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IN-SILICO AND DOCKING STUDIES OF DIHYDROARTEMISININ DERIVATIVES FOR ANTIMALARIAL ACTIVITY

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ABSTRACT

One of the most dangerous and pervasive parasitic diseases in the under developed world is still malaria. In 2022, there was 241 million malaria cases and 6,27,000 deaths were reported worldwide. In present work 80 compounds were designed using dihydroartemisinin as a pharmacophore. In-silico studies like Lipinski Rule of Five, Molinspiration and PreADMET were performed using online available tools. To reveal the ligand - protein binding affinity designed compounds were docked on PDB: 1AJ0 (Dihydropteroate Synthase) using docking software Molegro Virtual Docker. Compound D74 showed strong bonding interaction with GLY29, GLY32, THR97, GLY99, PHE100, THR101 and ASN140 amino acids with high hydrogen bond affinity and best Moldock score- 16.9698 and - 204.1319 respectively.

KEYWORDS: Anti-malaria, Dihydroartemisinin, Molecular docking, Molinspiration, Lipinski rule of five.

1. INTRODUCTION

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.[1]

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."[2]

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*.[3]

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.[4]

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.[5] Due to the high levels of mortality and morbidity caused aby malaria-especially the P. falciparum species-it has placed the greatest selective pressure on the human genome inrecent 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.[6]

2. MATERIAL AND METHODS

For designing of compounds Dihydroartemisinin pharmacophore was selected on the basis of literature study. Chem Draw ultra 8.0 software (2D and 3D) was used for designing ofcompounds and Molegro virtual docker (MVD 2007.2.0) which is available in CADD lab of GRY institute of pharmacy, Borawan. *In-silico* predictions was performed using online available tools: 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, is a general guideline for determining how drug-like a chemical compound is, or how to categorise it as having characteristics that would likely make it an orally active drug in humans. Christopher A. Lipinski intended the idea in 1997. The rule asserts that molecular characteristics, including their absorption, distribution, metabolism, and elimination (ADME), are crucial for a drug's pharmacokinetics in the human body.

Lipinski rule of 5 helps in distinguishing between drug like and non-drug like molecules. It predicts high probability of success or failure due to drug likeness for molecules complying with 2 or more of the following rules:

- ✓ Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms).
- ✓ Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms).
- ✓ A molecular weight less than 500.
- ✓ An octanol-water partition coefficient log P not greater than 5.
- ✓ Molar refractivity should be between 40 and 130.

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 compound's potential for hydrogen bonds is related to TPSA. The calculation of the volume elaborated at Molinspiration is established for group contributors. Numerous rotatable bonds are used to gauge molecular flexibility. By calculating the activity scores of GPCR ligands, ion channel modulators, nuclear receptor ligands, kinase inhibitors, protease inhibitors, and enzyme inhibitors, the bioactivity score of the medicine can be calculated. 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.

2.1.3. PreADMET

PreADMET is a web-based application for predicting ADME data and building drug-like library using *in-silico* method.[25] This program resides entirely on a Web server, and can be accessed by browsers. The application is written mainly in PHP, a scripting language commonly used for Web application which communicates with the browser through a CGI interface. The PHP code in turn uses a set of C program that implement much of the functionality of PreADMET. It consists of four main parts as following: Molecular Descriptor, Druglikeness, ADME prediction and Toxicity prediction.

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.

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.

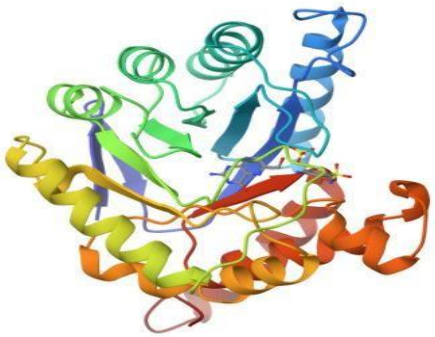


Figure-1: Dihydropteroate Synthase (PDB Code: 1AJ0).

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.

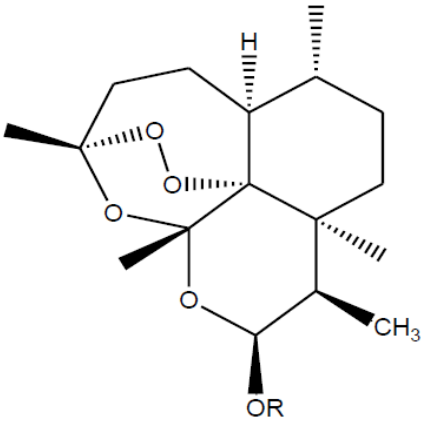


Figure 2: Dihydroartemisinin pharmacophore.

