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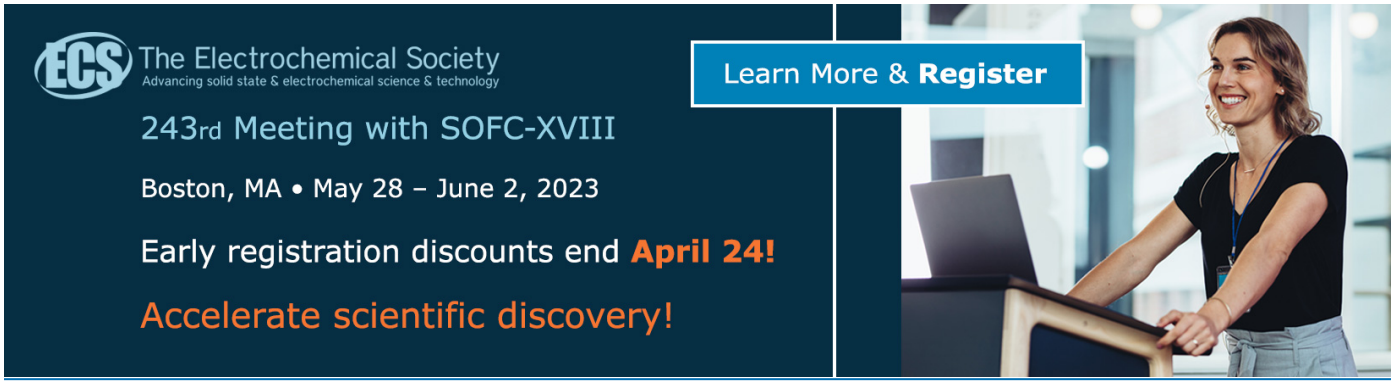

Molecular docking studies of Amidoxime-containing heterocyclic compounds from Zinc database against homology modelled *Pf*ADSL

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Abstract. Malaria remains one of the most infectious life-threatening diseases in the world. The lingering effect of drug resistance by malarial parasites, especially *Plasmodium falciparum,* has made it essential for the continuous search for novel antimalarial drugs that can act on new protein targets and through new modes of action. Amidoxime functional groups have, in recent years, shown to be good incorporations in heterocyclic backbones due to their vast biological activities. Hence, the antimalarial activities of some amidoxime-containing heterocyclic compounds have been predicted using molecular docking studies to determine the binding affinities and the inhibition constants of the compounds. The amidoxime-containing compounds were downloaded from the ZINC database and docked, using Auto Dock vina, against the active sites of homology modelled *Plasmodium falciparum*adenylosuccinate lyase (*Pf*ADSL) as obtained from the SWISS-MODEL. The grid box was constructed using 80, 80, and 80, pointing in x, y, and z directions, respectively, with a grid point spacing of 0.375 Å. The post-docking analysis, which entails determining the hydrogen bond formed and the bond length between the compounds and the protein target, was carried out using AutoDockTools, LigPlot and PyMOLmolecular viewer. The docking studies showed that the compounds possess binding affinities ranging from -8.6 to-5.7 kcal/mol, with **ZINC2268942** having the lowest binding affinity. The presence of the amidoxime-functional group on the best hit contributed significantly to the hydrogen bonds formed between the compound and the binding sites of *Pf*ADSL,which were observed atThr 124D, Ser 125D, Thr 172C, His 173C, Gln 250D, and Ser 299A. The results obtained from the molecular docking studies will be helpful in the development of a potential antimalarial drug that can target *Pf*ADSL after careful experimental validation of the target, then *in vitro* and *in vivo* screening.

Keywords: Malaria, Antimalarial drug, Benzothiazole, Benzoxadiazole, Drug design.

