Molecular docking studies of antimalarial drugs for the treatment of malaria

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Abstract

The emergence of drug resistant strains of Plasmodium spp. creates a critical need for the development of Novel antimalarial. Formation of hemozoin, a crystalline heme detoxification process vital to parasite survival serves as an important drug target. Docking of indolo [3,2-c]quinolones complexes with 3DGA (wild type *Plasmodium falciparum di hydrofolate reductage-thymidylate synthase* [pf-DHFR-TS] complexed with RJF01320, NADPX and DUMP was performed to gain insight into the structural requirements and preferred conformations of these inhibitors. The study was conducted on a selected set of 100 compounds with variation in structure and activity. We found that the most active compounds established three hydrogen bonds, but some of the less active compounds have other binding modes. The application of docking study allowed conclusions to be drawn for the choice of suitable β-hematin inhibitors.

Keywords: QSAR, pf-DHFR, molecular docking, PDB, antimalarial activity, malaria

Introduction

The parasites of the genus Plasmodium are the primary cause of the infectious illness malaria [1]. There are five different types of malaria parasites that have been identified: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi* [2]. Plasmodium falciparum is responsible for 90% of malaria-related fatalities, which mostly affect children in Africa [3, 4]. The World Health Organisation (WHO) estimates that there are 216 million people worldwide who are infected with malaria in 2016, up 5 million cases over the previous year's total [5].

Notwithstanding the significant efforts made to find a potent antimalarial medication, these attempts face several challenges, including problems with drug resistance [6, 7]. One of the most popular solutions to this issue is the idea of hybrid compounds, which involves linking together two or more pharmacophores to concurrently block two traditional targets [8]. Regarding this, 1,3,5-triazine derivatives such cycloguanil,

chlorcycloguanil and WR99210 are previously recognised as efficient dihydrofolate reductase (DHFR) inhibitors that specifically impede biochemical processes necessary for parasite proliferation [9]. Additionally, the quinoline nucleus has drawn the attention of medicinal chemists as a crucial pharmacophore responsible for delivering antimalarial activity [10, 11]. Additionally, a unique synthetic compound needs to follow certain requirements in order to become a medicine a very long journey. As a result, the pharmaceutical industry is adopting novel research techniques that include foreseeing the actions of compounds even before they are created. In the last year, results using molecular modelling approaches like molecular docking have been quite outstanding [12, 13]. In an effort to continue our earlier works [14, 15]. Using docking investigations, we performed molecular modeling of the Isocryptolepine (Figure 1) as possible antimalarial drugs in this article [16].

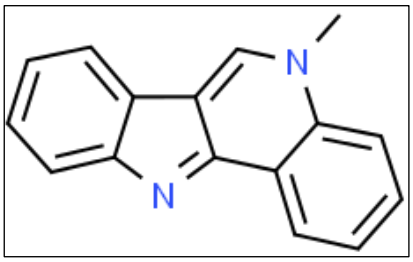

Fig 1: The structure of the Isocryptolepine

Several validation procedures, including Y-randomization techniques and internal and external validations, have been used to assess the established model's predictive power. The most crucial target for the development of antimalarial drugs is the dihydrofolate reductase of Plasmodium falciparum (pf-DHFR).

Material and Method

Data Set

The primary structures and activities of 49 indolo[3,2-c]quinolines as β-haematin inhibitros were taken from the literature [17]. Inhibitory activities were collected and transformed into log (10^6/IC50) values. IC50 values represent the compound nM concentrations that inhibit the β-haematin inhibition activity by 50%. Compounds and inhibitory biological activities used in this study.

Docking studies

This investigation included retrieval of the 3D structure of target enzymes and ligands from PDB and PubChem databases (http://www.rscb.org/pdb), respectively. The 3D structure of isocriptolepine derivatives docking was performed by molegro virtual docker by mvd tool, (https://molegro-virtual-docker.software.informer.com/), whereas docking complexes were visualized by molegro molecular viewer (https://molegro-molecular-viewer.software.informer.com/). Drug Bank is a unique Bioinformatics/Cheminformatics resource that combines detailed drug (i.e. chemical) data with comprehensive drug target (i.e. protein). Each Drug Card entry contains

greater than 80 data fields with half of the information being devoted to drug/chemical data and the other half devoted to drug target or protein data (Drug Bank, 2006). The PDB (Protein Data Bank) is the single worldwide archive of Structural data of Biological macromolecules, established in Brookhaven National Laboratories (BNL) in 1971(The Protein Data Bank, 2000). It includes macromolecule structural data derived from X-ray crystallography, NMR, and other technologies.