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

S. No.	Compound code	R
1.	D1	3,4-dimethoxyphenyl
2.	D2	Oxan-4-yl
3.	D3	2,5-dimethylphenyl
4.	D4	2,4-dichlorophenoxy
5.	D5	2,4-dichloro phenyl
6.	D6	2- Fluorophenyl
7.	D7	2,4- Bis(2-methylbutan-2-yl) phenoxy
8.	D8	2- methoxy phenyl
9.	D9	1,3-benzodioxol-5-yl
10.	D10	4-propan-2-yl phenoxy
11.	D11	2-methoxyphenyl
12.	D12	4-fluorophenoxy
13.	D13	2- methylphenyl
14.	D14	4-methylphenoxy
15.	D15	4-chlorophenyl
16.	D16	4-methylsulfonylphenyl
17.	D17	4-methylpurazol-1-yl
18.	D18	2,4-di(pentan-2-yl)phenoxy
19.	D19	1,3-dimethyl-2,6-dioxopurin-7-yl
20.	D20	2-methylphenoxy
21.	D21	4-nitrophenoxy
22.	D22	2,3,4,5,6- Pentafluorophenoxy
23.	D23	2,6-dichlorophenyl
24.	D24	4-nitrophenylmethylphenoxy
25.	D25	3-methylphenoxy
26.	D26	3-(trifluoromethyl) phenoxy
27.	D27	3-(5-methyltertrazol-2-yl)
28.	D28	4-ethyl-3,5-dimethylpyrazol-1-yl
29.	D29	2,3,4,5,6-pentafluorophenyl
30.	D30	3,4-dichlorophenyl
31.	D31	4-methoxyphenoxy
32.	D32	3-chlorophenyl
33.	D33	tetrazol-1-yl
34.	D34	2-bicycloheptanyl
35.	D35	3-bromophenoxy
36.	D36	2,3-difluorophenyl
37.	D37	2-bromo-4,5-dimethoxyphenyl
38.	D38	5-methyl-3-pyrazol-1-yl
39.	D39	4-chloro-3-methylpyrazol-1-yl

40.	D40	2,3-dichlorophenyl
41.	D41	3,4,5-trimethoxyphenyl
42.	D42	4-chloro-2-methylphenoxy
43.	D43	3,5-dimethylphenoxy
44.	D44	2,5-dimethylphenoxy
45.	D45	2,3-dimethylphenoxy
46.	D46	7-methoxynaphthalen-1-yl
47.	D47	4-trifluoromethylphenoxy
48.	D48	1,3-benzothiazol
49.	D49	2-chloro-4-fluorophenyl
50.	D50	2,4-dioxo-1,3-thiazolidin-5-yl
51.	D51	4-chloro-3-methylphenoxy
52.	D52	2-chloro-6-fluorophenyl
53.	D53	4-phenylpropan-2-yl
54.	D54	2,4-dichoro-6-methylphenoxy
55.	D55	2,3-dichlorophenoxy
56.	D56	1H-indol-3-yl
57.	D57	2-fluorophenoxy
58.	D58	3,4-dimethylphenoxy
59.	D59	4-chloro-3,5-dimethylphenoxy
60.	D60	4-methylpyrazol-1-yl
61.	D61	3-methyl-1,2-oxazole-5-yl
62.	D62	2-chlorophenoxy
63.	D63	4-ethylphenoxy
64.	D64	3-chloro-4-fluorophenoxy
65.	D65	2,4-difluorophenoxy
66.	D66	4-nitropyrazo-1-yl
67.	D67	Furan-2-yl
68.	D68	3-nitrophenyl
69.	D69	2,4-dibromo-6-methylphenoxy
70.	D70	6-chloro-3-oxo-1,4-benzoxin-4-yl
71.	D71	4-bromo benzene
72.	D72	2-chloro benzene
73.	D73	P-dimethyl amino benzene
74.	D74	2- furaldehyde
75.	D75	4-methoxy benzene
76.	D76	4- methyl benzene
77.	D77	3-nitro benzene
78.	D78	2-dimethyl amino benzene
79.	D79	4-chloro benzene
80.	D80	3,5-chloro benzene

4. RESULT AND DISCUSSIONS

4.1 Lipinski Rule

According to Lipinski's rule, an orally active drug-like molecule shouldn't contain morethan 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, D37, D53, D54, D69, and D70. All the compounds are exhibiting the range of molecular weight. 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
41	D41	492	0	9	4.006	122.721
42	D42	466	0	7	4.006	111.672
43	D43	446	0	7	4.433	114.330
44	D44	446	0	7	4.433	114.330
45	D45	446	0	7	4.200	113.397
46	D46	482	0	7	5.142	127.123
47	D47	486	0	7	4.835	109.858
48	D48	489	0	8	4.564	122.195
49	D49	454	0	6	4.000	105.102
50	D50	441	1	9	2.479	102.454
51	D51	466	0	7	4.006	111.672
52	D52	454	0	6	4.000	105.102
53	D53	536	0	7	6.142	143.427
54	D54	501	0	7	3.887	113.751
55	D55	487	0	7	3.579	109.014

