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Pf Phosphatidylserine decarboxylase: Molecular Modeling and Inhibithors Prediction

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Abstract

Plasmodium falciparum (P.f) is a protozoan parasite responsible for the most severe and deadly form of malaria. The resistance of *Pf* to last resort antimalarial drugs has been reported, there is an urgent need to identify new therapeutic candidates for drug development. Advancements in bioinformatics technologies provide potential cost and time-effective solutions for predicting therapeutic candidates. *Phosphatidylserine decarboxylase (PSD)* is a member of the lyase family (more specifically, the carboxy-lyases), which cut carbon-to-carbon bonds. *PSD* catalyzes the decarboxylation of phosphatidylserine to generate phosphatidylethanolamine, which is a critical step in phospholipid metabolism in prokaryotes and eukaryotes. The model of *PSD* has not been previously characterized, but it is recognized as a structural pathway for the design of new potential inhibitors for developing future antimalarial drugs. Here we investigate and propose *PSD* as a promising new target for *Pf* and build his model to identify new potential inhibitors of this new therapeutic target. *PSD* was extracted from the Tropical Disease Research (TDR) Targets database, which facilitates the identification and prioritization of drugs and drug targets of neglected pathogens. The 3D structure of the target protein was predicted using the AlphaFold2 server and the ligands were extracted from the Zinc Database Chemical Library. Molecular docking was performed using Autodock-Vina. Ten *PSD* inhibitors were identified according to affinity docking score, which ranged from -8.5 to -8.3 kcal/mol and were consistent with the Lipinski rule of five. This study provides a promising building block for experimental studies in establishing novel antimalarial drugs.

Keywords: *Plasmodium falciparum*, *PhosphatidylSerine Decarboxylase*, virtual screening, molecular modeling

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INTRODUCTION

Malaria remains a major public health challenge, with 50% of the world's population still at risk of malaria infection [1]. There were an estimated 14 million more malaria cases and 47 000 more deaths in 2020 compared to 2019, due to disruptions to services during the pandemic [2]. Sub-Saharan Africa remains the most affected part of the world, where approximately 95% of the global malaria burden is concentrated [1]. Children under five years of age, infants, and pregnant women are the most vulnerable to malaria and maintain the highest burden of infection [1].

Plasmodium falciparum is the most deadly and is the leading cause of death due to vector-borne diseases [3]. High morbidity and mortality rates associated with *Pf* malaria represent an enormous

burden to the health and economic well-being of affected countries [4]. Recently, considerable progress has been made in reducing malaria morbidity and mortality through intensive malaria control initiatives such as the use of antimalarial drugs, artemisinin-based combination therapies (ACTs), intensive distribution and use of insecticide-treated nets (ITNs), and the implementation of massive indoor residual spraying (IRS) campaigns [5]. However, these gains are threatened by widespread resistance of the parasite to antimalarial drugs and of the vector to insecticides.

Although antimalarial drugs have been successful in mitigating epidemics in recent decades, clinical evidence of resistance to all commercial antimalarial drugs, including quinine, chloroquine, atovaquone, and ACTs, has been reported [6]. The rapid expansion of resistance to ACTs is moving beyond Southeast Asia and has reached Africa [7]. Faced with this spread of resistance, the discovery of new antimalarial drugs remains an essential tool for malaria prevention and control, which requires the identification and evaluation of new therapeutic targets.

Computational approaches are the most appropriate for predicting therapeutic candidates in a reasonable time and at a lower cost.

Computer-aided Drug Design to Accelerate the Drug Discovery Process

Drug discovery and development (DD&D) is a lengthy and complex process that takes around 12–15 years and costs multiple millions of dollars for a drug to reach the market [8]. Interdisciplinary DD&D begins with the identification and validation of a suitable drug target, followed by a hit to lead discovery and optimization, and finally preclinical and clinical studies. Despite the huge investments and time incurred for the discovery of new drugs, the success rates are so low that only five out of 10,000 compounds make their way to reach human testing after preliminary evaluation in animals and only one of five of these compounds reaches final clinical studies. Further, a majority (40–60%) of the drug failure has been observed at a later stage of the DD&D process due to a lack of optimal pharmacokinetic properties, that is, absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox). This all suggested and urged the need to develop new methodologies to facilitate and expedite the DD&D process [1].

Several computational methods can assist researchers in the identification and search for new drug candidates. These *in-silico* procedures include: virtual screening [9], 3D-QSAR (Three-Dimensional Quantitative Structure-Activity Relationship) [10], molecular dynamics simulations [11] and ADMET property prediction [12].

Two techniques are particularly useful for inhibitor prediction:

ligand-based drug discovery and structure-based drug discovery.

Ligand-based drug discovery (LBDD) refers to drug discovery efforts in absence of any target structures and in presence of chemical structures known to modulate the target [13].

Computational structure-based drug discovery (SBDD) methods simulate how potential ligands may interact with the putative binding site (target) under study [14].

The ultimate goal of SBDD is to rank known or de novo designed chemicals according to desired biological activity and, more importantly, to translate computer generated hypotheses into feasible experimental steps. In this work we have used structure-based drug discovery to identify *PSD* inhibitors.

Here we consider *Phosphatidylserine decarboxylase* (*PSD*) as a therapeutic target of *Plasmodium (P.) falciparum*. This protein is member of the lyase family, more specifically the carboxy-lyases,

which cut carbon-to-carbon bonds. *PSD*s catalyze the decarboxylation of phosphatidylserine to generate phosphatidylethanolamine, a critical step in phospholipid metabolism in prokaryotes and eukaryote [15]s. Most *PSD*s are membrane bound. An integral component of the mitochondrial inner membrane, *PSD* plays a central role in phospholipid metabolism and in the inter-organism trafficking of phosphatidylserine. *PSD* is strongly expressed during the intraerythrocytic stage of the *Pf* life cycle (80–100%), one of the criteria for TDR target selection. This intraerythrocytic phase constitutes the symptomatic phase of the disease, with massive destruction of erythrocytes and sometimes adherence to blood vessels of large organs like the brain, thus restricting the blood flow with serious consequences [16]. The high expression of this protein at this stage of the parasite life cycle makes it a good therapeutic target.

To our knowledge the three-dimensional (3D) structure of *PSD* has not been structurally characterized. For this reason, the present study aims to characterize the *PSD* 3D structure and to identify inhibitors for this promising new therapeutic target for *Pf* malaria.

METHODS

The Tropical Disease Research (TDR) Targets database (TDRtargets.org) is an open-access resource that facilitates the identification and prioritization of drugs and drug targets of neglected pathogens according to specific criteria [17]. This resource facilitates the prioritization of drug targets for major tropical disease pathogens, particularly malaria. The TDR Targets database was used for this study to establish a list of therapeutic targets. From this list, a single target was selected and retained that best satisfied the validation criteria for the therapeutic target, this is the *Phosphatidylserine decarboxylase*. The studies focused on the intra-erythrocytic stage [5].

Sequence Retrieval

The target protein for this study was *Phosphatidylserine decarboxylase* (*PSD)* with Universal Protein Resource (UniProt) accession number *Q8I2N0_PLAF7*. The sequence of the target protein was extracted from Uniprot database (www.uniprot.org) [18] using the search term "*Q8I2N0_PLAF7*". This protein includes 353 amino acid residues in FASTA format.

Human Orthology Search

The orthology search was performed using the OrthoDB [19], eggnog [20] and KEGG databases [21]. Sequences of the human orthologs were retrieved from the UNIPROT database with accession number "*Q9UG56*". After a multiple alignment with clustalW [22], the closest ortholog was identified. The *PSD* structure was compared with its ortholog structure using Template Modeling score (TM scores) [23].

Subcellular Localization and Solubility Prediction

The subcellular location of *PSD* protein was predicted by ESLpred (https://webs.iiitd.edu.in/cgibin/eslpred/eslpred.pl) [24], SOSUI (http://harrier.nagahama-i-bio.ac.jp/sosui/) [25] calculates average hydrophobicity and determines the solubility of the protein.

