Prediction of In-silico Physicochemical Properties and Molecular Docking Studies of Dihydroartemisinin Derivatives for Antimalarial Activity against protein target Dihydropteroate Synthase

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Abstract- **One of the most dangerous and pervasive parasitic diseases in the underdeveloped world is still malaria. In 2022, there was 241 million malaria cases and 6,27,000 deaths were reported worldwide. The objective of this work was to evaluate the physical-chemical, pharmacokinetic parameters (absorption, distribution, metabolism, excretion and toxicity) and pharmacodynamic parameters (bioactivity and adverse reactions) of artemisinin as a pharmacophore by means of in-silico computational prediction. Online software such as Pre-ADMET, Molinspiration and Rule of Five were used for the analysis. In-silico results allow us to conclude that substituted artemisinin is predicted to be a potential future drug candidate, due to its relevant Drug-likeness profile, bioavailability, excellent liposolubility and adequate pharmacokinetics, including at the level of CNS, penetrating the blood-brain barrier. Molecular docking studies of 40 designed compounds have also been performed to screen the inhibitory activity towards against protein target Dihydropteroate Synthase (PDB: 1AJ0). Compound D19 and D31 showed strong bonding interaction with GLY29, GLY32, THR97, GLY99, PHE100, THR101 and ASN140 amino acids with high hydrogen bond affinity and best Moldock score- 169.698 and - 204.1319 respectively.**

Keywords: **Malaria, Dihydroartemisinin, Molecular docking, Molinspiration, PreADMET.**

1. Introduction:

The pharmaceutical industry has been facing significant challenges since the past decade regarding the increased research and development (R&D) costs, looming patent expirations, and continuously declining number of new drug approvals. Due to the loss of the roaring success of drugs' market share to generic competition, it has become a serious concern that innovation in first-in-class drug discovery has stagnated and the new approved drugs would not be able to replace the losses incurred by expiring patents.[1-3] The significant contribution of computational and theoretical studies of quantum chemistry has allowed medicinal chemists to obtain more precise molecular properties and bioactivity of drugs in a shorter time.[4]

Malaria has been a significant public health issue for many years. It is mentioned in several passages of the Bible as well as in the writings of Hippocrates. Despite treatments to treat it, many people still believe that malaria is the most serious infectious disease impacting humanity. The disease is directly to blame for 1 million to 2.5 million fatalities and is thought to cause 200 million to 500 million new cases annually.[5]

An infectious disease spread by mosquitoes that affects both people and other animals, malaria is brought on by protists of the genus *Plasmodium*. The word malaria comes from the mediaeval Italian mala aria, which means "bad air." [6]

The parasites of the genus *Plasmodium* four species have been identified which can cause disease in humans: *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, Plasmodium knowlesi*.[7]

Quinine was first drug was discovered and used to treat malaria as early as the beginning of the 17th century, and became the standard therapy for malaria from the mid-19th century to the 1940s. The extraction of quinine is still more economically viable than its synthetic production.[8]

Dihydroartemisinin, a derivative of artemisinin, is the active metabolite of artemisinin. Dihydroartemisinin is widely used in the clinical treatment of malaria and has saved countless lives, due to its 100% efficiency against malaria parasites and low toxicity. DHA kills plasmodium parasites by damaging their membranes, disrupting their mitochondrial function and causing oxidative stress through producing excessive reactive oxide species.[9]

Due to the high levels of mortality and morbidity caused by malaria-especially the P. falciparum species-it has placed the greatest selective pressure on the human genome in recent history. Several genetic factors provide some resistance to it including sickle cell trait, thalassaemia traits, glucose-6-phosphate dehydrogenase deficiency, and the presence of Duffy antigens on red blood cells.[10]

2. Material and Methods

For designing of compounds Dihydroartemisinin pharmacophore was selected on the basis of literature study. ChemDraw ultra 8.0 software (2D and 3D) was used for designing of compounds and Molegro virtual docker (MVD 6.0) which is available in CADD lab of GRY institute of pharmacy, Borawan. *In-silico* predictions was performed using online available tools i.e Lipinski rule of Five, Molinspiration and PreADMET.

2.1. *In-Silico* studies:

2.1.1. Prediction of Lipinski's rule of five: The Lipinski Rule of Five, also known as the Pfizer Rule of Five or simply the Rule of Five. Online web tool http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp is used for prediction of drug likeness.[11]

2.1.2. Molinspiration

Web-based programme called Molinspiration was used to obtain parameters including MiLogP, TPSA, and drug-likeness. MiLogP is calculated to assess excellent permeability through the cell membrane. The software Molinspiration drug-likeness score, which is available online at www.molinspiration.com, was used to investigate these factors. For organic molecules, the possibility is that they are active if the bioactivity score is greater than zero, moderately active if it is between -5.0 and zero, and inert if it is below -5.0.[12]

2.1.3. PreADMET

PreADMET is a web-based application for predicting ADME data and building drug-like library using *in-silico* method.[13] This program resides entirely on a Web server, and can be accessed by browsers.

