gmail.com

Abstract

Partial blindness occurs and a patient is unable to differentiate colors in a typical manner. It is otherwise called variety lack generally acquired, however, can likewise be brought about by eye sicknesses, drugs, and aging. Color visual impairment frequently happens when somebody cannot recognize specific colors and at least one of the variety cone cells is missing, not working, or there is an unexpected variety in comparison to the typical and normal. Partial blindness is more normal in males and influences around 8% of males and 0.5% of females around the world. In current efforts, the molecular docking approach was applied to screen the novel compounds from the ZINC compound database that may show effectiveness against color blindness. Various computational strategies including homology modeling, threading, and *ab initi*o methods were applied for the 3D structure prediction of the target protein OPN1LW. The 3D structures of OPN1LW were additionally evaluated and their efficacy was calculated. It was observed that the overall quality of the predicted structure was 95.88%. Ramachandran plot showed reliable results as the conserved residues were falling in the most favored region. After structure evaluation the energy of the top-picked structures was minimized and molecular docking analyses were performed against the FDA database from the ZINC compounds database. The suitable docked compounds were analyzed and ADMET analyses were performed. After analyzing the molecular docking and ADMET results concluded that the screened compound (ZINC000000005560) with interacting residues Thr-118, Glu-122, Ile-189, Tyr-191, Met-207, Phe-212, Trp-265, Tyr-268, Ala-269, Ala-272, can be used against color blindness and may prove reliable results.

Keywords: OPN1LW, Color Blindness, CADD, Bioinformatics, Molecular Modeling

1. Introduction

Color blindness, also known as Color Vision Deficiency (CVD), is a common visual impairment affecting a substantial portion of the population, with an estimated prevalence of approximately 8% of males and 0.5% of females of Northern European ancestry (Delpero et al. 2005). The multifaceted aspects of color blindness, encompass its causes, types, diagnosis, and implications while drawing from established scientific research to provide a thorough analysis.

Color blindness, driven by genetic mutations affecting cone cell photopigments, is a widespread visual impairment with far-reaching implications (Marey, Semary, and Mandour 2015). Scientific research sheds light on the intricate genetic and neural mechanisms underlying this condition (Maule, Skelton, and Franklin 2023). Accurate diagnosis and assessment play a crucial role in understanding the extent of color vision deficiency and tailoring interventions (Okubo et al. 1998). OPN1LW, formally known as Opsin 1 (Cone Pigments), Long-Wave-Sensitive, stands as a sentinel of perception, orchestrating the symphony of color vision in the intricate depths of the retina. Within the photoreceptor-laden tapestry of eyes, OPN1LW unfurls its biological narrative by giving rise to a remarkable protein. The cone opsins, carefully detect the light of diverse wavelengths, bestowing upon us the gift of seeing a spectrum of colors (Nathans, Thomas, and Hogness 1986).The long-wave-sensitive opsin protein encoded by *OPN1LW* is an exquisite example of nature's ingenuity. Opsin intricately structured, captures photons with remarkable specificity, and upon their absorption (Hunt et al. 1995). The cascade involves a series of molecular events, each building upon the other, culminating in the generation of electrical signals that herald the advent of color perception. The hereditary changes can disturb its congruity. Changes inside the OPN1LW can prompt a variety of vision problems, most usually red-green tone blindness (Nathans, Thomas, and Hogness 1986). The changes adjust the construction of the cone opsin protein, impeding the capacity to see specific frequencies. People with these changes might battle to recognize specific shades of red and green, offering a brief look into the sensitive harmony that empowers the bright impression of the world (Neitz and Neitz 1998).Bioinformatics can likewise assist with assessing the properties and cooperation of medication competitors, like their dissolvability, absorption, harmfulness, digestion, and so forth, by utilizing strategies (Chandra and Sharma 2018). Bioinformatics can also help to assess the efficacy and safety of drug candidates by using methods such as gene expression analyses, which measure how a drug candidate alters the expression of genes in cells. (Sheikh Arslan Sehgal et al. 2015; Tur Razia et al. 2023).Bioinformatics showed success in solving various biological problems through computer-aided drug design, vaccine design and pharmacoinformatics (Sheikh Arslan Sehgal, Mirza, et al. 2018; Baxevanis, Bader, and Wishart 2020). Various novel compounds have been reported against cancer and neurological disorders. Moreover, *in silico* vaccine design has also been reported against numerous virus (Waseem et al. 2023; Waqas et al. 2020; Sajid et al. 2022; Tahir et al. 2020). The current study utilized high throughput virtual screening for the identification of novel compounds against OPN1LW. Virtual screening was applied to screen against the selected drug library. The experimental validation of OPN1LW by using X-ray crystallography and Nuclear Magnetic Resonance (NMR) has not been reported yet. The 3D structure of OPN1LW was predicted by utilizing various bioinformatics techniques. Currently, no drug or literature focuses on color blindness by targeting OPN1LW, current study focuses on color blindness and targeting OPN1LW to screen a drug by using a virtual screening approach against OPN1LW that can be used to treat color blindness.