1. Introduction

Malaria is one of the most virulent diseases globally caused by the *Plasmodium* protozoan parasite, a member of the phylum Apicomplexa [1,2]. Currently, malaria is regarded as the first among the significant tropical diseases identified by the World Health Organization, and it is fast becoming the biggest infectious killer [3]. The estimated malaria cases globally were 229 million in 2019, with 9 million fewer cases than in 2000 [4]. Over 94% of the cases (215 million) reported globally in 2019 were in the WHO African region, which means Africa still has the highest malaria burden. The advent of computer-aided drug design (CADD) methods has revolutionized the discovery processes, as compounds activities can be predicted even before synthesis [5]. Molecular docking is an integral part of *in silico* drug design, and it has become a standard in modern chemistry tool kit [6,7]. It involves the detailed study of the binding mode, interaction, and affinity of drug candidates with known targets or receptors, e.g. enzymes and proteins [8,9]. The binding of the drug candidates to the target's interaction sites is due to the electrostatic, hydrogen bonds and non-covalent interactions [10]. As a result of the binding of the molecules to the target, the function of the target is either inhibited or activated. Thus, the molecules act as drugs [11]. The receptor is selected based on the pharmacological effect of interest, such as antiviral, anticancer, antibiotics, antifungal, antitubercular, antimalarial, etc. Preclinical tests can be negatively affected by the designing of drug candidates without adequate knowledge of the mode of action upon the probable targets [12]. One of the protein targets in *Plasmodium falciparum* is the adenylosuccinate lyase (*Pf*ADSL), an essential enzyme in purine metabolism in *P. falciparum*[13]. Adenylosuccinate lyase (ADSL) is responsible for the final step in Adenosine monophosphate (AMP) synthesis [14]. Heterocyclic compounds are the most studied organic compounds due to their diverse pharmacological activities and wide therapeutic applications in medicinal research [15]. The addition of functional groups to drug candidates is one way to successfully alter a parent molecule's physical qualities, including acidity, lipophilicity, and stability [16]. A drug's absorption, distribution, metabolism, and excretion (ADME) characteristics are modulated as a result of this change [17]. Amidoximes are non-basic functional groups [18] generally utilized to address the limited oral bioavailability of amidines, which are pharmacologically useful as antimalarial [19,20], antibacterial [21], and anticancer [22] drug candidates **(Figure 1)**. The amidoxime groups are oxime derivatives of amides with general structure $R^1C(=NOH)NR^2R^3$. Amidoxime derivatives are also referred to as DNA interaction chemicals, and they have been employed in medicine for a long time, particularly in the treatment of protozoal diseases [19]. They are usedas prodrug classes for the amidine [20]. Therefore, this study deals with the docking analyses of some amidoxime-containing heterocyclic compounds from the ZINC database against the three-dimensional (3D) structure of homology modelled *Plasmodium falciparum*adenylosuccinate lyase.