3. Molecular docking:

To determine the conceivable binding interaction and to propose more knowledge into the understanding of the binding affinity of aurones, molecular docking examination was done utilizing the Molegro Virtual Docker. The crystal structures were recovered from RCSB Protein Data Bank. Every attached ligand and non-bridging water molecules have been eliminated from the outset, and the polar hydrogen atoms were added. Different parameters are set up by default in software. MVD depends on a differential evolution algorithm called MolDock; MolDock Score energy, E score, is characterized by, where E inter is the ligand- receptor interaction energy and E intra is the interior energy of the ligand. [14-16]

3.1. Selection of Protein

On the basis of literature study, PDB Code: 1AJ0 (dihydropteroate synthase) is a crystal structure of a ternary complex of e. coliprotein which can show good hydrogen bond interaction and MolDock Score. Dihydropteroate synthase is a compound which is analysed and determined by the X-ray diffraction method. The site of action is the de novo folate biosynthesis enzyme dihydropteroate synthase (DHPS) where sulfonamides act as analogues of one of the substrates, para-aminobenzoic acid (pABA). We report here the crystal structure of E.coli DHPS at 2.0 A resolution refined to an R-factor of 0.185. The single domain of 282 residues forms an eight-stranded alpha/beta-barrel. The 7, 8-dihydropterin pyrophosphate (DHPPP) substrate binds in a deep cleft in the barrel, whilst sulfanilamide binds closer to the surface. The DHPPP ligand site is highly conserved amongst prokaryotic and eukaryotic DHPSs. [17-18]

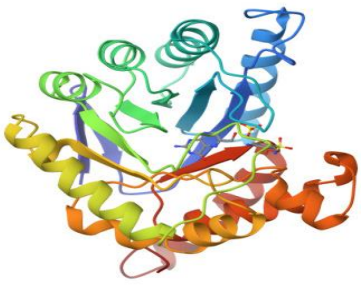

Figure-1: Dihydropteroate Synthase (PDB Code: 1AJ0)

3.2. Selection of compounds

On the basis of the literature survey Dihydroartemisinin pharmacophore were used to design new antimalarial derivatives. Data set of 80 compounds prepared summarised in table no.1.

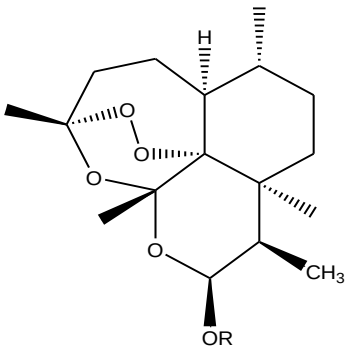

Figure: 2-Dihydroartemisinin pharmacophore

Table-1: Data set of designed Dihydroartemisinin antimalarial derivatives.

code	R	Code	R
D1	3,4-dimethoxyphenyl	D21	4-nitrophenoxy
D2	Oxan-4-yl	D22	2,3,4,5,6-
D3	2,5-dimethylphenyl	D23	2,6-dichlorophenyl
D4	2,4-dichlorophenoxy	D24	4-nitrophenylmethylphenoxy
D5	2,4-dichloro phenyl	D25	3-methylphenoxy
D6	2- Fluorophenyl	D26	3-(trifluoromethyl) phenoxy
D7	2,4- Bis(2-methylbutan-2-yl) phenoxy	D27	3-(5-methyltertrazol-2-yl)
D8	2- methoxy phenyl	D28	4-ethyl-3,5-dimethylpyrazol-1-yl
D9	1,3-benzodioxol-5-yl	D29	2,3,4,5,6-pentafluorophenyl
D10	4-propan-2-yl phenoxy	D30	3,4-dichlorophenyl
D11	2-methoxyphenyl	D31	4-methoxyphenoxy
D12	4-fluorophenoxy	D32	3-chlorophenyl
D13	2- methylphenyl	D33	tetrazol-1-yl
D14	4-methylphenoxy	D34	2-bicycloheptanyl
D15	4-chlorophenyl	D35	3-bromophenoxy
D16	4-methylsulfonylphenyl	D36	2,3-difluorophenyl
D17	4-methylpurazol-1-yl	D37	2-bromo-4,5-dimethoxyphenyl
D18	2,4-di(pentan-2-yl)phenoxy	D38	5-methyl-3-pyrazol-1-yl
D19	1,3-dimethyl-2,6-dioxopurin-7-yl	D39	4-chloro-3-methylpyrazol-1-yl
D20	2-methylphenoxy	D40	2,3-dichlorophenyl