2. Materials and Methods

In the current research, a meticulous exploration of OPN1LW by integrating advanced computational methods and molecular modeling techniques was applied. The primary

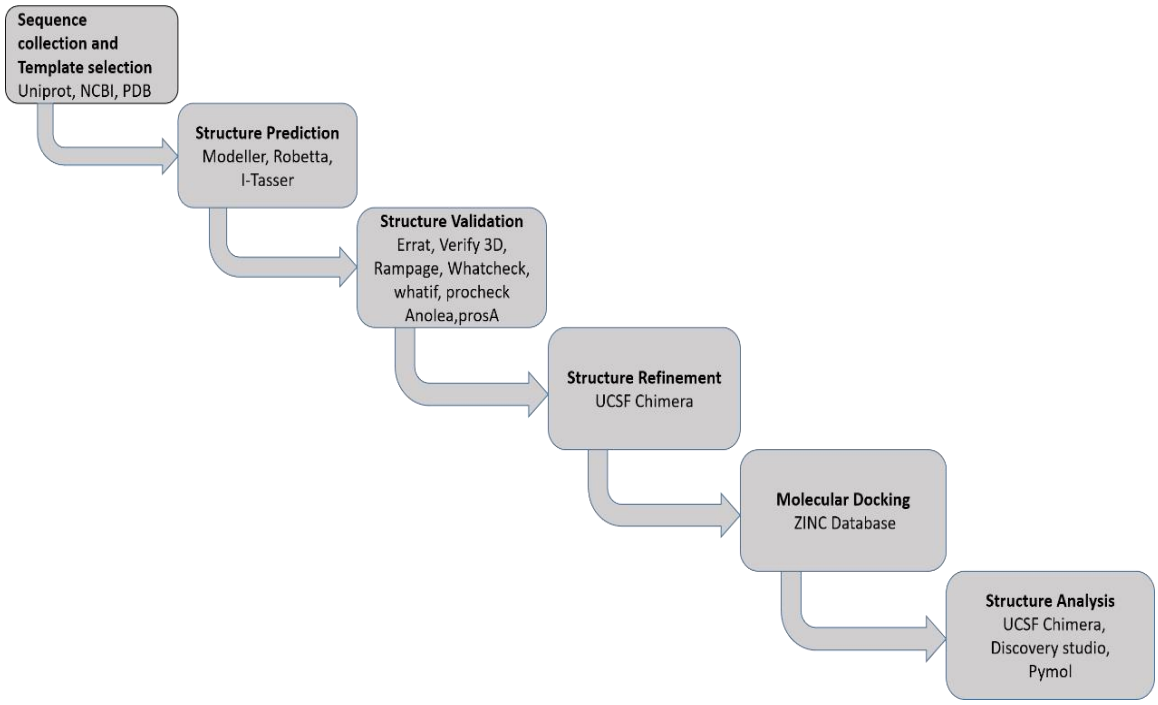

Figure 1: Methodology followed for the elucidation of novel compounds

the objective was to gain profound insights into the structural characteristics of the 3D predicted structure for OPN1LW, emphasizing its potential as a therapeutic target. To initiate the studies, a vast repository of biological knowledge stored in the UniProt Knowledgebase (UniProtKB) (Consortium 2015) was utilized to retrieve the amino acid sequence of OPN1LW. Homology modeling, threading, and *ab intio* approaches were applied for the 3D structure prediction of the selected protein.MODELLER 10.2 an automated and most cited tool for protein structure prediction (Webb and Sali 2016), was applied to predict the 3D structure of the selected protein OPM1LW. The amino acid sequence of the selected protein was subjected to BLASTp (Korf, Yandell, and Bedell 2003)for the templates to be scrutinized for homology, and the top-ranked five templates were picked on the basis of, maximum score, query coverage, percentage identity and resemblance. The top-ranked five templates were picked and further employed to predict the 3D structure of OPN1LW (Sheikh A Sehgal, Hammad, et al. 2018). The protein sequence was also submitted to I-tesser (Yang et al. 2015), Robetta (Kim, Chivian, and Baker 2004), RaptorX, Quark (Gasser and Leutwyler 1982), M4T (Fernandez-Fuentes et al. 2007), A number of evaluation tools including ERRAT (Laskowski et al. 1993), Anolea (Melo et al. 1997), prosA (Wiederstein and Sippl 2007), Whatif (Vriend 1990) and ProCheck (Laskowski et al. 1993) were utilized to evaluate the predicted 3D structures of OPN1LW to cross verify the accuracy and reliability of OPN1LW predicted structures. For high throughput virtual screening the Food and Drug Association (FDA) compounds library was extracted from the ZINC commercial database of compounds(Irwin and Shoichet 2005) and was utilized to analyze, evaluate, and scrutinize the interacting residues of the selected protein OPN1LW. ChemDraw and ChemDraw ultra were utilized for the optimization of bond angles

Table 1: The top-ranked five templates for the prediction of the 3D structure of OPN1LW

Accession ID	Total score	Query coverage	Maximum Identity	E-value
1F88	291	93%	42.32%	2e-96
3C9M	290	92%	42.44%	8e-96
4BEY	290	92%	42.44%	1e-95
2X72	288	92%	42.15%	3e-95
6FK6	281	85 %	43.35%	1e-92