Figure 1. Structure of amidoximes

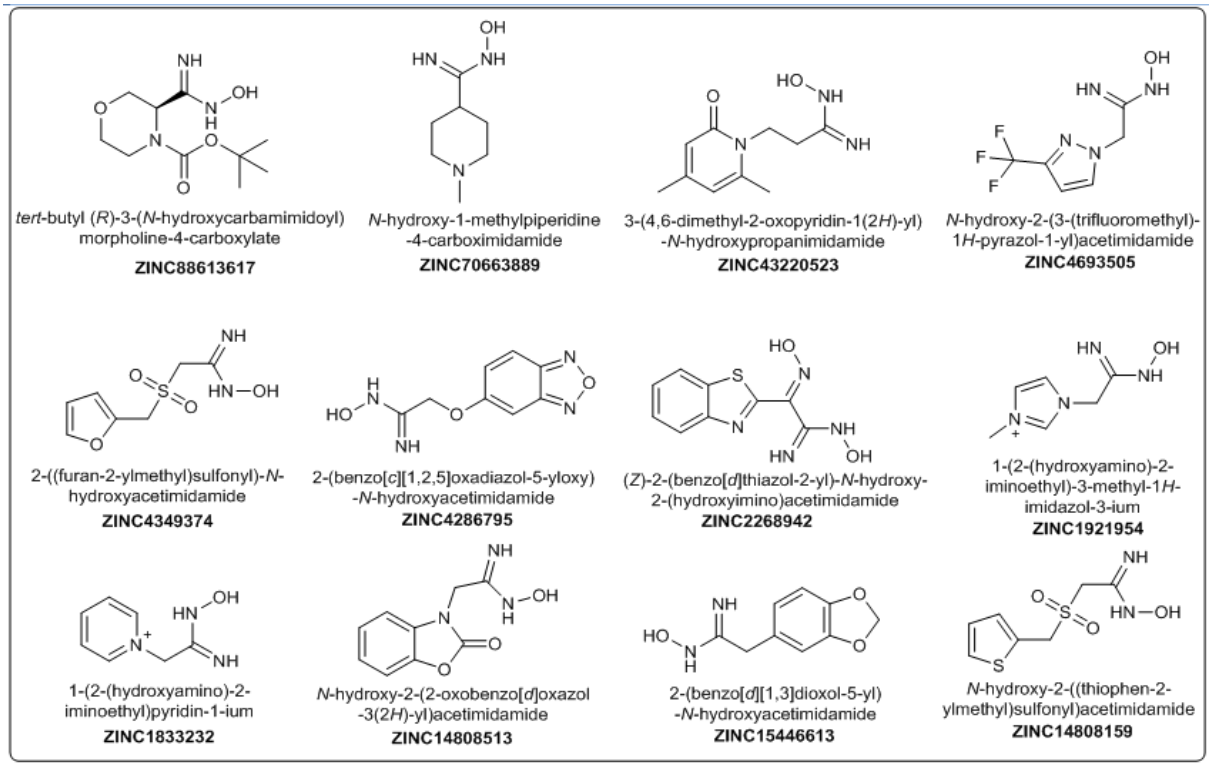
2. Materials and Methods

2.1. Preparation of the Protein target

The homology modelled 3D structure of the target protein, *Pf*ADSL, was downloaded from SWISS-MODEL in itsProtein Data Bank (pdb) file format[23]. The modelled protein structure was defined as receptor while the non-amino acid residueswere removed using Chimera software to make the biomolecule suitable for the docking process[24]. Furthermore, the protein 3D structure was prepared by removing water molecules, computation of Gasteiger charges, adding polar hydrogens, and merging the non-polar hydrogens using AutoDockTools 1.5.6.

2.2 Preparation of the Ligand

A series of amidoxime-containing heterocyclic compounds were downloaded from the ZINC database[25] as ligands for molecular docking **(Scheme 1)**. The amidoxime functional group (SMILE: CC(=N)NO) was set as the input for the template search, and twelve heterocyclic compoundswith amidoxime functional groups were downloaded in their Structure-Data Files (sdf) format. The downloaded compounds in their sdf formats were converted totheir Autodock docking formats (pdbqt) using the Open Babel software package [26].



Scheme 1. Amidoxime-containing heterocyclic compounds downloaded from the ZINC database

2.3 In silico toxicity and drug-likeness predictions

Drug-likeness is a prediction that determines whethera pharmacological agent exhibits characteristics compatible with it being an orally active drug[27]. These predictions are based on an already established concept by Lipinski, called Lipinski's rule of five [28]. The rule predicts that there is likely to be poor absorption or permeation when a compound possesses more than 5 H-bond donors, 10 H-bond acceptors, molecular weight bigger than 500 and the calculated Log P (CLogP) bigger than 5. The compounds' *in silico drug-likeness and toxicity prediction*s were carried out using OSIRIS Property Explorer [29]. The OSIRIS Property Explorer tool calculates mutagenic, tumorigenic, irritating, and reproductive risks, as well as hydrophilicity (log P), solubility (log S), topological polar surface area (TPSA), molecular weight, drug-likeness, and drug score for the compounds[30].

2.4 Molecular DockingStudies

The grid box was prepared for the docking process using AutoDockTools, a free graphic user interface (GUI) for the AutoDock4.2 program [31]. The construction of grid box was achieved by utilizing 80, 80, and 80, pointing in x, y, and z directions, respectively, with a grid point spacing of 0.375 Å. The centre grid box is of 15.930 Å, 54.398 Å, and -5.213 Å around Arg 17A, Tyr 18A, Asn 312A, His 173C, Asn 90D, Asp 92D, Gln 250D, Arg 338D, Ser 343D and Arg 347D. These amino acids were selected based on the CASTp result and the alignment of the modelled 3D structure to the template structure. The molecular docking studies were carried out using Autodock vina installed on Autodock vina installed on Covenant University Bioinformatics Research (CUBRe) high-performance computer (HPC). Nine possible conformations were generated and ranked based on their binding energies using AutoDock vina scoring algorithms for each ligand. For the post-docking studies, AutoDockTools, PyMOL[32], and LigPlot[33] were used.