Model Construction

The 3D structures of the target proteins were built using AlphaFold2 (https://AlphaFold2.ebi.ac.uk/) [26]. Structure visualization was done with Chimera [27] and Pymol [28].

Quality Assessment

The evaluation and validation of the quality of the models was done with the tools: ERRAT [29], Procheck [30], verify 3D [31] included in the SAVESv6.0 server (https://saves.mbi.ucla.edu/) [32].

Active Site Determination

PrankWeb is an online resource providing an interface to P2Rank, a state-of-the-art method for

ligand binding site prediction. P2Rank is a template-free machine learning method based on the prediction of local chemical neighborhood ligandability centered on points placed on a solvent-accessible protein surface. Points with a high ligandability score are then clustered to form the resulting ligand binding sites. It was used to identify the binding pockets of our ligands to the target protein [20]. Pocket 1 was identified as the most promising.

Computational platform

All computational analyses were performed on Linux 20.04 using HP computer

Processor Intel(R) Core (TM) i7-10750H CPU@ 2.60GHz 2.59GHz, RAM memory 32.0 GB, Operating system 64 bit, Processorx64.

Virtual Screening

Receptor Preparation

The target protein structure (*PSD*) obtained from the AlphaFold2 server in pdb format was loaded into AutoDock Tools (ADT). It was treated by adding hydrogen and Kollman charges, and then converted to pdbqt format by AutoDock Tools (ADT) [33].

Ligand Preparation

The ligands in sdf format were extracted from the Zinc virtual chemical library [21] of Food and Drug Administration (FDA) approved molecules according to Drugbank [22]. The present study aims to contribute to the acceleration of antimalarial drug development efforts by exploring the potential of existing FDA-approved drugs by targeting a promising therapeutic target, *Phosphatidylserine decarboxylase* from *Plasmodium falciparum.* Energy minimization was performed on Ubuntu using the MMFF94 force field [34], a total of 1615 molecules in sdf format were converted to pdbqt format in command line using Open Babel [35].

Multiple Ligand Docking

Virtual screening was performed using Autodock Vina [36].

The grid was generated using the grid generation module included in the autodock tool. The grid box was adjusted to cover the catalytic site residues of the *PSD* target protein.

Finally, a conf.txt file was created, this file includes the receptor in *. pdbqt format, the center of the grid with x,y,z coordinates in Å obtained from Prankweb server, the grid size in Å, and a docking run number 10.

ADMET analysis

The SMILES structures of the compounds with the best binding energies were extracted from the Zinc database. Prediction of absorption, distribution, metabolism, elimination and toxicity (ADMET) was performed using the Swiss-ADME server (http://www.swissadme.ch/) [37].

The 10 compounds with the lowest binding energies and compliance with Lipinski's rule of 5 were selected as potential *PfPSD* inhibitors [38].

Protein-ligand Interaction Study

Protein-ligand interaction studies were carried out with Discovery studio between the top ten (10) ligands and the *PfPSD* target protein [39]. The top ten (10) ligands selected for interaction studies were those with the best binding energies and best compliance with Lipinski's rule of 5.

RESULTS

Human Orthology Research

The orthology search performed with the OrthoDB, eggNoG and KEGG databases allowed us to

identify *Phosphatidylserine decarboxylase proenzyme, mitochondrial* (*PISD_HUMAN*), *Homo sapiens* with UniProt access code Q9UG56 as the closest human orthologue to our target protein with an identity score of 26.0623% obtained through a multiple sequence alignment performed with clustalw. The 3D structure of the orthologue was determined with Alphafold2 (Q9UG56). The comparison of the structure of *PfPSD* with its human orthologue (Q9UG56) was done with the TMscore and gave us 0.13 as similarity score [40].

The criteria were: 0.0 < TM-score < 0.17, random structural similarity

0.5 < TM-score < 1.00, in about the same fold.

This suggests that the two proteins are not similar and reinforces our approach since one of the basic criteria for a protein to be considered as a good therapeutic target is that it must not have a human orthologue**.**

Solubility Prediction and Subcellular Localization

The subcellular localization of the target protein (*PfPSD*) was predicted using ESLpred [13] and allowed us to identify *Phosphatidylserine decarboxylase* as a mitochondrial protein with precision scores:

- Reliability Index: 1
- Expected Accuracy: ~53

SOSUI server [14] analysis shows that *Phosphatidylserine decarboxylase* is a soluble protein, hydrophobic and with positive charge as shown in Figure 1.

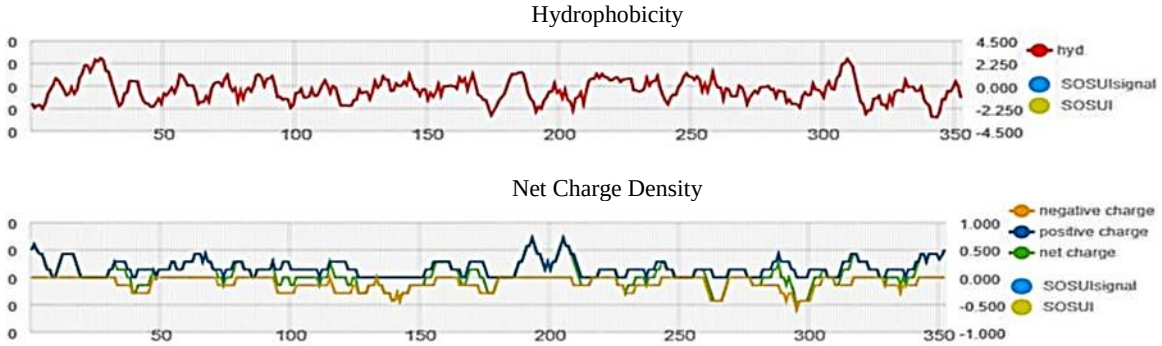

Figure 1. Hydrophobicity and Charge plot.

PSD Structure Prediction with AlphaFold2 server v2.1.0

Panel A shows the best AlphaFold2 predicted structure with alpha-helix in yellow and beta-sheet in green. It was chosen for the next part of the study. Panel B displays the Local Distance Difference Test (lDDT). It evaluates the local distance differences of all atoms of a model. The model 1 represented on the B panel by blue plot shows a high score around 80. Panel C is the predicted aligned error (PAE) plot from the AlphaFold2 server and shows the expected position error at residue x if the predicted and actual structures are aligned to residue y (using Cα, N and C atoms). This Figure 2 shows that all parts of the structure are predicted to be well-correlated with each other, other than the N-terminal region

Validation of the 3D Model of Phosphatidylserine Decarboxylase

Several tools were used to validate the 3D model of *Phosphatidylserine Decarboxylase*. In particular:

The PROCHECK server was used to evaluate the structural quality of the modeled structure, in fact, Procheck verifies the stereochemical quality of the structure of a protein by analyzing the geometry residue by residue and the global geometry of the structure. Procheck's evaluation of the

predicted model of *Phosphatidylserine decarboxylase* showed that 91.3% of the residues were in favored regions while a good quality model should have more than 90% of the residues in the most favored region in the Ramachandran plot. We can therefore say that our structure is of high quality.