and bond lengths of all the molecules selected from the retrieved library. (Mendelsohn 2004). The energy minimization of the predicted 3D structure of OPN1LW was also performed by using UCSC Chimera 1.9 (Pettersen et al. 2004). Energy minimization was performed for the optimization of the geometry of all the compounds present in the selected dataset for high throughput virtual screening. Autodock vina was utilized for molecular docking analyses of all the retrieved compounds (Trott and Olson 2010). While performing molecular docking studies grid was set on the protein having values as x = 15.34, y = -6.09, z = -8.58. The drug properties including H-bond acceptors, H-bond donors, and the number of rotatable bonds present in all the compounds were calculated by employing the PubChem (Hahnke, Kim, and Bolton 2018). mCule (Kiss, Sandor, and Szalai 2012) and Molinspiration (Jarrahpour et al. 2012) were used to calculate the efficiency and reliability of the selected molecules and also Lipinski's rule of five. Toxicity calculation and carcinogenicity of all the scrutinized top-ranked compounds were measured. The conserved binding regions of all the docked complexes of the target protein and the final screened compounds were analyzed and also visualized the docked complexes by ligplot (Wallace, Laskowski, and Thornton 1995) and UCSC Chimera 1.9. AdmetSAR online server was utilized to calculate absorption, distribution, metabolism, excretion, and toxicity, (ADMET) properties and verify the reliability and key role of the selected compounds (Cheng et al. 2012). The utilized methodology (Figure1) showed reliable results (Waqas et al. 2021; Tahir et al. 2019).

3. Results and Discussions

The aims and objective of current studies were to screen novel compounds against OPN1LW. Extensive literature was done to study relation between color blindness and OPN1LW and detailed *in silico* examinations were performed to scrutinize novel targets related to OPN1LW. The 3D structure of OPN1LW was not predicted by NMR and X-ray crystallography. To analyze structural features 3D structure was to be predicted. Different approaches of protein 3D structure prediction including homology modeling, *ab initio*, and threading were implied to predict the 3D structure of the target protein. The canonical sequence of OPN1LW was subjected to retrieve some suitable templates for homology modeling. Numerous templates were analyzed and the top-ranked five significantly aligned acceptable 3D templates with the total score, PDB accession number, maximum score, percentage identity, the query coverage of the templates, and the targets and the E-values were selected for the 3D homology modeling of the OPN1LW (Table 1). All the picked templates were utilized to predict the 3D structure of the target protein. Fifty different structures were predicted and compared by homology modeling. Threading and *ab initio* methods were also utilized to cross-refer and find the optimized