3. Results and Discussion

3.1. In silico toxicity and drug-likeness predictions

The *in silico* toxicity and drug-likeness, as predicted by OSIRIS Property Explorer, showed that all the compounds have various drug-relevant properties within acceptable ranges**(Table 1)**. The clog P is a measure of a compound's hydrophilicity or lipophilicity, and it is calculated using the logarithm of the partition coefficient between n-octanol and water. A clog P greater than 5.0 signifies low hydrophilicity or poor absorption, while the acceptable clogP values are those lower than 5.0. All the screened amidoxime-containing compounds have clogP values within the acceptable range, which means they have good predicted absorptions. Topological polar surface area is highly associated with a molecule's hydrogen bonding and is an excellent predictor of drug molecule bioavailability [34]. The acceptable range for TPSA is a value lower than 160 $Å^2$, which means that the molecule will have good oral bioavailability[35]. All the screened amidoxime-containing compounds had predicted TPSA lower than 160 $Å^2$ except for **ZINC15446613**with a TPSA value of 194 $Å^2$. The solubility prediction also determines the distribution and absorption characteristics, measured in log S (a logarithm of the solubility measured in mol/dm^3). All the compounds possess estimated log S values greater than -4, which corresponds to more than 80% of marketed drugs. The drug-

likeness of the compounds are predicted on a positive or negative basis. A positive number indicates that the molecule has a high percentage of fragments that are often seen in commercial medicines. **ZINC4349374, ZINC4693505, ZINC14808159, ZINC14808513, ZINC88613617** were predicted to have negative values, while the other compounds have positive values. The drug score parameter combines drug-likeness, cLogP, logS, molecular weight, and toxicity risk into one easy-to-understand number that may be used to assess a compound's overall potential to become a drug.The higher the drug score value, the higher the compound's chance to be considered a drug candidate [36]. Compound **ZINC70663889** has the highest drug score.Furthermore, toxicity properties like effect on the reproductive system, irritating effect, and tumorigenicity are evaluated and colour coded green, yellow or red. The properties displayed in red suggest a high danger of unwanted consequences, yellow suggests mild toxicity, whereas the properties given in green imply drug conformity, compatibility, and safety *in vivo.* The toxicity results indicated that all the compounds showed no tumorigenic or irritant risks, while **ZINC4286795** and**ZINC14808159** showed high mutagenic risk and **ZINC43220523** showed predicted high toxic risk against the reproductive system. The high mutagenic risk of **ZINC4286795** is accounted for by the C=N-O-N=C fragment of the compound, while that of **ZINC14808159** is attributed to the S-C-C-S=O fragment. The high toxic risk of against the reproductive system **ZINC43220523** against the reproductive system is attributed to the C=CC(C)=CC(O)N fragment.

Table 1. Physicochemical properties and toxicity risks of the amidoxime-containing compoundsas estimated using OSIRIS Property Explorer tool.

Compound codes	Physicochemical properties					Toxicity risks			
	cLogP	TPSA ($Å^2$)	Solubility Prediction (log S)	Drug likeness	Drug score	Mutagenic	Tumorigenic	Irritant	Reproductive effective
ZINC1833232	-1.33	59.35	0.01	2.54	0.95	Green	Green	Green	Green
ZINC1921954	-1.97	62.59	0.19	3.35	0.97	Green	Green	Green	Green
ZINC2268942	-0.03	129.8	-1.87	2.11	0.90	Green	Green	Green	Green
ZINC4286795	-0.24	104.2	-0.50	1.67	0.54	Red	Green	Green	Green
ZINC4349374	-1.86	111.7	-1.00	-2.63	0.52	Green	Green	Green	Green
ZINC4693505	-1.31	73.93	-0.12	-8.34	0.49	Green	Green	Green	Green
ZINC14808159	-1.19	126.80	-1.32	-0.76	0.38	Red	Green	Green	Green
ZINC14808513	-0.32	85.65	-1.72	-1.62	0.56	Green	Green	Green	Green
ZINC15446613	0.34	194.00	-1.76	0.92	0.83	Green	Green	Green	Green
ZINC43220523	-0.33	76.42	-0.62	1.04	0.51	Green	Green	Green	Red
ZINC70663889	-0.92	157.00	0.15	6.33	0.99	Green	Green	Green	Green
ZINC88613617	-0.63	94.58	-0.57	-33.16	0.49	Green	Green	Green	Green