56	D56	441	1	6	4.461	114.922
57	D57	436	0	7	3.955	104.814
58	D58	446	0	7	4.200	113.397
59	D59	480	0	7	4.314	116.409
60	D60	406	0	7	2.942	99.883
61	D61	407	0	8	3.276	97.863
62	D62	452	0	7	3.698	106.935
63	D63	446	0	7	4.378	114.234
64	D64	470	0	7	3.837	106.893
65	D65	454	0	7	4.094	104.772
66	D66	437	0	9	2.479	102.541
67	D67	392	0	7	3.573	95.331
68	D68	447	0	8	3.888	109.720
69	D69	588	0	7	5.650	124.993
70	D70	507	0	9	3.044	119.288
71	D71	430	0	5	5.035	101.597
72	D72	394	0	5	4.154	95.976
73	D73	403	0	6	4.339	108.224
74	D74	340	0	6	3.866	86.163
75	D75	390	0	6	4.281	100.449
76	D76	374	0	5	4.581	98.634
77	D77	405	0	7	4.181	100.552
78	D78	403	0	6	4.339	108.224
79	D79	394	0	5	4.154	95.976
80	D80	428	0	5	4.157	98.262

4.2 Molinspiration

4.2.1 Properties

D1, D2, D9, D11, D16, D17, D20, D21, D28, D33, D38, D39, D41, D50 D60, D61, D67 and D74 compounds are under the range e.g., MilogP is under the range of 5, TPSA is underthe 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.

S. No.	Code	Mi LogP	TPSA	Natoms	MW	nON	NOHNH	N violations	N rotb	Volume
1	D1	4.73	81.71	33	462.54	8	0	0	6	423.34
2	D2	4.18	72.47	29	410.51	7	0	0	4	383.02
3	D3	5.12	81.71	33	462.54	8	0	1	6	423.34
4	D4	6.24	72.47	32	487.38	7	0	1	5	408.31
5	D5	6.36	63.24	31	471.38	6	0	1	4	399.32
6	D6	5.20	63.24	30	420.48	6	0	1	4	377.18
7	D7	8.66	72.47	40	558.76	7	0	2	9	547.21
8	D8	5.09	72.47	31	432.51	7	0	1	5	397.79
9	D9	4.97	81.71	32	446.50	8	0	0	4	396.18
10	D10	6.47	72.47	33	460.57	7	0	1	6	431.18
11	D11	4.57	81.71	32	448.51	8	0	0	6	406.78
12	D12	5.12	72.47	31	436.48	7	0	1	5	386.17
13	D13	5.48	63.24	30	416.51	6	0	1	4	388.81
14	D14	5.41	72.47	31	432.51	7	0	1	5	397.79
15	D15	8.08	72.47	41	597.03	7	0	2	7	497.50
16	D16	3.95	97.38	33	480.58	8	0	0	5	420.24
17	D17	3.73	81.07	29	406.48	8	0	0	4	370.07
18	D18	8.81	72.47	40	558.76	7	0	2	11	548.34