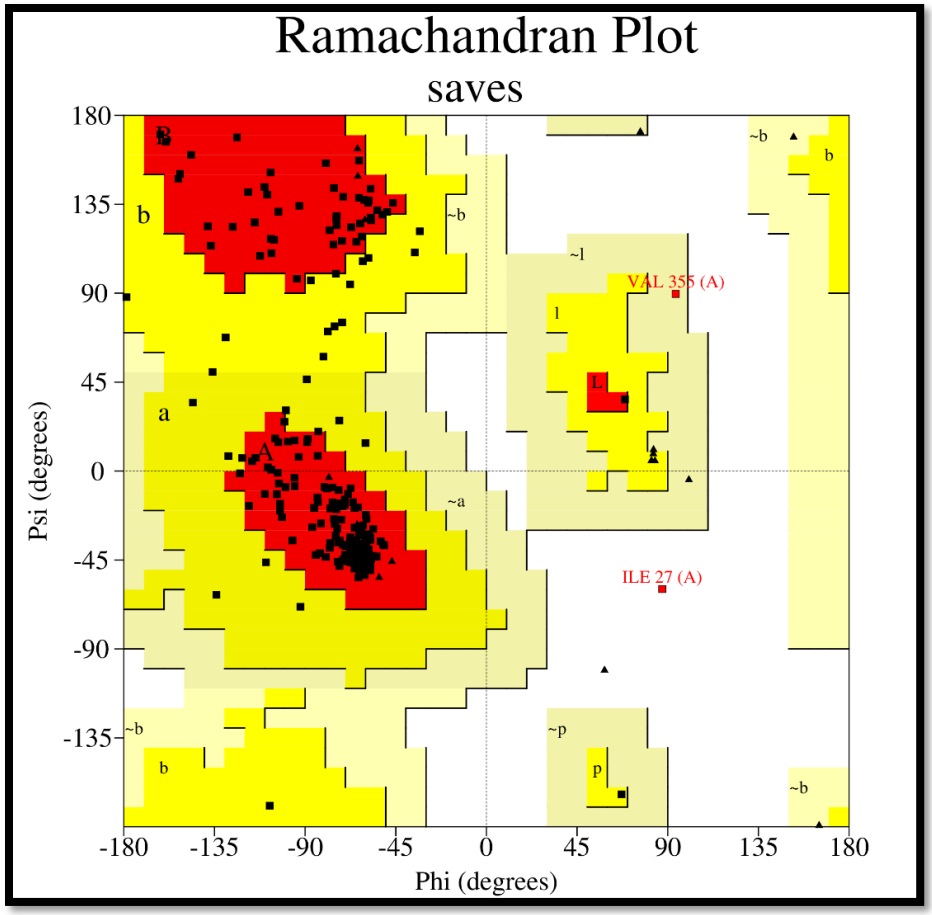

Figure 2: Ramachandran plot of the selected protein showing residues in favored, allowed and disallowed regions

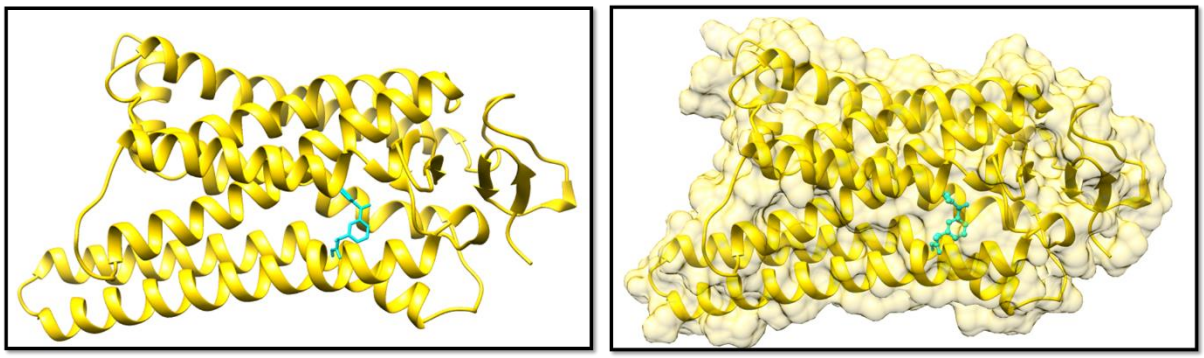

Figure 4: Binding site of the target protein observed by molecular docking analyses

structure for the target protein. After 3D protein structure prediction, all the structures were verified using different tools. The most suitable 3D structure of the target protein among all having fewer errors was predicted for further analysis.