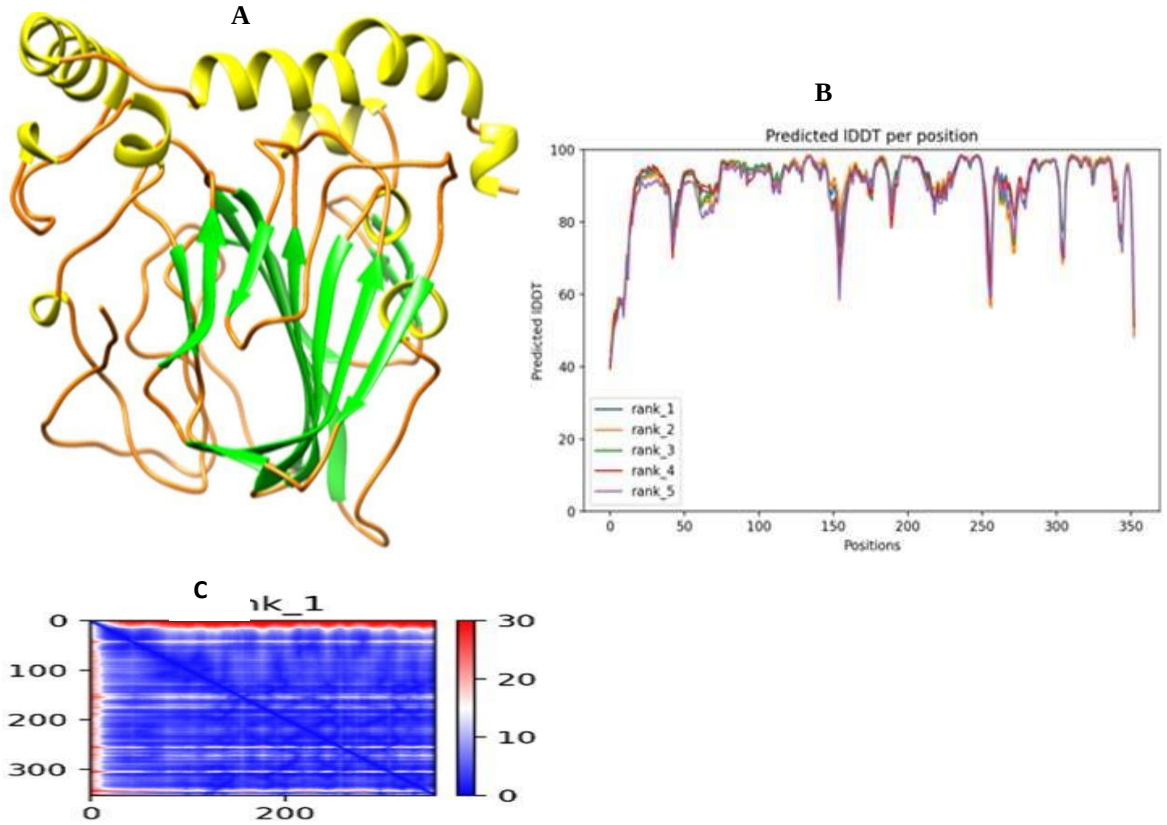

Figure 2. *P.f PSD* 3D structure Prediction and evaluation with AlphaFold2 server v2.1.0.

VERIFY 3D determines the compatibility of an atomic (3D) model with its own amino acid sequence (1D) by assigning it a structural class based on its location and environment (alpha, beta, loop, polar, non-polar, etc.) and comparing the results to the correct structures. The evaluation of the quality of the model of our target protein by 3D verification showed that 86.41% of the residues have an average 3D-1D score >= 0.2. We can therefore conclude that our protein is of high quality.

ERRAT analyzes the statistics of non-bonded interactions between different types of atoms and plots the value of the error function as a function of the position of a sliding window of 9 residues, calculated by comparison with the statistics of highly refined structures. The analysis of the structure of *Phosphatidylserine decarboxylase* by ERRAT showed an overall quality score of 97.3333% which clearly exceeds the average which is around 95%. We can say that the structure of our protein has a very high resolution. The Table 1 given below represents Assessment of *Phosphatidylserine decarboxylase* model quality

Table 1. Assessment of *Phosphatidylserine decarboxylase* model quality

Target Protein	**Ramachandran Plot Statistics (%)**				**ERRAT**	**VERIFY3D**
	Core	***Allowed***	***General***	***Disallowed***	***Quality Factor***	***Compatibility Score (%)***
PSD	91.3%	8.3%	0.4%	0.0%	97.3333	86.41%

Binding Site Identification

The exploration of the surface structure of the target protein and the identification of the binding pockets were carried out with Prank web server [41]. The coordinates of pocket 1 considered as the most promising were used to generate the Grid Box.

These coordinates were: Center X coordinate: 11.6659, Center y coordinate: 0.9370, Center z coordinate: -1.5817

Virtual Screening

Virtual screening was performed using autodock_vina [42] from the Zinc15 DB virtual chemical library [43] using FDA approved molecules [44]. A total of 1615 FDA-approved molecules were used for the virtual screening, from which we selected the 10 best scoring ones with the lowest energies and best compliance with Lipinski's rule of 5. These results are shown in Table 2.

These top 10 ligands were used to perform the virtual screening with the ortholog (*PISD_HUMAN*) using autodock-vina with the same parameters, the goal being to find out whether or not the ligands have the same binding sites to the orthologue. This results are shown in Table 2.

After the virtual screening, the two structures were superimposed and visualized with chemera X (Q8I2N0_PLAF7, Q9UG56) to see the position of ligands in the different pockets. We found that the docked ligands were in different pockets as shown in Figure 3, which supports our approach. Results of the virtual screening of the human orthologue with the 10 best ligands are given in Table 3.

ADMET Analysis

The evaluation of the absorption, distribution, metabolism, excretion, and toxicity (ADMET) made with the SwissADME [37] servers allowed us to identify the following inhibitors considered as the most promising and respecting Lipinski's rule of 5. In total 10 potential inhibitors were selected. Table 4 show the ADMET properties

Table 2. The top 10 compounds with the lowest energies and that most respect Lipinski's rule of 5

Target Proteins	Compound ID's	Compound Names	Molecular formula	Docking Score (kcal/mol)
Phospatidylserine Decarboxylase	ZINC11679756	Eltrombopag	C25H22N4O4	-8.8
	ZINC100016084	Trospium	C25H30NO3+	-8.5
	ZINC3920266	Idarubicin	C26H27NO9	-8.5
	ZINC897301	Anzemet	C19H20N2O3	-8.5
	ZINC40430143	Olaparib	C24H23FN4O3	-8.4
	ZINC30691797	Perampanel	C23H15N3O	-8.4
	ZINC1481815	Exjade	C21H15N3O4	-8.4
	ZINC43207238	Canagliflozin	C24H25FO5S	-8.4
	ZINC12503068	Trosec	C25H30NO3+	-8.4
	ZINC2568036	Dantrolene	C14H10N4O5	-8.3

Table 3. Results of the virtual screening of the human orthologue with the 10 best ligands

Target Proteins	Compound ID's	Compound Names	Molecular formula	Docking Score (kcal/mol)
Phospatidylserine Decarboxylase (Q8I2N0_PLAF7)	ZINC3920266	Idarubicin	C26H27NO9	-9.4
	ZINC40430143	Olaparib	C24H23FN4O3	-8.9
	ZINC11679756	Eltrombopag	C25H22N4O4	-8.7
	ZINC43207238	Canagliflozin	C24H25FO5S	-8.6
	ZINC1481815	Exjade	C21H15N3O4	-8.4
	ZINC30691797	Perampanel	C23H15N3O	-8.1
	ZINC100016084	Trospium	C25H30NO3+	-7.6
	ZINC2568036	Dantrolene	C14H10N4O5	-7.6
	ZINC12503068	Trosec	C25H30NO3+	-7.6

	ZINC897301	Anzemet	C19H20N2O3	-7.2

Superposition of the 3D Structures of PfPSD and PISD_HUMAN

The configuration shows Pf-PSD in green with orange ligand and PISD_HUMAN in cyan with red ligand. Perampanel and XZ have protein structures that bind in opposite pockets.