4. Result and Discussions

4.1 Lipinski Rule

According to Lipinski's rule, an orally active drug-like molecule shouldn't contain more than one violation of the following standards: Molecules with masses under 500 Dalton and high lipophilicity (defined as a Log P 5), molar refractivity should be between 40 to 130, with less than five hydrogen bond donors and ten hydrogen bond acceptors. All the compounds were exhibited in the range of data, adhering to Lipinski's rule of five except D7, D15, D18, D19, D22, D27 and D37. Results of Lipinski rule was described in below table no.2.

Table-2: Result of Lipinski rule.

S. No.	Code	Mass	HBD	HBA	Log P	MR
1	D1	462	0	8	3.997	116.169
2	D2	410	0	7	3.554	101.079
3	D3	462	0	8	3.997	116.169
4	D4	487	0	7	3.579	109.014
5	D5	471	0	7	3.743	107.223
6	D6	420	0	6	4.119	103.023
7	D7	558	0	7	7.191	151.491
8	D8	432	0	7	3.988	109.617
9	D9	446	0	8	3.708	109.188
10	D10	460	0	7	4.940	118.945

11	D11	448	0	8	3.825	111.408
12	D12	436	0	7	3.955	104.814
13	D13	416	0	6	3.993	107.609
14	D14	432	0	7	4.125	109.593
15	D15	596	0	7	6.458	136.254
16	D16	480	0	8	4.464	116.219
17	D17	406	0	7	2.942	99.883
18	D18	558	0	7	7.623	151.503
19	D19	504	0	11	2.276	121.039
20	D20	448	0	8	3.825	111.408
21	D21	463	0	9	3.724	111.511
22	D22	508	0	7	4.512	104.646
23	D23	471	0	6	3.743	107.223
24	D24	447	0	7	3.888	109.720
25	D25	432	0	7	4.125	109.593
26	D26	486	0	7	4.835	109.858
27	D27	542	0	9	4.436	136.730
28	D28	448	0	7	3.348	112.132
29	D29	492	0	6	4.675	102.855
30	D30	471	0	6	3.743	107.223
31	D31	448	0	8	3.825	111.408
32	D32	436	0	6	3.861	105.144
33	D33	394	0	9	1.424	90.736
34	D34	420	0	6	4.563	106.474
35	D35	496	0	7	4.579	112.556
36	D36	438	0	6	4.258	102.981
37	D37	540	0	8	4.760	123.869
38	D38	474	0	7	3.961	104.885
39	D39	440	0	7	2.824	101.962
40	D40	471	0	6	3.743	107.223

4.2 Molinspiration

4.2.1 Drug likeness Properties

D1, D2, D9, D11, D16, D17, D20, D21, D28, D33, D38 and D39 compounds are under the range e.g., MilogP is under the range of 5, TPSA is under the 140Å MW is under range of 500, nrotb is under 10, nON is under 10, nOHNH is under the range of 5 and Violations should be 0. Results of properties of molinspiration was described below in table no.3

Table-3: Result of properties of molinspiration.

Code	Mi LogP	TPSA	N atoms	MW	n ON	N OHNH	N violations	N rotb	Volume
D1	4.73	81.71	33	462.54	8	0	0	6	423.34
D2	4.18	72.47	29	410.51	7	0	0	4	383.02
D3	5.12	81.71	33	462.54	8	0	1	6	423.34
D4	6.24	72.47	32	487.38	7	0	1	5	408.31
D5	6.36	63.24	31	471.38	6	0	1	4	399.32
D6	5.20	63.24	30	420.48	6	0	1	4	377.18
D7	8.66	72.47	40	558.76	7	0	2	9	547.21
D8	5.09	72.47	31	432.51	7	0	1	5	397.79
D9	4.97	81.71	32	446.50	8	0	0	4	396.18
D10	6.47	72.47	33	460.57	7	0	1	6	431.18
D11	4.57	81.71	32	448.51	8	0	0	6	406.78