The selected evaluation tools showed reliable values of all the predicted structures. The perceived results indicated the efficiency, efficacy and stability of the 3D predicted structure of OPN1LW with an overall quality

Table 3: Interacting residues of top 5 compounds observed during molecular docking analyses

Ligand	Binding affinity (Kcal/mol)	Interacting residues
ZINC000000005560	-9.5	Thr-118, Glu-122, Ile-189, Tyr-191, Met-207, Phe-212, Trp-265, Tyr-268, Ala-269, Ala-272
ZINC000002570817	-8.8	Ala-117, Thr-118, Ile-189, Tyr-191, Val-204, Met-207, Phe-208, Tyr-268, Ala-272
ZINC000002599970	-8.5	Met-86, Ala-117, Thr-118, Ile-119, Tyr-191, Phe-208, Phe-212, Trp-265, Tyr-268, Ala269, Ala-272, Ala-295, Lys-296,
ZINC000003956788	-8.2	Thr-118, Gly-188, Ile-189, Tyr-191, Val-204, Met-207, Phe-208, Phe-212, Trp-265, Tyr-268, Ala-269
ZINC000000005895	-8.0	Thr-118, Ile-189, Tyr-191, Val-204, Met-207, Phe-212, Trp-265, Tyr-268, Ala-269, Ala-272

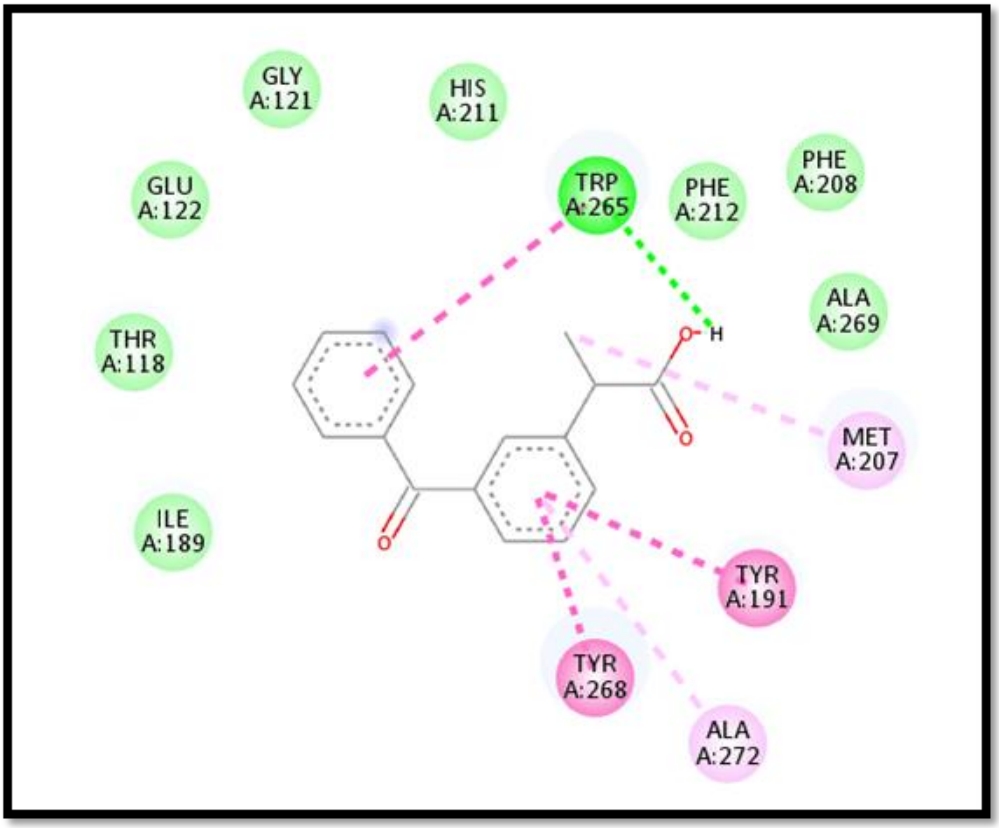

Figure 5: 2D diagram showing interactions revealed through molecular docking analyses

factor of 95.88%. The selected 3D structure of OPN1LW showed 91.3% residues in the favored region of the generated Ramachandran plot for structure evaluation, 8.4% residues in the allowed region of the generated plot, and 0.3% residues from the predicted structure were observed in the outlier region (Figure 2).