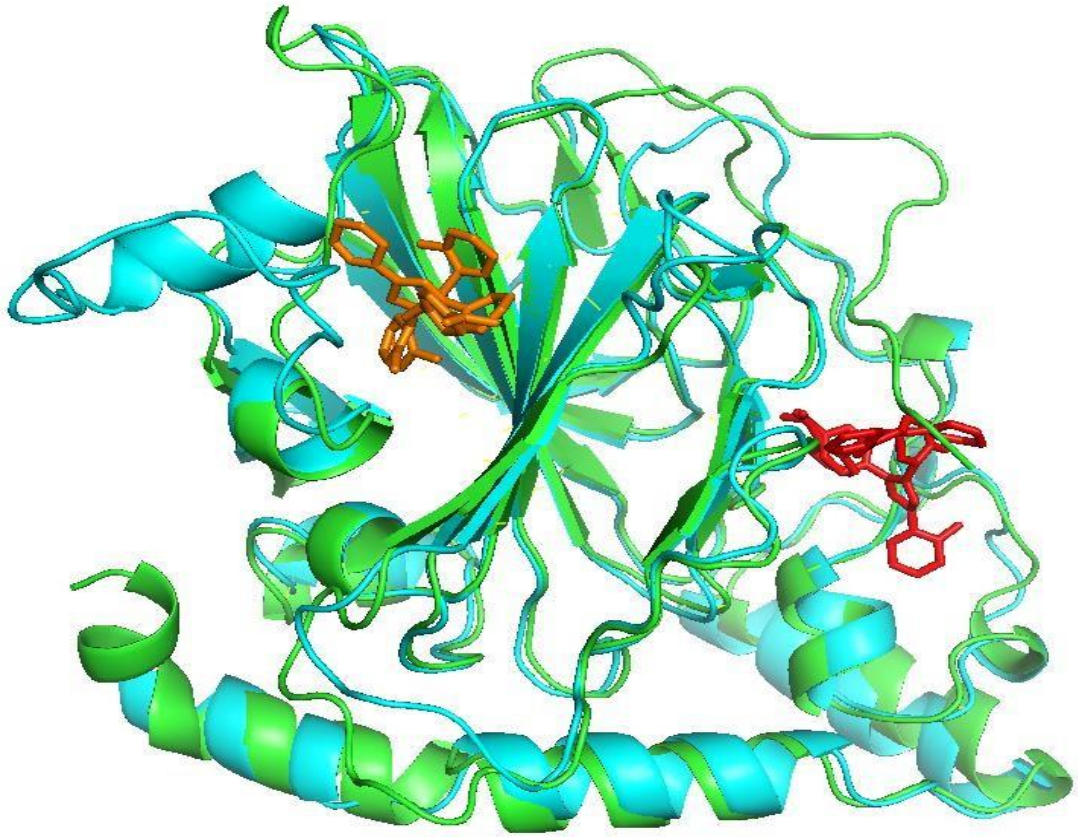

Figure 3. Superposition of the structure of *Pf-PSD* in green with docked ligands in orange and *PISD_HUMAN* structure in cyan with the docked ligands in red. The best view was obtained with the ligands (Perampanel, Exjade) distributed in opposite binding pockets of the protein structures (*Pf PSD and Human PSD*)

Table 4. Druglikeness predictions of the top 10 compounds

Compound Names	Molecula r Weight (g/mol)	Number of H-bond acceptors	Number of H-bond donors	LOGP	Rotatable Bonds	Lipinski's rule of 5 violation
Eltrombopag	442.47	6	3	3.74	5	0
Trospium	392.51	3	1	1.69	5	0
Idarubicin	497.49	10	5	1.14	3	0
Anzemet	324.37	4	1	2.34	3	0
Olaparib	434.46	5	1	2.78	6	0
Perampanel	349.38	3	0	3.71	3	0
Exjade	373.36	6	3	3.07	4	0
Canagliflozin	444.52	6	4	3.27	5	0
Trosec	444.52	6	4	3.27	5	0
Dantrolene	314.25	7	1	1.06	4	0

2D Structure of Potential PSD Inhibitors

Figure 4 below shows the 2D structure of the top 10 ligands with the lowest energies and best compliance with Lipinski's 5 rule.

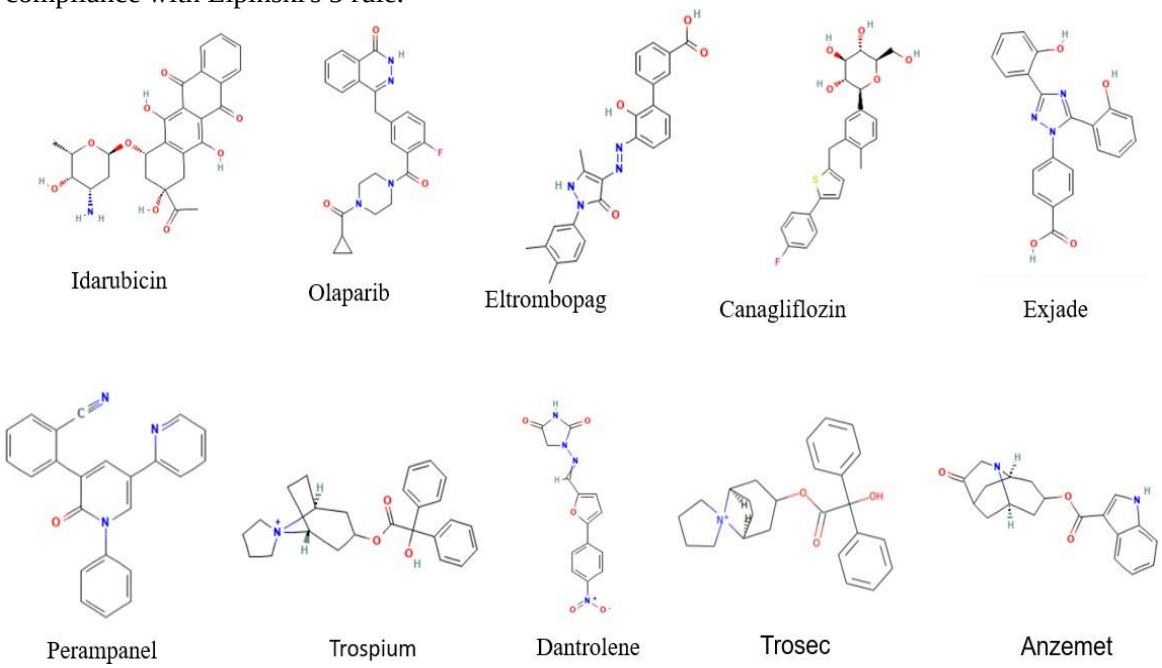

Figure 4. 2D structures of the 10 *PSD* potential inhibitors.

Protein-ligand Interaction

The protein-ligand interaction studies carried out with discovery studio between the 10 promising ligands and the *PfPSD* target protein identified the key residues involved in these interactions given in Figure 5.

The different kinds of bond involved in these interactions are legended at the bottom of the figure.