Protein Preparation

For Docking analysis all compounds were selected to evaluated Antimalarial activity as series under consideration. Docking was done using two PDB code 3DGA, using molegro virtual Docker 6.0. (https://molegro-virtual-docker.software.informer.com/), Moreover, the obtained structure also combined with water molecules and co-factors. Once the PDB's imported into the MVD (Molegro Virtual Docker version 6.0. software) manual procedure was done to remove water molecules and co-factors. Furthermore, to execution the absent charges, protonation states, and allocating of polar hydrogen.

Ligand preparation

Mol format (*.mol) had been chosen to save 3D structures of Isocryptolepine derivatives. The conversion of 2D to 3D structures was done by CHEMDROW. Ultra 12.0 software followed by energy minimization by using MM2 force field method in the same software, these procedures are essential before ligands import for docking process. To get perfect results of docking study.

Cavity (or active sites) detection and selection

The Cavity detection algorithm is an inbuilt function of MVD v.6.0.0 software, which automatically detects the possible binding sites (cavities) the cavities found inside 30 × 30 × 30 Å3 cube, which uses for ligand binding. After cavities are recognized through the cavity detection algorithm, in this process the algorithm focus on pursuit the specific area or volume during the simulation process. Here, the program detected five different binding sites of protein structure Hence, this particular cavity had been considered for the ligand binding process [18].

3DGA PDB

- 3DGA (wild type *Plasmodium falciparum* dihydrofolate reductare-thymidylate synthase [Pf DHFR-TS] complexed with RJF01320, NADPX and DUMP).
- **Name of ligand:** RJ1.
- **Chemical name of ligand:** N-[2-chloro-5-(trifluromethyl)phenyl]imido di carbonimidicdiamide.
- Chemical Formula of ligand: $C_9H_9ClF_3N_5$

Structure of ligand: Structure of ligand RJ1 shows Hydrogen bond with two hydrophobic or non-polar amino acids i.e. Isoleucin (Ile14A) and Phenylalanine

(Phe58A) and with one negatively charged amino acid Aspartate (Asp54A) (two hydrogen bonds). However the ligand explorer map of ligand RJ1 shows it has no futher hydrophobic interactions.

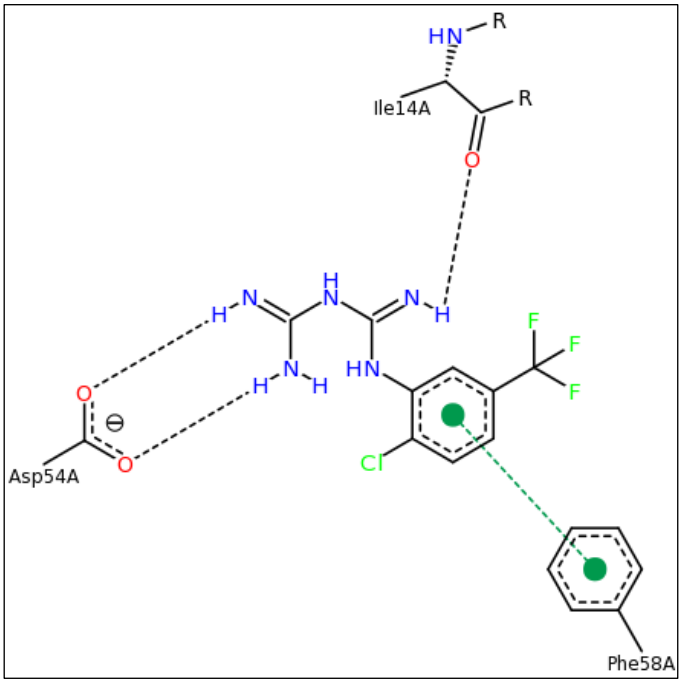

Fig 2: Showing interaction of ligand RJ1 with different amino acids of PDB 3DGA

Molegro Virtual Docker allows the flexible docking of ligands into its site of action. It has the ability to use all the rotatable bonds of the ligands to give a number of conformations from which the best mode could be achieved.

Potential binding site in pfLDH

Q site finder server was used for the identification of the most potential active site where the ligand can bind and interact with the target protein; The Protein Data Bank (PDB) database's protein target was downloaded. The PDB ID 3DGA, for the target protein is pfLDH. The protein has a 2.70 Å resolution.