The selected structure was analyzed and visualized to check the efficiency of the predicted 3D structure. Energy minimization of

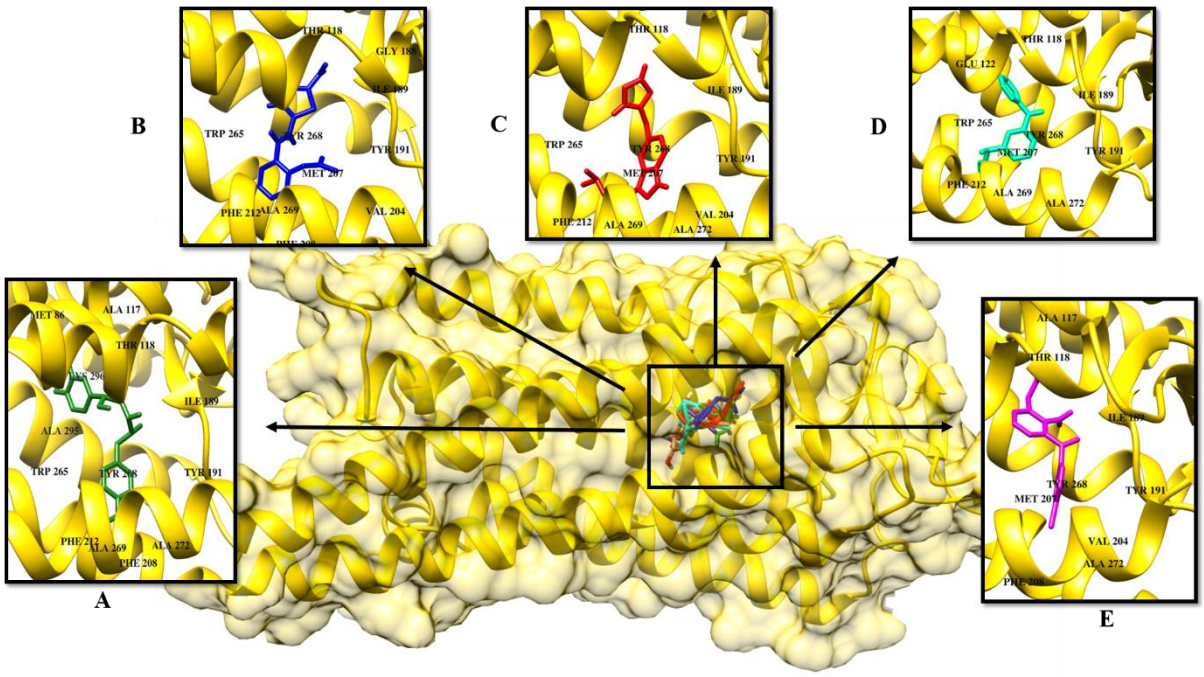

Figure 6: Binding site residues of the selected target protein observed by molecular docking analyses A) ZINC000002599970 showed interaction with the selected receptor, B) ZINC000003956788, C) ZINC000000005895, D) ZINC000000005560, E) ZINC000002570817

the predicted protein structure was also performed to fix the torsion angles and steric collisions to relax the system.

Molecular docking studies and high throughput virtual screening were performed by utilizing the selected FDA compounds library from the freely available ZINC commercial database.

The molecular docking results and the docked complexes showed reliable values and the deduced conclusion from the generated docked complexes of all the compounds available in the FDA library against OPN1LW. The efforts were initiated to reveal the novel lead compounds for the target protein and the top-ranked compound was selected from the FDA library for further analyses (Figure 4).

The selected molecule from the molecular docking studies with the lowest binding energy was revealed. The observed interacted residues were Thr-118, Glu-122, Ile-189, Tyr-191, Met-207, Phe-212, Trp-265, Tyr-268, Ala-269 and Ala-272from the target protein OPN1LW and showed maximum binding affinity (Table 3).