D12	5.12	72.47	31	436.48	7	0	1	5	386.17
D13	5.48	63.24	30	416.51	6	0	1	4	388.81
D14	5.41	72.47	31	432.51	7	0	1	5	397.79
D15	8.08	72.47	41	597.03	7	0	2	7	497.50
D16	3.95	97.38	33	480.58	8	0	0	5	420.24
D17	3.73	81.07	29	406.48	8	0	0	4	370.07
D18	8.81	72.47	40	558.76	7	0	2	11	548.34
D19	3.02	125.08	36	504.54	12	0	2	4	439.27
D20	4.57	81.71	32	448.35	8	0	0	6	406.78
D21	4.92	118.30	33	463.48	10	0	0	6	404.57
D22	5.49	72.47	35	508.44	7	0	2	5	405.89
D23	6.34	63.24	31	471.38	6	0	1	4	399.32
D24	5.04	109.06	32	447.04	9	0	1	5	395.58
D25	5.38	72.47	31	432.51	7	0	1	5	397.79
D26	5.83	72.47	34	486.48	7	0	1	6	412.53
D27	4.83	106.85	40	556.70	10	0	1	5	512.89
D28	4.63	81.07	32	448.56	8	0	0	5	419.94
D29	5.61	63.24	34	492.44	6	0	1	4	396.90
D30	6.36	63.24	31	471.38	6	0	1	4	399.32
D31	5.01	81.71	32	448.51	8	0	1	6	406.78
D32	5.73	63.24	30	436.93	6	0	1	4	385.79
D33	2.28	106.85	28	394.43	10	0	0	4	345.15
D34	5.15	63.24	30	420.55	6	0	1	4	396.85
D35	5.74	72.47	31	497.38	7	0	1	5	399.12
D36	5.31	63.24	31	438.47	6	0	1	4	382.11
D37	5.46	81.71	34	541.43	8	0	2	6	441.23
D38	4.71	81.07	33	474.48	8	0	0	5	401.32
D39	4.18	81.07	30	440.92	8	0	0	4	383.56
D40	6.34	63.24	31	471.38	6	0	1	4	399.32

4.2.2 Bioactivities: Results for bioactivities of molinspiration was described below in table no. 4

Table-4: Results of bioactivities of molinspiration.

S. No.	Code	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	D1	-0.05	-0.22	-0.37	0.08	-0.00	0.28
2	D2	0.03	-0.16	-0.33	0.08	0.12	0.39
3	D3	-0.05	-0.23	-0.39	0.14	-0.02	0.27
4	D4	-0.08	-0.33	-0.37	0.11	-0.10	0.22
5	D5	-0.00	-0.16	-0.40	0.09	0.01	0.27
6	D6	-0.01	-0.18	-0.36	0.12	0.09	0.31
7	D7	0.02	-0.40	-0.40	0.23	-0.10	0.20
8	D8	-0.04	-0.23	-0.40	0.13	-0.01	0.29
9	D9	-0.02	-0.23	-0.41	0.06	0.02	0.30
10	D10	-0.06	-0.28	-0.41	0.16	-0.02	0.26
11	D11	-0.09	-0.33	-0.39	0.06	-0.06	0.24
12	D12	-0.06	-0.31	-0.38	0.15	-0.03	0.26
13	D13	-0.02	-0.21	-0.41	0.12	0.02	0.31
14	D14	-0.10	-0.36	-0.44	0.11	-0.06	0.23
15	D15	0.04	-0.48	-0.42	0.11	0.04	0.08
16	D16	-0.02	-0.28	-0.35	0.18	0.21	0.44

17	D17	-0.13	-0.44	-0.37	-0.28	-0.17	0.24
18	D18	-0.04	-0.46	-0.48	0.12	-0.05	0.13
19	D19	-0.05	-0.61	-0.54	-0.53	-0.21	0.28
20	D20	-0.09	-0.33	-0.39	0.06	-0.06	0.24
21	D21	-0.18	-0.33	-0.49	0.04	-0.13	0.17
22	D22	-0.09	-0.37	-0.36	0.13	0.02	0.21
23	D23	-0.05	-0.18	-0.40	0.09	0.00	0.30
24	D24	-0.13	-0.20	-0.47	0.04	-0.05	0.23
25	D25	-0.10	-0.37	-0.45	0.12	-0.06	0.23
26	D26	-0.02	-0.22	-0.34	0.23	0.00	0.25
27	D27	-0.04	-0.54	-0.68	-0.47	-0.25	0.07
28	D28	-0.20	-0.59	-0.52	-0.35	-0.18	0.12
29	D29	-0.02	-0.10	-0.36	0.07	0.07	0.34
30	D30	0.00	-0.15	-0.39	0.11	0.04	0.31
31	D31	-0.09	-0.32	-0.40	0.10	-0.04	0.25
32	D32	-0.00	-0.16	-0.41	0.10	0.04	0.32
33	D33	-0.06	-0.67	-0.44	-0.22	0.04	0.29
34	D34	0.06	-0.27	-0.59	0.12	0.01	0.30
35	D35	-0.15	-0.37	-0.46	0.05	-0.14	0.19
36	D36	0.00	-0.15	-0.35	0.12	0.09	0.31
37	D37	-0.12	-0.31	-0.045	-0.03	-0.17	0.20
38	D38	-0.14	-0.34	-0.44	-0.23	-0.01	0.22
39	D39	-0.26	-0.62	-0.40	-0.42	-0.27	0.02
40	D40	0.00	-0.14	-0.42	0.10	0.03	0.28