Result and Discussion

The primary structures and activities of 49 indolo[3,2-c]quinolines as β-haematin inhibitors were taken from the literature [17] and Designed the 100 molecules on the basis of QSAR study. Ligand molecule preparation the 2D structures of compounds 1-100 were generated using chemdrow ultra 12.0 softwere (https://chemistry.com.pk/software/free-download-chemdraw-ultra-12/). PfLDH Protein Data Bank (PDB code 3DGA). The Isocryptolepine derivative structure was prepared using Molegro virtual Docker. The missing residues were incorporated.

All water molecules and co-crystallize legend or competitive inhibitor of the binding of RJF01320, NADPX and DUMP, were removed so that a new ligand could enter the active site.

Table 1: Designed compound for the Mol Dock Score and Hydrogen Bonding

S. No.	Name of compound	Mol Dock Score	H bond
1.	PN-1	-117.393	-0.309764
2.	PN-2	-135.69	-2.07424
3.	PN-3	-136.856	0
4.	PN-4	-120.774	-0.427258
5.	PN-5	-127.701	-4.84792
6.	PN-6	-130.071	-2.28501
7.	PN-7	-141.388	-0.14039
8.	PN-8	-129.04	-2.06302
9.	PN-9	-122.705	0
10.	PN-10	-128.608	-0.494816
11.	PN-11	-147.644	-3.70678
12.	PN-12	-139.778	-0.0492956
13.	PN-13	-120.267	-0.32762
14.	PN-14	-124.68	-0.687912
15.	PN-15	-134.426	-0.689788
16.	PN-16	-131.53	-0.648186
17.	PN-17	-128.217	-2.77207
18.	PN-18	-130.264	-2.18684
19.	PN-19	-145.918	0
20.	PN-20	-130.77	-1.85047
21.	PN-21	-118.012	-1.23905
22.	PN-22	-137.639	-2.63269
23.	PN-23	-137.896	-2.80275
24.	PN-24	-129.517	-2.08633
25.	PN-25	-118.691	-0.503412
26.	PN-26	-138.09	-4.38338
27.	PN-27	-131.559	-2.88591
28.	PN-28	-141.245	-0.70614
29.	PN-29	-128.505	0
30.	PN-30	-129.907	-2.43827
31.	PN-31	-141.498	-0.283781
32.	PN-32	-140.036	0
33.	PN-33	-123.523	-0.297549
34.	PN-34	-123.327	-1.12556
35.	PN-35	-141.6	-2.8388
36.	PN-36	-131.811	-0.147189
37.	PN-37	-116.637	-0.722382
38.	PN-38	-122.471	0
39.	PN-39	-125.146	-2.77754
40.	PN-40	-127.879	-1.55505
41.	PN-41	-130.938	0
42.	PN-42	-143.458	0

43.	PN-43	-130.593	-0.111179
44.	PN-44	-139.148	-0.685822
45.	PN-45	-127.473	-1.20165
46.	PN-46	-121.073	-0.52193
47.	PN-47	-138.076	-2.04763
48.	PN-48	-127.166	-2.19026
49.	PN-49	-119.442	-0.44344
50.	PN-50	-133.755	-2.70114
51.	PN-51	-127.598	0
52.	PN-52	-128.387	-1.94695
53.	PN-53	-133.454	-2.58457
54.	PN-54	-125.45	-0.520367
55.	PN-55	-146.406	-0.0513906
56.	PN-56	-131.304	-1.67436
57.	PN-57	-123.466	-0.656356
58.	PN-58	-118.915	-1.2882
59.	PN-59	-138.288	-7.46078
60.	PN-60	-126.56	-1.34994
61.	PN-61	-119.191	-1.88755
62.	PN-62	-127.384	-4.80337
63.	PN-63	-129.159	-2.5
64.	PN-64	-142.502	-4.3804
65.	PN-65	-130.95	-5
66.	PN-66	-141.556	-0.317075
67.	PN-67	-144.224	-0.0679622
68.	PN-68	-130.803	-2.24449
69.	PN-69	-126.893	-1.54769
70.	PN-70	-130.618	-0.526883
71.	PN-71	-143.027	-5.04907
72.	PN-72	-131.391	-1.39909
73.	PN-73	-119.221	-0.639501
74.	PN-74	-138.84	-3.65598
75.	PN-75	-130.366	-1.30934
76.	PN-76	-119.277	-0.275912
77.	PN-77	-155.905	0
78.	PN-78	-130.4	-2.38952
79.	PN-79	-130.62	-1.41309
80.	PN-80	-126.425	-1.24479
81.	PN-81	-117.347	-0.0562247
82.	PN-82	-128.387	-0.266851
83.	PN-83	-146.534	-3.62058
84.	PN-84	-134.208	-0.719667
85.	PN-85	-119.222	-0.465923
86.	PN-86	-138.842	-3.65767
87.	PN-87	-137.611	-0.531353
88.	PN-88	-136.611	0.468647