3.2. Molecular docking studies results

The molecular weights of all the amidoxime-containing compounds were within the range of 152.18 and 245.28 g/mol, indicating that all the compounds had molecular weights lower than the 500 g/mol mark set by Lipinski's rule of five. Also, all the compounds have acceptable hydrogen bond donors and hydrogen bond acceptors lower than 5 and 10, respectively. AICAR (5-aminoimidazole-4-carboxamide ribonucleotide) and its analogues have been reported to be good inhibitors of *Plasmodium falciparum*adenylosuccinate lyase (*Pf*ADSL)

[13,14,37]. Therefore, AICAR was considered as the control ligand in the molecular docking study and chloroquine was used as the standard drug. The molecular docking studies were performed to gain insights into the binding affinities and inhibition constants (K_i) of all the compounds in comparison to AICAR and chloroquine in the binding site of the 3D structure of *Plasmodium falciparum*adenylosuccinate lyase **(Table 2)**. All the compounds possessed binding affinities within the range of -8.6 and -5.7 kcal/mol, while the control ligand has a binding affinity of -7.4 kcal/mol **(Figure 2)**. The calculated inhibition constants for all the compounds were also within the range of 0.471 and 64.072 µM. **ZINC2268942** had the best binding affinity and inhibition constant of -8.6 kcal/mol and 0.471, respectively. This could be attributed to the four hydrogen bond donors and five hydrogen bond donors possessed by this compound, making it have four donatable hydrogen atoms that can partake in hydrogen bond formation with the amino acids of the protein target. Only six compounds (**ZINC2268942, ZINC4286795, ZINC14808159, ZINC14808513, ZINC43220523 and ZINC88613617**) had better binding affinities than AICAR, and all the compounds except **ZINC1921954** showed better binding affinities than the reference drug, chloroquine.

Table 2. The binding affinities and inhibition constantsof the amidoxime-containingcompounds, AICARand chloroquine in the binding pocket of *Pf*ADSL

S/N	Compound codes	Molecular Weight (g/mol)	HBD	HBA	Binding affinities (kcal/mol)	Inhibition constant (K_i) (µM)
1	**ZINC1833232**	152.18	3	2	-6.9	8.392
2	**ZINC1921954**	**155.18**	**3**	**2**	**-5.8**	**54.088**
3	**ZINC2268942**	236.25	4	5	-8.6	0.471
4	**ZINC4286795**	208.18	3	6	-8.3	0.783
5	**ZINC4349374**	218.23	3	5	-6.9	8.392
6	**ZINC4693505**	208.14	3	6	-7.0	7.084
7	**ZINC14808159**	234.29	3	4	-7.5	3.037
8	**ZINC14808513**	207.19	3	4	-7.9	1.542
9	**ZINC15446613**	194.19	3	4	-7.3	4.262
10	**ZINC43220523**	209.25	3	4	-7.7	2.164
11	**ZINC70663889**	157.22	3	3	-5.7	64.072
12	**ZINC88613617**	245.28	3	5	-7.5	3.037
13	**AICAR**	258.23	5	6	-7.4	3.598
14	**Chloroquine**	319.87	1	3	-6.0	38.545