5. PreADMET

Drug likeness: CMC like rule- All the compounds are not qualified for CMC like rule. **MDDR like rule-** Compounds which the in the range of mid-structure are moderately active and the compounds which are under the range of drug like structure are highly active. **Rule of Five-** Suitable compounds are obey the rules of five or Lipinski rule of five and Violated compounds are disobey the rule of five. Results for drug likeness are described below in table no. 5

Table-5: Results of Drug likeness

Druglikeness		**Compound**
CMC_like_Rule	Not qualified	All Compound are Not Qualified
MDDR like Rule	Mid structure	D2, D4, D5, D6, D8, D9, D12, D13, D14, D16, D17, D19, D21, D22, D23, D24, D25, D26, D27, D28, D29, D30, D32, D33, D34, D35, D36, D38, D39, D40
	Drug like	D1, D3, D7, D10, D11, D15, D18, D20, D31, D37
Rule of Five	Suitable	D1, D2, D3, D4, D5, D6, D8, D9, D10, D11, D12, D13, D14, D16, D17, D20, D21, D23, D24, D25, D26, D28, D29, D30, D31, D32, D33, D34, D35, D36, D38, D39, D40,
	Violated	D7, D15, D18, D19, D22, D27, D37

ADME Study: BBB- All the compounds are the CNS inactive compounds except D7, D18, **$CaCO_2$-** All the compounds have moderately permeability. **HIA-** All the compounds have higher absorption. **MDCK-** All the compounds have lower absorption. **PPB-** All the compounds are strongly bounded except D2, D17, D19, D27, D33. **Skin permeability-** All the compounds of skin permeability are in acceptable range. Results for ADME are described below in table no. 6.

Table-6: Results of ADME.

S. No.	**Code**	**BBB**	**Caco2**	**HIA**	**MDCK**	**Plasma Protein Binding**	**Skin Permeability**

1	D1	0.065	50.780	98.942	0.045	90.360	-2.918
2	D2	0.115	48.178	97.574	0.126	88.393	-3.513
3	D3	0.089	50.592	98.942	0.044	90.903	-2.913
4	D4	0.164	34.405	97.975	0.050	100	-2.717
5	D5	0.338	33.369	97.484	0.044	99.407	-2.549
6	D6	0.102	44.790	98.518	0.046	95.813	-2.830
7	D7	2.151	55.763	97.911	0.045	96.034	-0.788
8	D8	0.058	48.543	98.876	0.046	91.625	-2.644
9	D9	0.089	44.304	98.747	0.049	90.799	-3.396
10	D10	0.116	53.368	98.845	0.227	93.497	-2.293
11	D11	0.089	52.862	98.747	0.061	91.117	-2.817
12	D12	0.108	51.010	98.818	0.064	92.931	-3.030
13	D13	0.136	50.204	98.439	0.047	91.904	-2.318
14	D14	0.073	51.321	98.876	0.100	92.322	-2.555
15	D15	0.422	46.885	97.512	0.043	100	-1.610
16	D16	0.075	4.789	98.966	0.045	89.145	-0.965
17	D17	0.462	44.498	97.620	0.072	90.407	-3.792
18	D18	3.502	55.529	97.911	0.187	96.449	-1.480
19	D19	0.199	26.084	94.669	0.044	86.428	-4.519
20	D20	0.089	52.862	98.747	0.061	91.117	-2.817
21	D21	0.107	7.666	90.057	0.056	91.530	-2.716
22	D22	0.105	51.440	98.843	0.043	99.263	-3.608
23	D23	0.337	33.120	97.484	0.043	94.908	-2.521
24	D24	0.222	22.298	93.166	0.048	91.547	-2.607
25	D25	0.084	52.414	98.876	0.076	92.642	-2.567
26	D26	0.104	39.215	98.883	0.044	92.960	-1.814
27	D27	0.244	24.881	97.954	0.043	89.957	-4.511
28	D28	0.314	50.449	98.672	0.043	91.588	-3.641
29	D29	0.239	47.807	98.495	0.043	100	-3.489
30	D30	0.338	33.549	97.484	0.045	100	-2.558
31	D31	0.147	53.703	98.747	0.073	91.814	-2.837
32	D32	0.166	31.702	97.950	0.052	100	-2.560
33	D33	0.337	9.533	87.090	2.642	81.651	-1.050
34	D34	0.350	44.365	98.528	0.055	91.901	-3.289
35	D35	0.087	28.695	98.190	0.020	100	-2.572
36	D36	0.125	45.532	98.513	0.044	96.432	-3.080
37	D37	0.081	30.158	98.647	0.042	91.883	-2.864
38	D38	0.069	30.092	98.133	0.043	90.040	-2.537
39	D39	0.410	28.115	99.001	0.048	93.983	-3.864
40	D40	0.338	33.446	97.484	0.044	100	-2.530