Protein-ligand complex	**2D interactions**

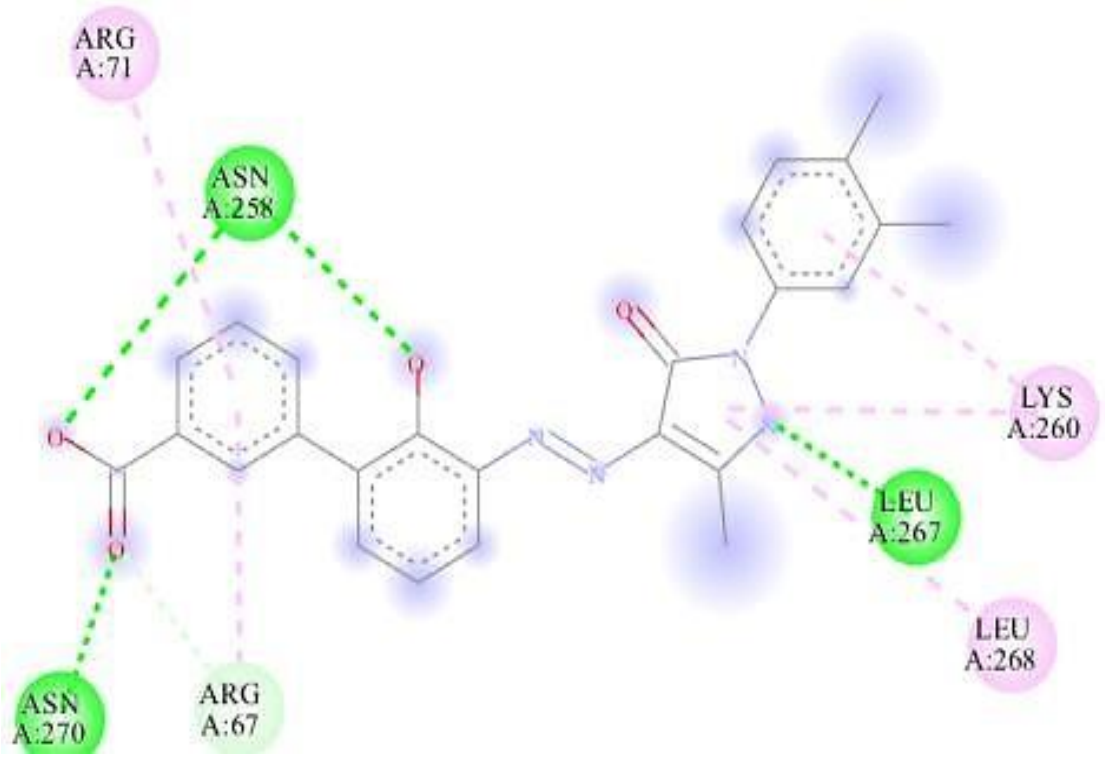

Figure 5. (a) *Pf Phospatidylserine Decarboxylase and* Eltrombopag (ZINC11679756).

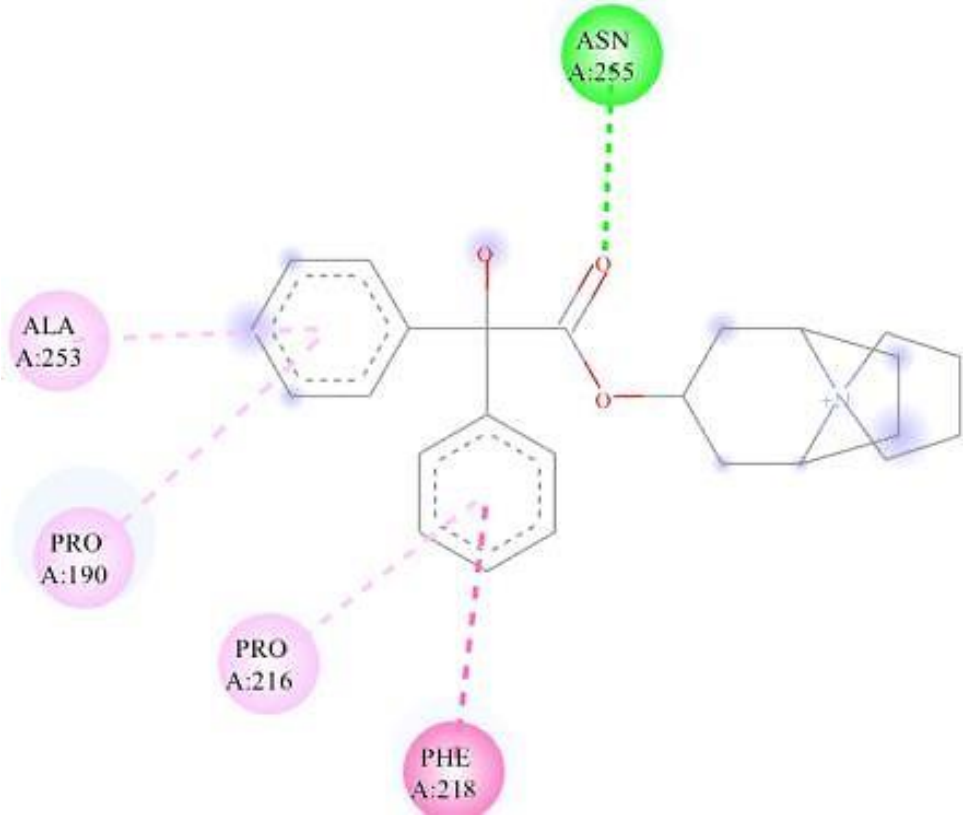

Figure 5. (b) *Pf Phospatidylserine Decarboxylase and* Tropism (ZINC100016084).

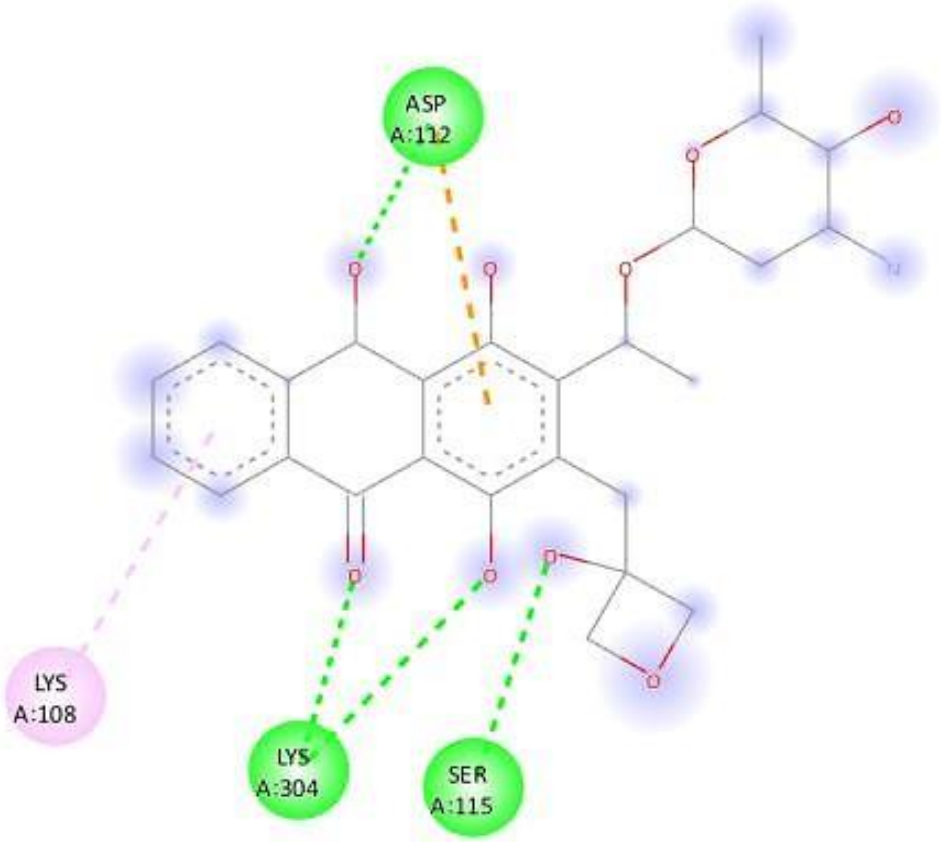

Figure 5. (c) *Pf Phospatidylserine Decarboxylase* and Idarubicin (ZINC3920266).