89.	PN-89	-135.611	1.468647
90.	PN-90	-134.611	2.468647
91.	PN-91	-133.611	3.468647
92.	PN-92	-132.611	4.468647
93.	PN-93	-131.611	5.468647
94.	PN-94	-130.611	6.468647
95.	PN-95	-129.611	7.468647
96.	PN-96	-128.611	8.468647
97.	PN-97	-120.106	-1.94117
98.	PN-98	-127.859	0
99.	PN-99	-134.103	-0.962746
100.	PN-100	-139.468	-3.50496
101.	Artimisinin	-57.5696	-2.11285
102.	Chloroquine	-101.71	-1.82226
103.	Mefloquine	-91.0098	0
104.	Quinine	-83.1193	-4.67412

Docking Analysis

The drug and its derivatives' docking results using Molegro virtual Docker docking software show most active analogue PN-11 MolDock score (-147.644) and Hydrogen Bond -(3.70678) is superior to the original's artemisinin (-57.5696), chloroquine(-101.71), mefloquine (-91.0098), quinine (-83.1193) on PDB 3DGA.

Designed Molecules showed the important interacting residues in the active site of receptor are Lys321(c), Try322(c) and Asn330(c) with ligands. The best score docking solution of Isocryptolepine derivative with the selected crystal structure of [Pf DHFR-TS] complexes. Amino acids in the active site are presented in lines and ligand is presented in thick lines with fix colour. Blue lines represent the hydrogen bonds between the ligand and the active site of Protein.