Toxicity Study: Ames test- The compounds D21, D24, D35, D37 mutagenic as these compounds are changing the DNA and show the gene mutation. **Carcino mouse-** The compounds D15 and D26 carcinogenic in mouse **Carcino rat-** The compounds D2, D13, D17, D24, D27, D28, D33, D34, D38 carcinogenic in rats. **hERG inhibition-** The compounds D6, D15, D17, D19, D27, D28, D33, D38, D39, D46, D53, D56, D60 and D66 are have medium risk for cardiotoxicity and the remaining compounds have low risk for cardio toxicity. Results for toxicity are described below in table no.7.

Table-7: Results of toxicity

Toxicity		**Compound**
Ames_test	Mutagen	D21, D24, D35, D37
	Non- Mutagen	D1, D2, D3,D4, D5, D6, D7, D8, D9, D10, D11, D12, D13, D14, D15, D16, D17, D18, D19, D20, D22, D23, D25, D26, D27, D28, D29, D30, D31, D32, D33, D34, D36, D38, D39, D40

Carcino_Mouse	Negative	D1, D2, D3, D4, D5, D6, D7, D8, D9, D10, D11, D12, D13, D14, D16, D17, D18, D19, D20, D21, D22, D23, D24, D25, D27, D28, D29, D30, D31, D32, D33, D34, D35, D36, D37, D38, D39, D40,
	Positive	D15, D26
Carcino_Rat	Negative	D1, D3, D4, D5, D6, D7, D8, D9, D10, D11, D12, D14, D15, D16, D18, D19, D20, D21, D22, D23, D25, D29, D30, D31, D32, D35, D36, D37, D39,
	Positive	D2, D13, D17, D24, D27, D28, D33, D34, D38,
hERG_inhibition	Low Risk	D1, D2, D3, D4, D5, D7, D8, D9, D10, D11, D12, D13, D14, D16, D18, D20, D21, D22, D23, D24, D25, D26, D29, D30, D31, D32, D34, D35, D36, D37, D40
	Medium Risk	D6, D15, D17, D19, D27, D28, D33, D38, D39,

6. Docking study

Molecular docking studies were conducted with Molegro Virtual Docker (MVD 6.0) to obtain insights into the inhibitors' binding affinities and interaction patterns. Table no .8 and 9.

Table-8: Results of docking study.