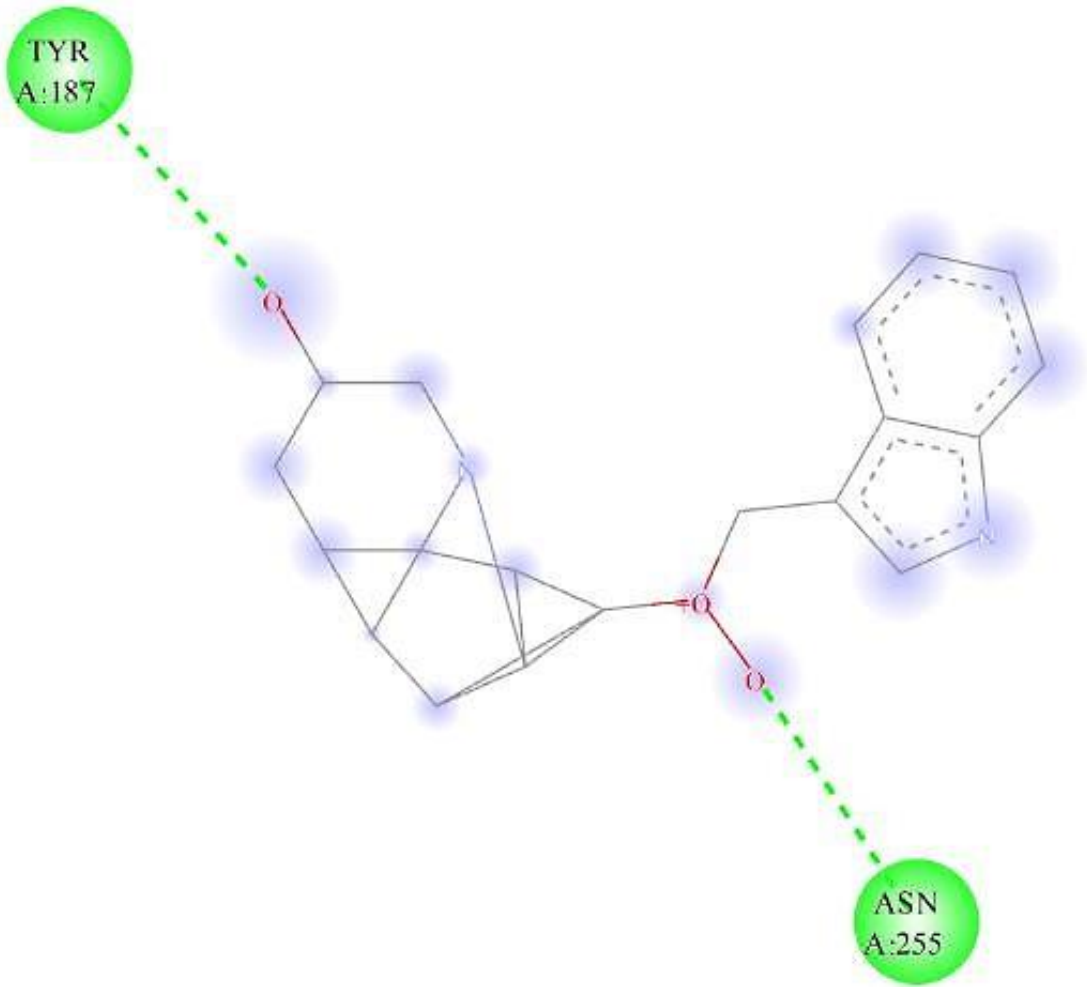

Figure 5. (d) *Pf Phospatidylserine Decarboxylase* and Anzemet (ZINC897301)

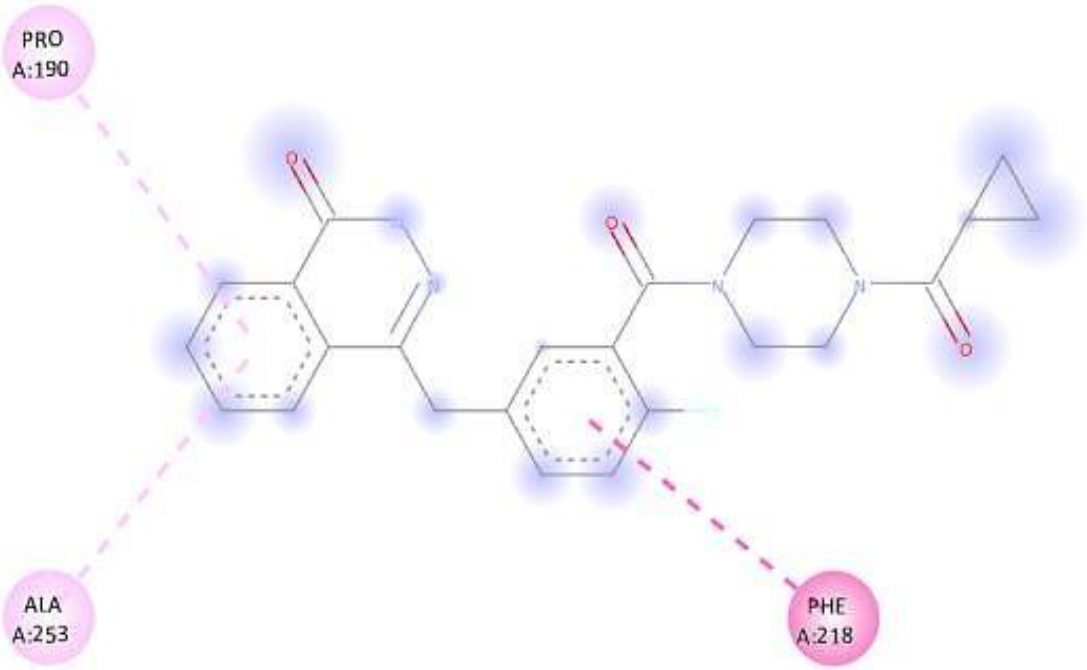

Figure 5. (e): *Pf Phospatidylserine Decarboxylase* And Olaparib (ZINC40430143).

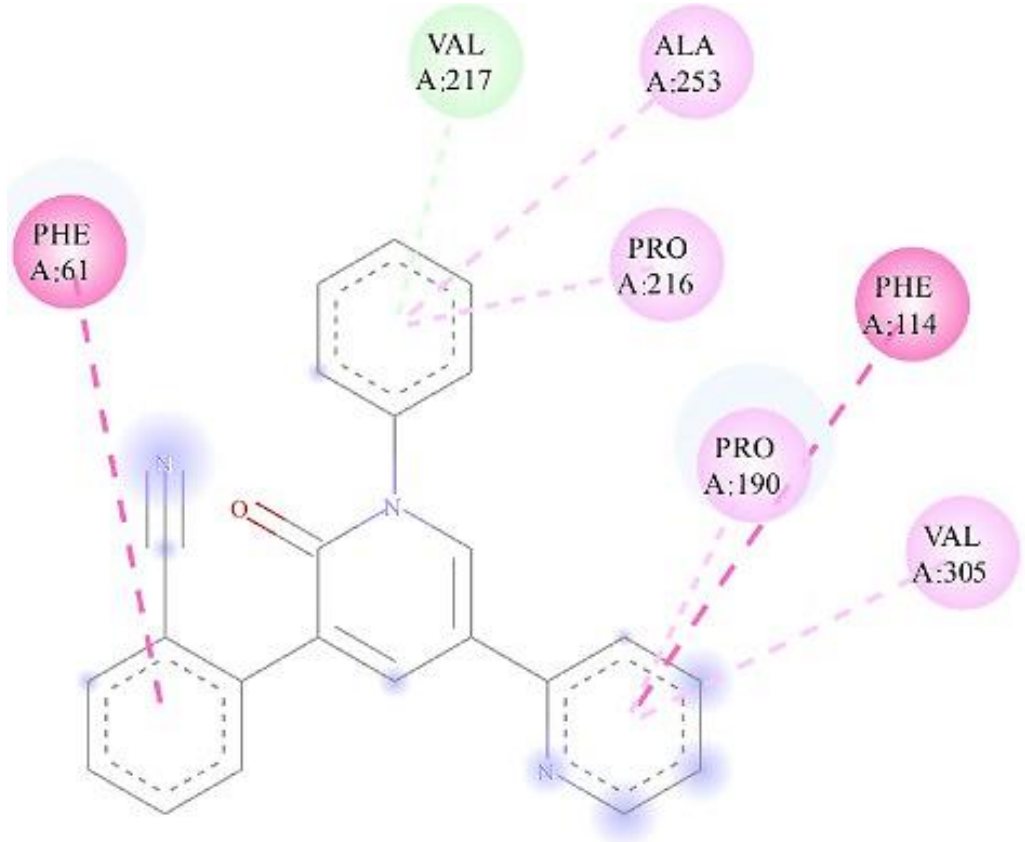

Figure 5. (f) *Pf Phospatidylserine Decarboxylase* And Perampanel (ZINC30691797).