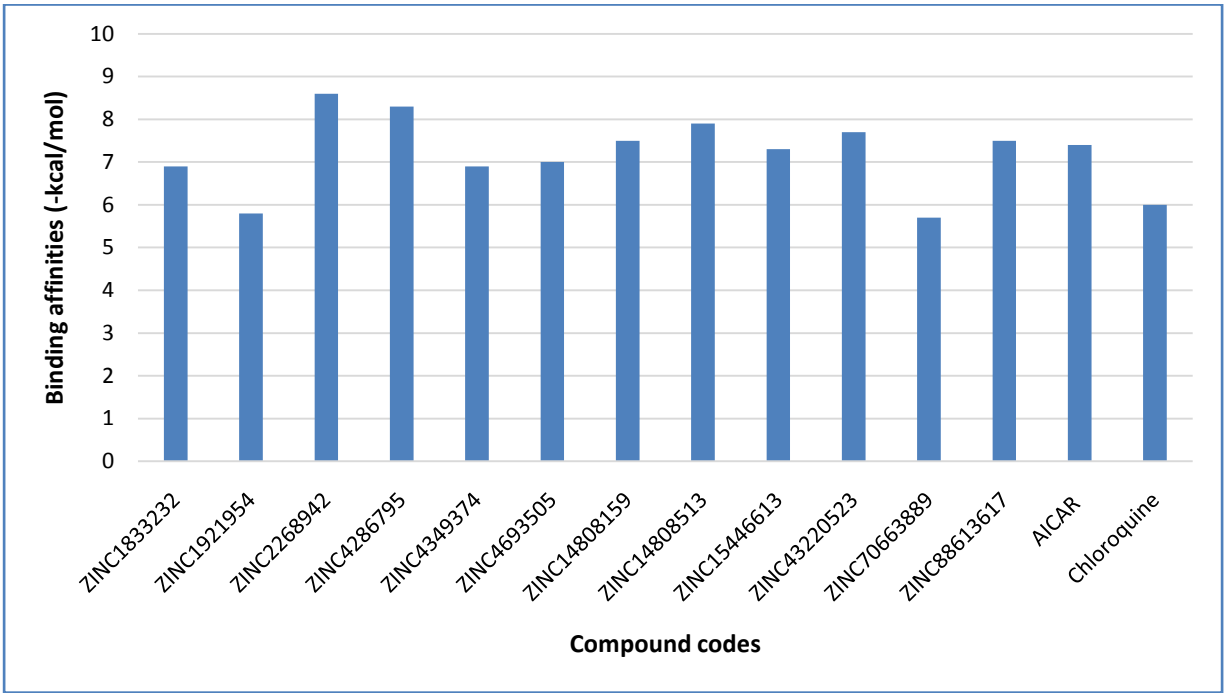


Figure 2. Chart showing molecular docking results between *Pf*ADSL and the amidoxime-containing compounds (the binding affinity values are expressed in minus kcal/mol)

3.3. Post-docking analysis

The 2D and 3D models of the interactions between the atoms of the compounds and the amino acid residues of the *Pf*ADSL were carried out using Ligplot and PyMol, respectively. The hydrogen bond interactions and the bond lengths are presented in **Table 3**. **Figure 3** and **Figure 4** illustrate the docking orientations of the control ligand **ZINC2268942**and **ZINC4286795** (the best two hits from the molecular docking studies). The heterocyclic backbone for **ZINC2268942** is benzothiazole, a benzene ring fused with a thiazole ring. The compound also has hydroxyimine and amidoxime functional groups attached to the benzothiazole template, which are readily available for hydrogen bond formations.**ZINC2268942**, with the best binding affinity,formed hydrogen bonds with Thr 124D, Ser 125D, Thr 172C, His 173C, Gln 250D, and Ser 299A. The OH of the hydroxyimine functional group on **ZINC2268942** formed hydrogen bonds with the N of Gln 250D and O of Thr 172C with bond lengths of 2.83 Å and 3.12 Å, respectively. The NH of the hydroxyimine functional group also formed a hydrogen bond with one of the N of His 173C with a bond length of 3.20 Å. The OH of the amidoxime functional group on **ZINC2268942** formed hydrogen bondswith one of the O of Ser 299A, O of Thr 124D, O of Ser 125D and N of Ser 125D with bond lengths of 2.70 Å, 2.84 Å, 3.09 Å and 3.20 Å respectively. The =NH of the amidoxime functional group on **ZINC2268942** formed a hydrogen bond with one of the O of Ser 299A with a bond length of 2.85 Å (**Figure 3**).

The heterocyclic backbone for **ZINC4286795** is benzoxadiazole, a benzene ring fused with an oxadiazole ring. The benzoxadiazole template is joined to an amidoxime functional group via

oxygen linkage.**ZINC4286795** formed hydrogen bonds with Lys 330C, Lys 330B, Ser 322B, Lys 325D, Ser 329C. The OH of the amidoxime functional group on **ZINC4286795**formed hydrogen bondswith one of the N of Lys 330C and O of Ser 329C with bond lengths of 2.89 Å and 2.96 Å, respectively. The NH of the amidoxime functional group also formed a hydrogen bond with one of the O of 322B with a bond length of 2.88 Å. The =NH of the amidoxime functional group formed hydrogen bonds with one of the O of Ser 329C, O of Lys 325C, N of Lys 325D with a bond length of 3.19 Å, 3.16 Å and 3.33 Å. The O of the benzoxadiazole template on **ZINC2268942** also formed a hydrogen bond with the N of Lys 330B with a bond length of 3.01 Å (**Figure 4**).