Code	Dock Score	H-Bond Interaction	Steric Interaction
D1	-132.2	Gly32, Thr97, Gly29, Asn140, Ser245	Thr97, Phe100, Gly99, Gly32, Gly29, Met30, Asn140, Ser245, Val138
D2	-104.01	Gly32, Thr97,Gly29, Asn140, Ser245, Ile31	Thr97, Asn140, Gly99,Ser245
D3	-143.90	Ser245, Asn140, Gly29, Thr97	Thr101, Gly32, Gly29, Met30, Gly99, Ser245,Asn140, Ser245, Val138
D4	-121.80	Thr97, Gly99, Ser145, Asn140	Gly99, Thr101, Thr97, Gly29, Leu112, Val138, Ile31
D5	-119.36	Thr97, Gly29, Gly32, Asn140, Ser245	Met30, Leu112, Phe100, Gly99, Thr97, Ser245,Ile31
D6	-116.16	Thr139, Thr97, Ser245, Asn140	Gly29, Met30, Ser245, Asn140, Ser245, Val138
D7	-119.71	Thr97, Ile31, Asn140, Ser245	Thr101, Gly32, Gly29, Asn140, Ser245, Val138
D8	-117.42	Thr97, Phe100,Ser245, Asn140	Asn140, Ser245, Phe100, Gly99, leu112, Val138,Ile31
D9	-140.6	Asn140, Phe100, Asn116, Ser45	Leu112, Met30, Val138, Ile31, Ser245
D10	-110.59	Thr97, Phe100,Ser245, Asn140	Phe100, Gly99, Thr101,Gly32, leu112, Asn140, Val138, Ile31
D11	-120.86	Thr101, Ile31,Gly32,	Gly99, Thr101, Gly32, Thr97, Gly29, Met30, leu112, Asn140, Ser245,
D12	-121.11	Thr97, Ser245, Asn140, Gly29	Gly99, Thr101, Ser245, Val138, Phe100, Ile31
D13	-117.75	Thr97, Ser245,Asn140, Gly29	Phe100, Gly99, Thr101, Gly32, Thr97, Gly29, Met30, leu112, Asn140, Ser245, Val138, Ile31
D14	-108.54	Thr97, Gly29, Asn140, Ser245	Thr101, Gly99, Thr97, Ile31
D15	-152.82	Gly29, Asn166, Thr101, Asn140,Arg171	Gly99, Thr101, Gly32,leu112,
D16	-119.30	Ala329, Phe100, Asn166, Pro246	Gly29, Met30
D17	-124.39	Gly32, Thr97, Gly29, Asn140, Ser245	Asn140, Ser245, Thr97, Gly29, leu112, Ile31
D18	-125.39	Ile31, Gly32, Asp32, Pro246	Ser245, Val138, Phe100, leu112, Asn140
D19	-119.28	Asn166, Asn100, Thr101, Ser245, Gly99	Gly32, Thr97, Phe100, Thr101, Gly29, Met30, Asn140, Ser245, Ile31

D20	-110.20	Gly99, Gly29, Ser245, Phe100	Phe100, Gly99, Thr101,Gly32, leu112, Asn140, Val138, Ile31
D21	-118.99	Asn166, Thr101, Ser245, Gly99	Gly99, Thr101, Gly32, Thr97, Met30, leu112,Asn140, Ser245,
D22	-108.84	Phe100, Ile31, Asn140	Gly99, Thr101, Ser245, Val138, Phe100
D23	-110.61	Val26, Ile31,Phe52, Ile54	Phe100, Gly99, Thr101, Gly32, Gly29, Met30, leu112, Asn140, Ser245, Val138, Ile31
D24	-124.20	Phe100, Gly29, Ser245, Asn100, Asn166	Phe100, Thr101, Gly32, Asn140, Val138, Ile31
D25	-118.66	Thr101, Asn140, Ser245, Phe100	Met30, Gly99, Thr101, Gly32, Asn140, Val138
D26	-132.83	Gly29, Gly32,Arg171	Gly99, Thr101, Gly32, Thr97, Met30, leu112,Asn140, Ser245,
D27	889.74	Phe100, Asn166, Pro246, Thr139, Thr97	Ile31, Phe52 Thr97, Gly29, Met30, leu112,
D28	-136.25	Thr97, Ile31, Gly29, Thr101	Gly32, Met30, leu112, Phe100, Gly99, Thr101, Ser245, Ile31
D29	-105.80	Ser245, Ile31, Thr101, Ser245	Phe100, Gly99, Thr101, Gly32, Thr97, Gly29, Met30, Ser245, Ile31
D30	-118.73	Pro246, Gly29	Thr101, Gly32, Gly29, Gly99, Ser245, Asn140,Val138
D31	-109.72	Ala329, Phe100,Asn166, Pro246, Ile31, Phe52	Gly29, Met30, Ser245, Asn140, Ser245, Val138
D32	-125.13	Phe100, Ile31, Asn140, Thr101, Ser245	Thr101, Gly32, Gly29,Asn140, Val138
D33	-112.72	Phe100, Asn140, Gly29, Thr101	Asn140, Ser245 Gly99, Gly32, Met30
D34	-121.22	Ile31, Gly29, Ser245	Gly32, Thr97, Thr101, Asn140
D35	-116.82	Gluy9, Ser246 Phe100, Asn116	Ser245, Gly99, Thr101, Gly32, Thr97, leu112, Asn140
D36	-113.19	Asn140 Asn166, Phe100, Ser245	Ser245, Met30, Thr101, Val138, Ile31
D37	-114.64	Arg171, Pro246, Thr101, Ser245, Thr97	Gly29, Met30 Gly99,Thr101
D38	-134.13	Asn140, Phe100	Gly99, Thr101, Thr97, Gly29, Met30, leu112,Asn140, Ser245,
D39	-127.22	Gly29, Thr97, Asn140, Pro246	Val138, Gly99, Ser245, Phe100, Thr101, Ile31
D40	-116.41	Ile31, Gly32, Thr97, Asn140, Ser245	Phe100, Val138, Gly29,Gly99