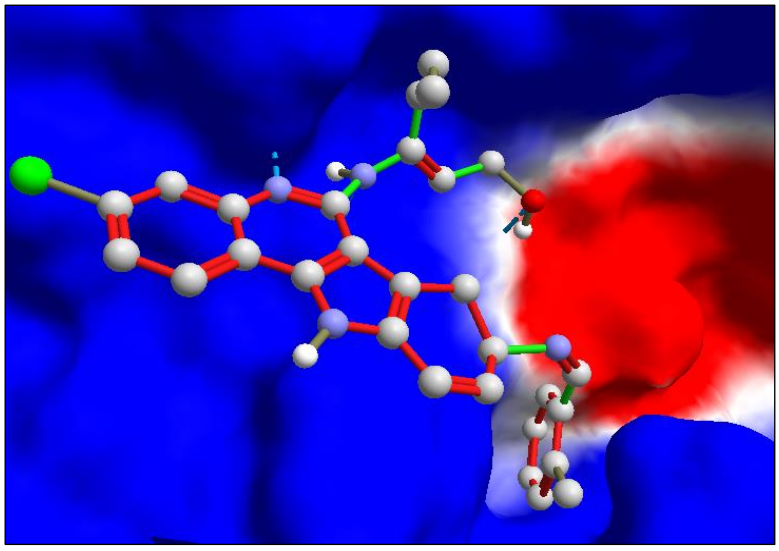

Fig 3: Compound PN-11 embedded in deep cavity

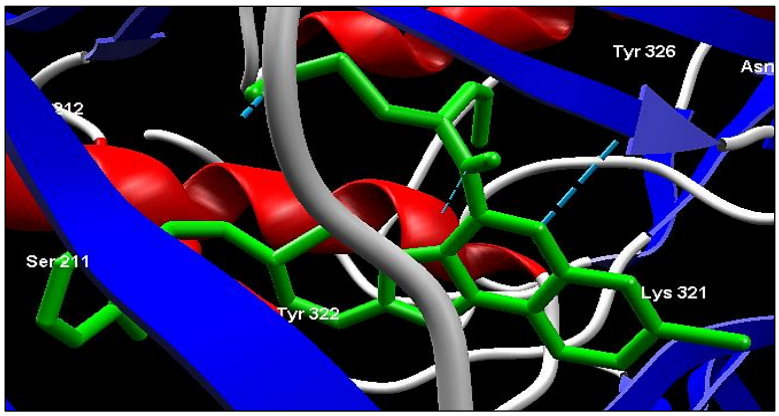

Fig 4: Hydrogen bond interaction between Compound PN-11 and receptor

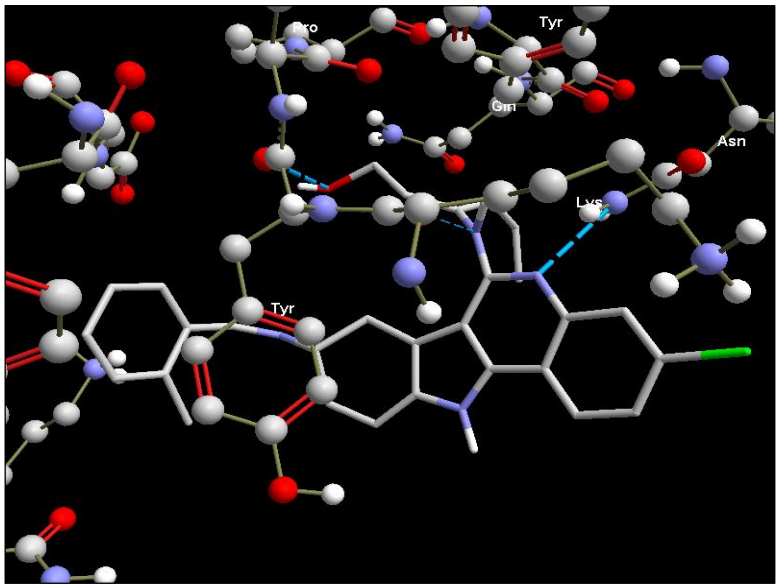

Fig 6: Compound PN-11 show H-bond interaction

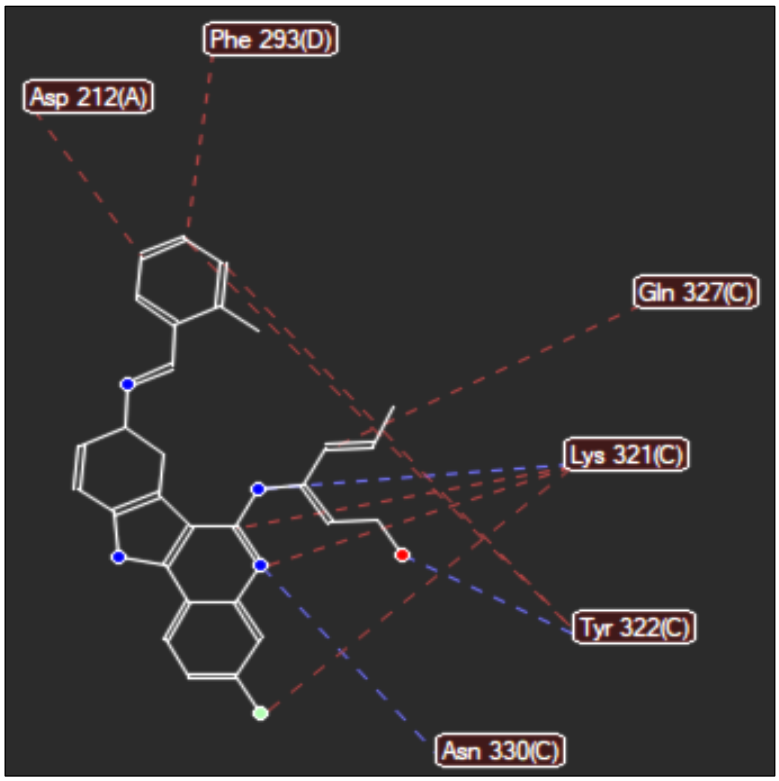

Fig 7: Compound PN-11 show binding with amino acid

Conclusion

An important factor in the creation of drugs with a structural basis is the protein-ligand interaction. In the docking study, Dihydrofolate Reductase inhibitor was considered for used to treatment of malaria. In present study docking studies on series of Isocryptolepine derivatives were applied successfully to identify the necessary structural, substituent requirements and potential interaction of N1-(11H-Indolo[3,2-c]quinolin-6-yl)propane-1,3-diamine Docking study showed the important interacting residues in the active site of receptor are Lys321(c), Try322(c) and Asn330(c) with ligands. It appears to be an attractive compound for the development of new antimalarial agents. This leads us to the conclusion that some of the designed molecules are superior to the standard molecules. Structural models of its interactions at the PfLDH active site are plausibly useful for the future design of antimalarial drugs.

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