Table 3. The hydrogen bond interaction and bond lengths of the amidoxime-containing compounds and AICAR with the amino acid residues of homology modelled *Pf*ADSL

S/N	**Compound codes**	**Hydrogen bond interactions and bond lengths**
1	**ZINC1833232**	Asp277B (2.88 Å), Glu185B (2.85 Å, 3.02 Å), Leu336A (2.89 Å, 3.02 Å), Gln 337A (3.02 Å)
2	**ZINC1921954**	Tyr18A (3.11 Å), Leu 340D (3.30 Å), Ser 343D (3.01 Å), Thr 344D (2.87 Å, 3.08 Å), Arg 347D (2.97 Å)
3	**ZINC2268942**	Thr 124D (2.84 Å), Ser 125D(3.09 Å, 3.20 Å), Thr 172C (3.12 Å), His 173C (3.20 Å), Gln 250D (2.83 Å), Ser 299A (2.70 Å, 2.85 Å)
4	**ZINC4286795**	Lys 330C (2.89 Å), Lys 330B (3.01 Å), Ser 322B (2.88 Å), Lys 325C (3.16 Å), Lys 325D (3.33 Å), Ser 329C (2.96 Å, 3.19 Å)
5	**ZINC4349374**	Arg 17A (3.16 Å), Tyr 18A (3.16 Å), Ser 343D (2.76 Å, 2.96 Å), Thr 344D (2.81 Å, 3.01 Å), Arg 347D (2.97 Å)
6	**ZINC4693505**	Asp 92D (3.04 Å, 3.33 Å), Glu 126D (2.85 Å), Ser 343D (2.80 Å, 3.33 Å)
7	**ZINC14808159**	His 91D (3.26 Å), Ser 299A (2.94 Å), Asn 306A (2.89 Å)
8	**ZINC14808513**	Arg 17A (2.84 Å), Tyr 18A (3.16 Å), Asn 312A (3.13 Å), Arg 347D (3.07 Å)
9	**ZINC15446613**	His 91B (2.90 Å), Thr 124B (2.90 Å), Ser 125B (3.10 Å, 3.31 Å), Asn 129B (3.06 Å), Ser 299C (2.91 Å, 2.97 Å)
10	**ZINC43220523**	Glu 126B (2.89 Å), Asn 129B (2.86 Å, 2.97 Å), Ser 343B (3.16 Å, 3.29 Å), Arg 347B (2.79 Å)
11	**ZINC70663889**	Ser 298A (2.85 Å, 3.29 Å), Met 301A (2.71 Å), Lys 304A (2.71 Å, 3.10 Å)
12	**ZINC88613617**	Arg 17C (2.99 Å), Glu 86B (3.12 Å), Arg 347B (2.89 Å),
13	**AICAR**	Thr 124B (2.66 Å), Thr 172A (2.98 Å, 3.16 Å), His 173A (2.93 Å), Gln 250B (2.62 Å, 3.19 Å, 3.25 Å), Arg 338B (3.03 Å)
14	**Chloroquine**	-

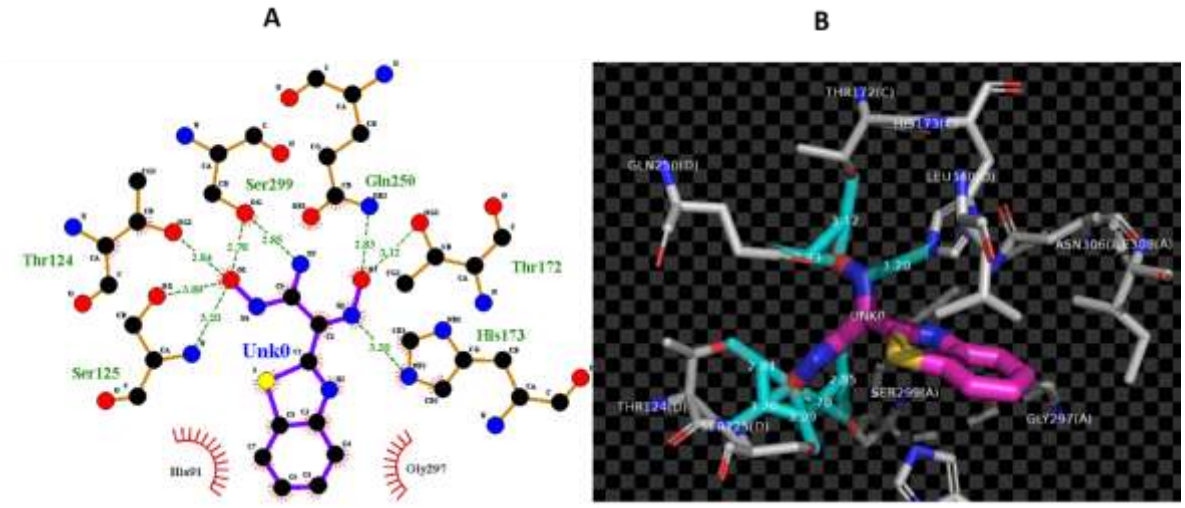


Figure 3. Molecular docking interactions between **ZINC2268942** and the binding sites of *Pf*ADSL: (a) 2D model of the interactions; (b) 3D model of the interactions