Table-9: Hydrogen bond interaction

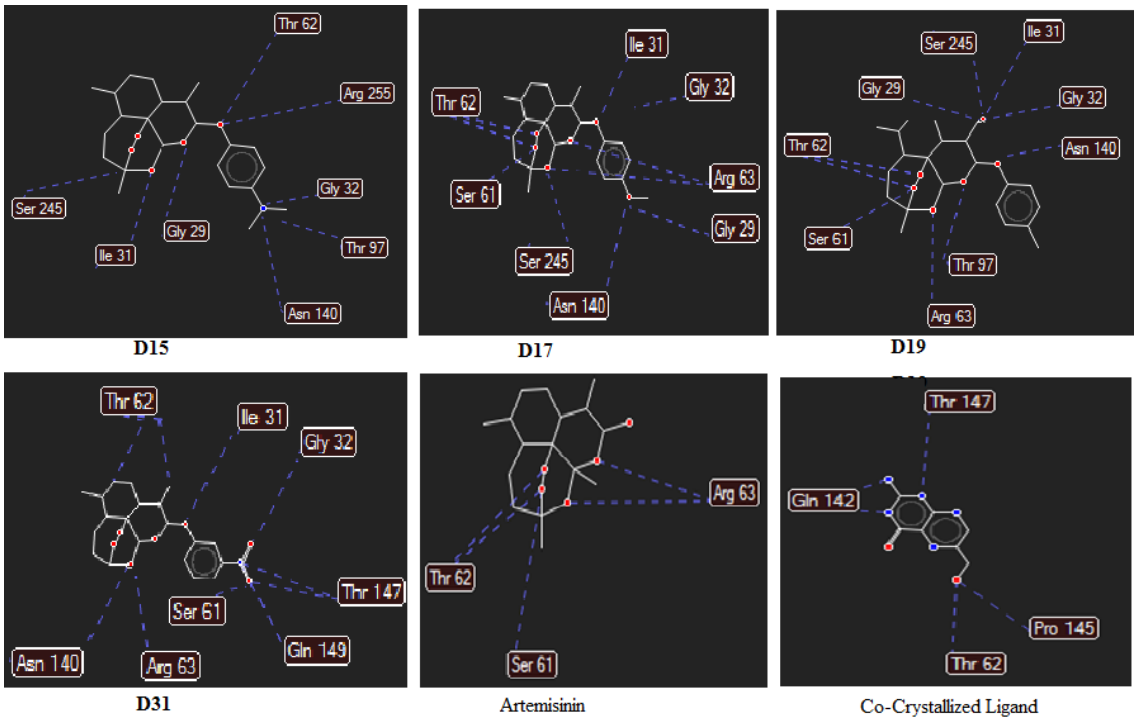

Figure 3: Hydrogen bond interaction of designed compounds, co-crystallized ligand and standard drug Artemisinin

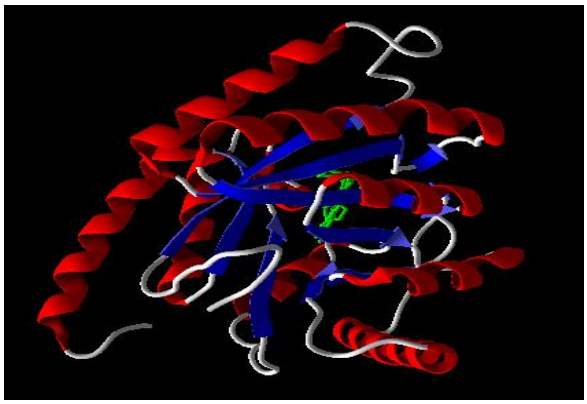

Figure-4: Binding pose of designed ligand in the active site of 1AJ0 (Dihydropteroate Synthase)

7. Conclusion

In Conclusion, Plasmodium parasites of diverse species are the cause of the parasitic disease malaria. However, the evolution of drug resistance to artemisinin is compromising the drug's efficacy, which increases the need for additional antimalarial medications. One of the most prized structures in medicinal chemistry, the Dihydroartemisinin scaffold, is linked to a variety of biological functions, including antimalarial activity. In the current study, the idea of molecular hybridization is used to create hybrid molecules. The objective is to increase efficacy and perhaps stop or delay the development of parasite resistance. A total of 40 different compounds were designed and analysed through online web tools and molecular docking. Compound D15, D17, D19 and D31 have a good interaction with amino acids of PDB: 1AJ0 and also having good hydrogen interaction.

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