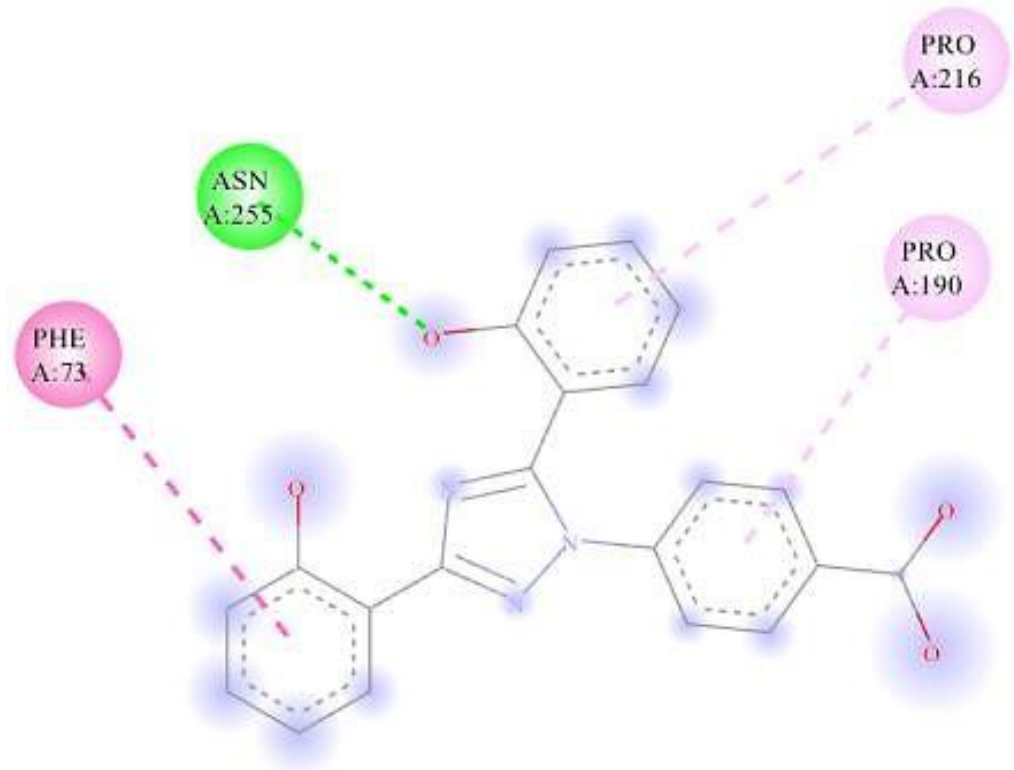

Figure 5. (g) *Pf Phospatidylserine Decarboxylase* and Exjade (ZINC1481815).

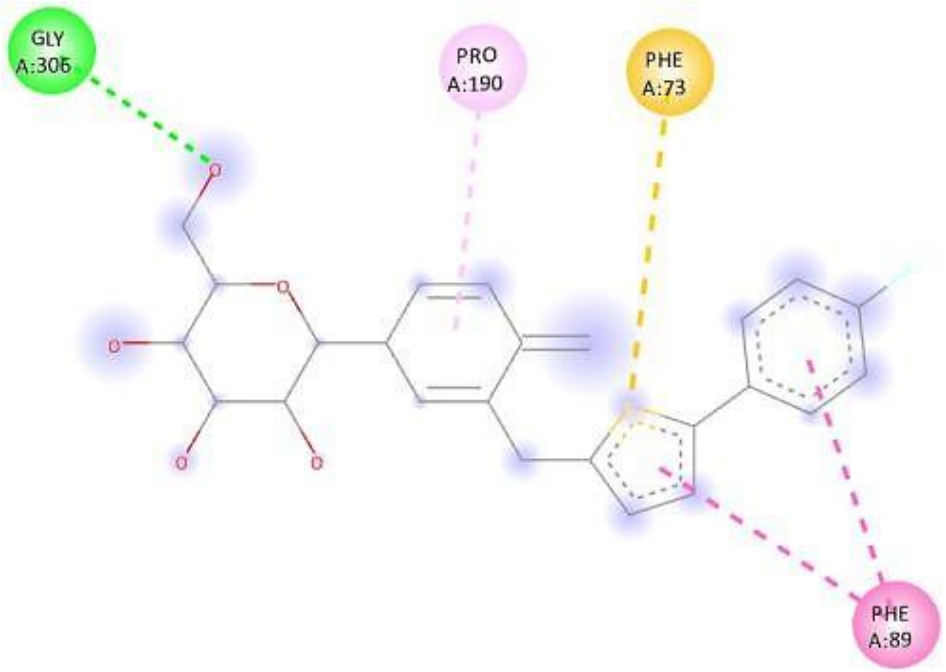

Figure 5. (h) *Pf Phospatidylserine Decarboxylase* and Canagliflozin (ZINC43207238).

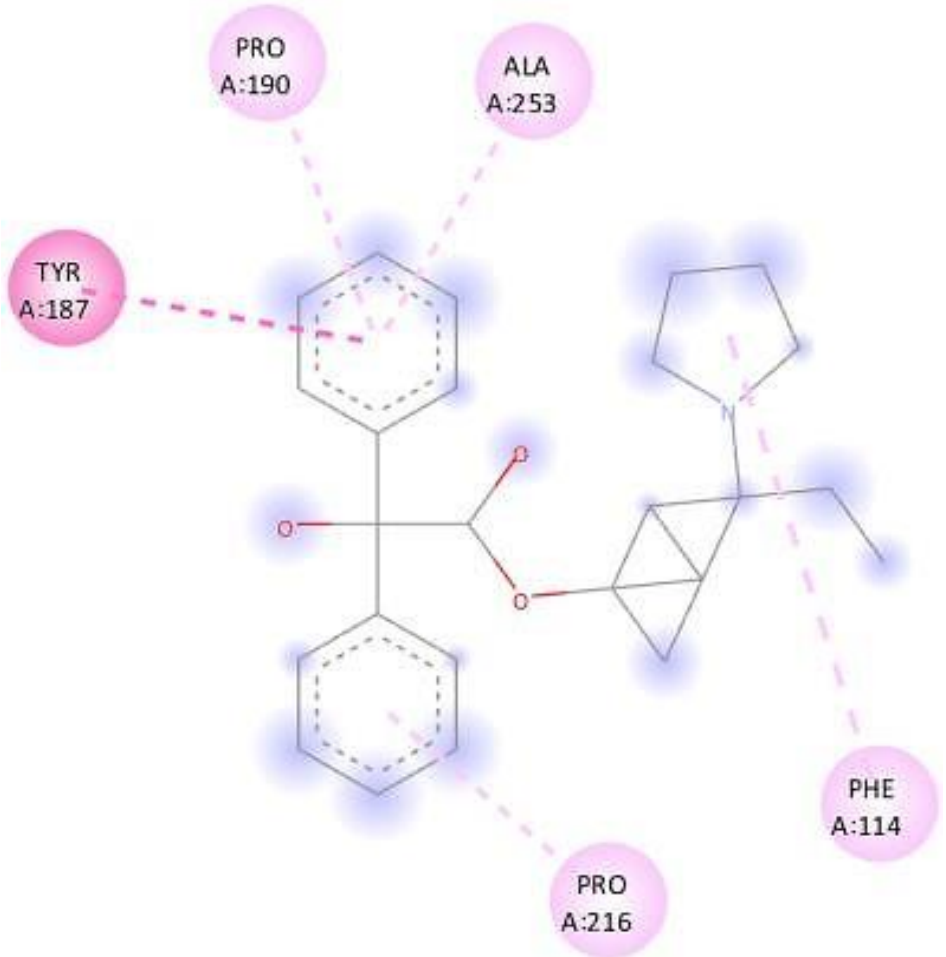

Figure 5. (i) *Pf Phospatidylserine Decarboxylase* and Trosec (ZINC12503068).