The interactions of the top-ranked compound were analyzed through molecular docking studies against OPN1LW and the interacting residues were visualized (Figure 5).

The top scrutinized compound was selected on the basis of its binding affinity after performing molecular docking analysis (Figure 6). ADMET analysis was performed and ADMET properties were calculated for the selected compound (Table 4).). The observed results of the molecular docking analyses showed reliable analyses of the studies and the conclusions were drawn from the docked complexes of the screened compounds by targeting the OP1NLW. The efforts were initiated through detailed experiments and to reveal the novel lead compounds against the selected target protein, the top-ranked reported molecule from the selected FDA library of ZINC database was revealed.

Table 4: ADMET and Drug like properties of the top-ranked selected compound

ADMET properties	ZINC000000005560	ZINC000002570817	ZINC000002599970	ZINC000003956788	ZINC000000005895
Blood-Brain Barrier	0.9382	0.8403	0.8026	0.7175	0.9406
Human Intestinal Absorption	0.9928	0.9133	0.8991	0.9045	1.0000
AMES Toxicity	0.9801	0.8800	0.7517	0.8322	0.5644
Carcinogens	0.6299	0.7301	0.8704	0.7746	0.9133
Fish Toxicity (mg/l)	0.8881	0.9802	0.9609	0.9908	0.9423
Honey Bee Toxicity	0.6266	0.8176	0.7820	0.7073	0.7762
Acute Oral Toxicity	0.7719	0.7076	0.6770	0.4862	0.6773
Carcinogenicity	0.7238	0.5596	0.6926	0.3731	0.7015
Aqueous solubility (LogS)	-3.6373	-4.5639	-3.7514	-3.0633	-2.3091
Caco-2 Permeability (cm/s)	1.1678	0.9736	0.3475	1.0444	0.9375
Rat Acute Toxicity (mol/kg)	2.2378	2.5564	2.4047	1.7902	2.5433
Tetrahymena Pyriformis Toxicity (ug/l)	0.8179	0.4936	0.4807	0.6217	0.3513

OP1NLW is involved in color blindness and is considered a therapeutic agent to treat color blindness. The *in silico* approaches for computational drug design help to screen the molecules against OP1NLW. The 3D predicted structure of OP1NLW and the structural insights of OP1NLW may lead to understanding the functional behavior and therapeutic targets of the selected protein.

In the current effort, *in silico* analyses were performed followed by the 3D structure prediction of OP1NLW. The predicted 3D structures of OP1NLW showed higher accuracy and reliability and the binding site of the predicted target protein OP1NLW was analyzed. The molecular docking studies were done to elucidate the interacting residues between the target protein OP1NLW and the screened molecule. The screened molecule showed potent binding interactions at the binding site of the protein and the critical interacting binding residues (Thr-118, Glu-122, Ile-189, Tyr-191, Met-207, Phe-212, Trp-265, Tyr-268, Ala-269, and Ala-272) were analyzed by molecular docking studies (Figure 6) and the binding pocket was observed. The Scrutinized compound showed the least binding energy score of the selected top-ranked compound through molecular docking analyses. The ADMET analyses suggested that the screened compound fulfills the drug-like properties. Current *in-silico-based* studies suggest that the compound (ZINC5560) may be potent against Color Blindness by targeting OP1NLW.

4. Conclusion

After performing extensive *in silico* experiments, the current studies concluded that the screened active compound may prove potential against Color Blindness by targeting OP1NLW. However, several dissimilarities might occur between the clinical analyses and the computational drug design methods although the *in silico-based* studies showed satisfactory results and seem reliable enough to suggest that the screened bioactive compound can be used against OP1NLW. In detailed studies and chemical synthesis of the lead compounds keeping these efforts under consideration may expect similar results.

Conflict of Interest

The authors declare that they have no competing interests.

Funding

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Study Approval

NA.

Consent Forms

NA.

Data Availability

All the raw data related to this study is mentioned in the article.

Authors Contributions

KS, AI, AZ, and SH retrieved the sequences and performed evaluation analyses. AA, MJS, AR, and KS performed data collection and literature review. AA, AY, RAR, and MMT performed screening. NS and HBW conceived the idea and performed the analysis and scientific drafting.

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