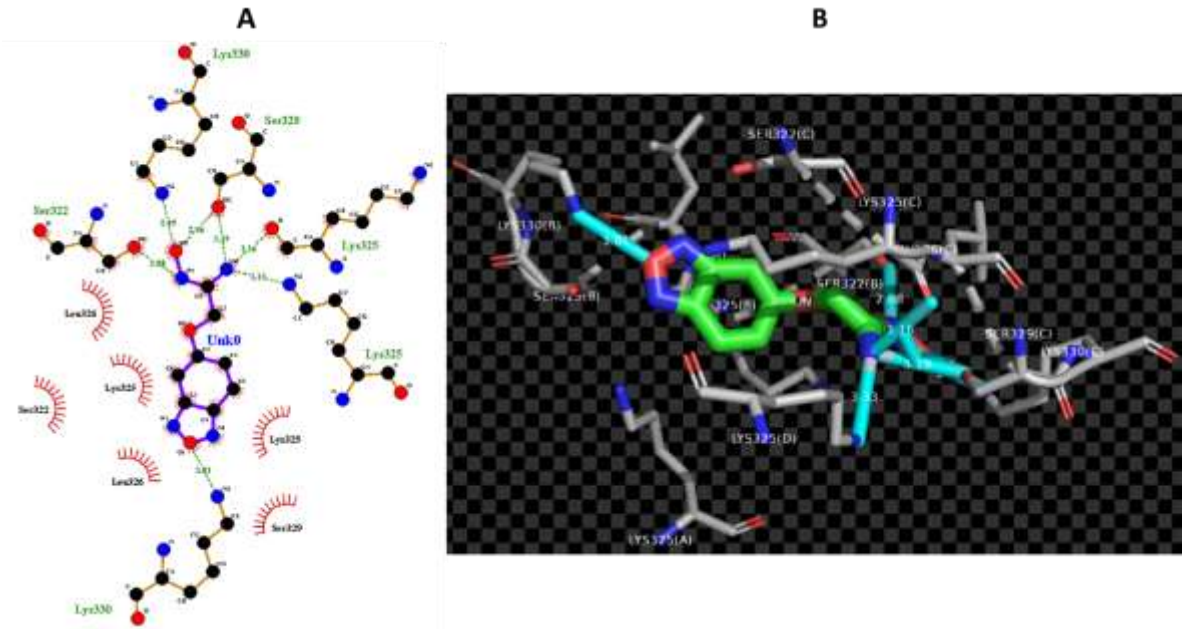


Figure 4. Molecular docking interactions between **ZINC4286795** and the binding sites of *Pf*ADSL: (a) 2D model of the interactions; (b) 3D model of the interactions

4. Conclusion and Recommendation

This study showed that all the amidoxime-containing heterocyclic compounds screened have good drug scores based on the toxicity and drug-likeness predictions. This is an indication that they all stand the chance of being considered as drug candidates. Also, the molecular docking studies identified a derivative of benzothiazole heterocyclic compound, (*Z*)-2-(benzo[d]thiazol-2-yl)-*N*-hydroxy-2-(hydroxyimino)acetimidamide (**ZINC2268942**), of possessing the best binding affinity and inhibition constant against *Plasmodium*

*falciparum*adenylosuccinate lyase (*Pf*ADSL) amongst the screened amidoxime-containing heterocyclic compounds. The post-docking analyses of all the compounds in their docking model against the binding sites of *Pf*ADSL showed that the amidoxime functional group contributed to the observed binding affinities and the hydrogen bonds formed. The results obtained from the molecular docking studies will be helpful in the development of a potential antimalarial drug that can target *Pf*ADSL after careful experimental validation of the target, then *in vitro* and *in vivo* screening of the compounds.

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