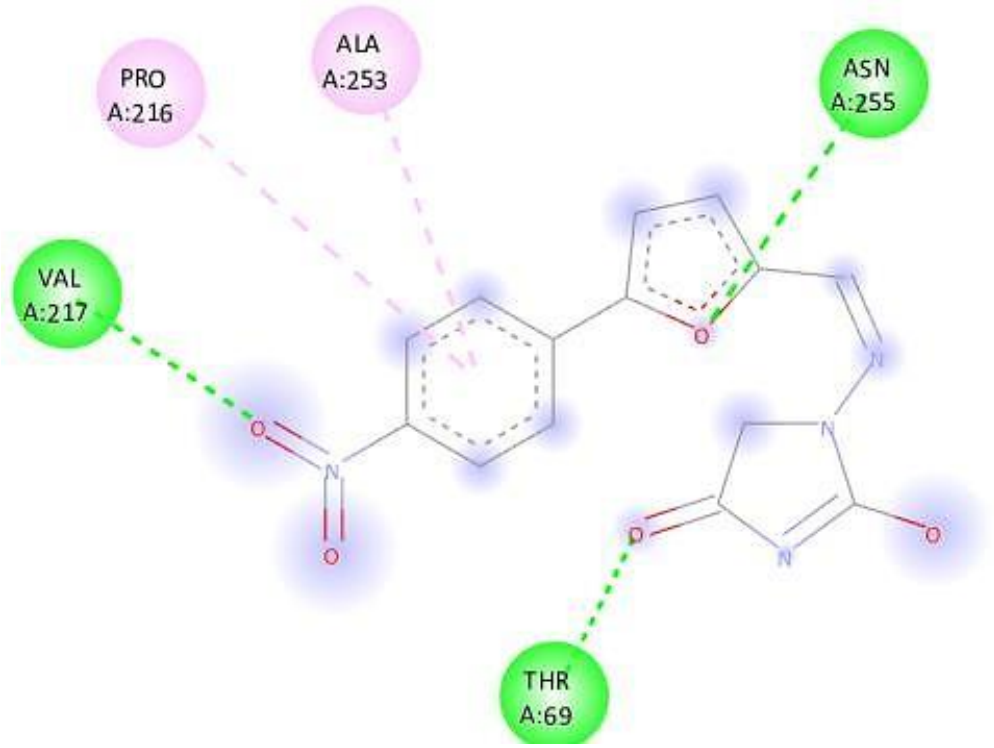

Figure 5. (j) *PfPhospatidylserine Decarboxylase* and Dantrolene (ZINC2568036).

: Conventional Hydrogen Bond
: Pi-Alkyl
: Pi-Pi Stacked
: Carbon Hydrogen Bond
: Pi-Pi T-shaped
: Pi-Anion

Figure 5: Represent the interaction between top 10 ligands and the target protein (*PfPSD*).

DISCUSSION

This study allowed us to identify *PSD* as a promising therapeutic target *of Plasmodium falciparum*, to propose its 3D structure, never realized before and to identify its potential inhibitors.

From 1615 compounds extracted from the zinc database of FDA approved molecules after virtual screening and toxicity and druggability studies we have selected 10 as having the best chance to be good antimalarial drug candidates.

We also performed interaction studies between the target protein (PfPSD) and these 10 potential inhibitors. The following residues were identified as being involved in the various interactions.

PfPSD and Eltrombopag (ZINC11679756): ARG 71, ASN258, LYS 260, LEU 267, LEU 268, ARG 67, ASN270;

Pf PSD and Tropism**:** ALA 253, ASN 255, PHE 218, PRO 216, PRO 190;

Pf PSD and Idarubicin: ASP 112, SER 115, LYS 304, LYS 108;

Pf PSD and Anzemet: TYR 187, ASN 255;

Pf PSD and Olaparib: PRO 190, ALA 253, PHE 218;

Pf PSD and Perampanel: PHE 61, VAL 217, ALA 253, PRO 216, PRO 190, PHE 114, VAL 305;

Pf PSD and Exjade: PHE 73, ASN 255, PRO 216, PRO 190;

Pf PSD and Canagliflozin: GLY 306, PRO 190, PHE 73, PHE 89;

Pf PSD and Trosec: TYR 187, PRO 190, ALA 253, PHE 114, PRO 216;

Pf PSD and Dantrolene: VAL 217, PRO 216, ALA 253, ASN 255, THR 69.

Different kinds of binding were observed through these interactions: Conventional Hydrogen Bond, Pi-Alkyl,

Pi-Pi Stacked, Carbon Hydrogen Bond, Pi-Pi T-shaped, Pi-Anion. The results of this study provide a solid basis for drug discovery against *Pf*.

Similar studies have been done with *Trisha Rajguru et al.,2022* who chose *Falcipain-2 (FP-2)* as a promising therapeutic target of *Pf* and from 800 compounds extracted from the Pubchem database after virtual screening and molecular dynamics studies, they retained 4 potential inhibitors of this target [45].

Rufus Afolabi et al.,2022 also conducted a related study using a machine learning approach to predict appropriate drug targets in *Pf*. They established a list of 5 protein targets that they considered as potential drug targets because they had no human homologues. From these, they determined the physicochemical properties, predicted the 3D structure and performed a virtual screening based on the docking of the putative *Pf RNA pseudouridylate synthase* (*Pf RPuSP*). At the end of their studies from 5261 compounds extracted from the Pubchem database after virtual screening, toxicity and protein ligand interaction studies, they selected 11 compounds as candidates for malaria treatment [46].

We proposed *Phosphatidylserine decarboxylase* as a promising therapeutic target of *Plasmodium falciparum* extracted from TDRtargets.org [9] which facilitates the identification and prioritization of drugs and drug targets of neglected pathogens according to specific criteria.

This protein is a member of the lyase family, specifically carboxy-lyases, which cut carbon-carbon bonds. *Phosphatidylserine decarboxylases* (*PSD*) catalyze the decarboxylation of phosphatidylserine to generate phosphatidylethanolamine, a critical step in phospholipid metabolism in prokaryotes and eukaryotes. It is expected to localize at the mitochondrial membrane. Moreover, *Phosphatidylserine decarboxylase* is strongly expressed during the intraerythrocytic phase of the life cycle of Plasmodium falciparum (80–100%), one of the criteria for the choice of the TDR target. However, this phase constitutes the symptomatic phase of the disease, with massive destruction of erythrocytes and sometimes adhesion to the blood vessels of large organs such as the brain, thus limiting the blood flow with serious consequences [5].

This high expression of *Phosphatidylserine decarboxylase* at this stage of the parasite life cycle makes it a good therapeutic target. Also, orthology studies allowed us to understand that this protein has no close human orthologue, one of the basic criteria for a protein to be considered as a good therapeutic target. (Also, the ligands that were chosen are aleady FDA approved drugs, so human side effects are already well understood.) Preventing the function of this protein at this stage of the parasite life cycle by designing an effective inhibitor may be a good start in the fight against malaria.

The first challenge in this work was to propose the 3D structure of this protein, which until now has no structure available in PDB, and then to identify its potential inhibitors.

At the end of this study we were able to propose a 3D structure of the target protein and identify 10 inhibitors according to their ADMET properties and respecting the Lipinski rule of 5.

CONCLUSION

This study allowed to predict the 3D structure of *Phosphatidylserine decarboxylase* which previously didn't have a structure available in the Protein Databank (PDB) *and* to identify its potential inhibitors (ten inhibitors).

We identified the 10 best ligands from their affinity scores and the evaluation of Adsorption, Distribution, Metabolism, Excretion and Toxicity.

Interaction studies were performed to better understand the interactions between the target protein and the ligands. the next step in this study will be to perform molecular dynamics simulations to validate the structural stability of the selected ligands. Subsequently, in vitro and in vivo tests will be carried out to obtain an accurate analysis of the compounds' activity.

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Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Study conception and design were completed by MS, CC and MW MS, CC, MW and PC interpreted the data.

The first draft was written by MS

MS, CC, MW, PC and JG writing and review

MS and PC carried out the virtual screening and interaction studies.

JL, SD and MW contributed to the final proof reading of the manuscript. MW supervised the work

All the authors reviewed and approved the final version of the manuscript.

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