19	D19	3.02	125.08	36	504.54	12	0	2	4	439.27
20	D20	4.57	81.71	32	448.35	8	0	0	6	406.78
21	D21	4.92	118.30	33	463.48	10	0	0	6	404.57
22	D22	5.49	72.47	35	508.44	7	0	2	5	405.89
23	D23	6.34	63.24	31	471.38	6	0	1	4	399.32
24	D24	5.04	109.06	32	447.04	9	0	1	5	395.58
25	D25	5.38	72.47	31	432.51	7	0	1	5	397.79
26	D26	5.83	72.47	34	486.48	7	0	1	6	412.53
27	D27	4.83	106.85	40	556.70	10	0	1	5	512.89
28	D28	4.63	81.07	32	448.56	8	0	0	5	419.94
29	D29	5.61	63.24	34	492.44	6	0	1	4	396.90
30	D30	6.36	63.24	31	471.38	6	0	1	4	399.32
31	D31	5.01	81.71	32	448.51	8	0	1	6	406.78
32	D32	5.73	63.24	30	436.93	6	0	1	4	385.79
33	D33	2.28	106.85	28	394.43	10	0	0	4	345.15
34	D34	5.15	63.24	30	420.55	6	0	1	4	396.85
35	D35	5.74	72.47	31	497.38	7	0	1	5	399.12
36	D36	5.31	63.24	31	438.47	6	0	1	4	382.11
37	D37	5.46	81.71	34	541.43	8	0	2	6	441.23
38	D38	4.71	81.07	33	474.48	8	0	0	5	401.32
39	D39	4.18	81.07	30	440.92	8	0	0	4	383.56
40	D40	6.34	63.24	31	471.38	6	0	1	4	399.32
41	D41	4.71	90.94	35	492.56	9	0	0	7	448.89
42	D42	6.01	72.47	32	466.96	7	0	1	5	411.33
43	D43	5.78	72.47	32	446.54	7	0	1	5	414.36
44	D44	5.78	72.47	32	446.54	7	0	1	5	414.36
45	D45	5.76	72.47	32	446.54	7	0	1	5	414.36
46	D46	6.15	81.71	36	498.57	8	0	1	6	450.77
47	D47	5.85	72.47	34	486.48	7	0	1	6	412.53
48	D48	5.02	85.37	34	489.59	8	0	1	6	428.58
49	D49	5.85	63.24	31	454.92	6	0	1	4	390.72
50	D50	2.58	109.41	30	441.50	9	1	0	4	375.32
51	D51	6.01	72.47	32	466.96	7	0	1	5	411.33
52	D52	5.83	63.24	31	454.92	6	0	1	4	390.72
53	D53	7.34	72.47	39	536.66	7	0	2	7	502.27
54	D54	6.62	72.47	33	501.40	7	0	2	5	424.87
55	D55	6.22	72.47	32	487.38	7	0	1	5	408.31
56	D56	5.23	79.03	32	441.52	7	1	1	4	401.23
57	D57	5.07	72.47	31	436.48	7	0	1	5	386.17
58	D58	5.78	72.47	32	446.54	7	0	1	5	414.36
59	D59	6.39	72.47	33	480.99	7	0	1	5	427.89
60	D60	3.73	81.07	29	406.48	8	0	0	4	370.02
61	D61	4.02	89.27	29	407.46	8	0	0	4	366.22
62	D62	5.59	72.47	31	452.93	7	0	1	5	394.77
63	D63	5.87	72.47	32	446.54	7	0	1	6	414.60
64	D64	5.73	72.47	32	470.92	7	0	1	5	399.70
65	D65	5.21	72.47	32	454.47	7	0	1	5	391.10
66	D66	3.24	126.89	31	437.45	11	0	1	5	376.79
67	D67	4.34	76.38	28	392.45	7	0	0	4	353.82
68	D68	5.01	109.06	32	447.48	9	0	1	5	395.58
69	D69	6.88	72.47	33	598.30	7	0	2	5	433.56
70	D70	4.58	92.78	35	507.97	9	0	1	4	432.50
71	D71	5.90	46.17	27	439.35	5	0	1	2	354.35
72	D72	5.72	46.17	27	394.89	5	0	1	2	350.00
73	D73	5.20	49.41	29	403.52	6	0	1	3	382.37
74	D74	4.24	59.31	25	340.41	6	0	0	2	318.03
75	D75	5.15	55.40	28	390.48	6	0	1	3	362.01
76	D76	5.54	46.17	27	374.48	5	0	1	2	353.02

77	D77	5.03	91.99	29	405.45	8	0	1	3	359.80
78	D78	5.15	49.41	29	403.52	6	0	1	2	382.37
79	D79	5.77	46.17	27	394.89	5	0	1	2	350.00
80	D80	5.94	48.25	27	428.37	5	0	1	2	369.84

4.2.2 Bioactivities

- **GPCR Ligand:** Among the 80 compounds D2, D7, D15, D36, D78 are the activecompounds (>0), hence all the compounds are moderately active (<0).
- **Ion channel modulator:** All the 80 compounds are moderately active (<0).
- **Kinase inhibitor:** All the 80 compounds are moderately active (<0).
- **Nuclear receptor ligand:** Among the 80 compounds D17, D19, D27, D28, D33, D37, D38, D39, D48, D60, D66, D67, D69, D70 are moderately active (<0), hence all the compounds are highly active (>0).
- **Protease inhibitor:** Among all the 80 compounds D2, D5, D6, D9, D13, D15, D16, D22, D23, D29, D30, D32, D33, D34, D36, D40, D47, D52, D56, D61 are highly active(>0), hence all the compounds are moderately active (<0).
- **Enzyme inhibitor:** All the 80 compounds are highly active (>0).

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
41	D41	-0.06	-0.22	-0.34	0.03	-0.02	0.26
42	D42	-0.10	-0.34	-0.43	0.13	-0.10	0.20
43	D43	-0.09	-0.35	-0.43	0.12	-0.05	0.23
44	D44	-0.11	-0.37	-0.44	0.13	-0.09	0.20
45	D45	-0.09	-0.37	-0.46	0.14	-0.06	0.23
46	D46	-0.03	-0.30	-0.28	0.16	-0.01	0.27
47	D47	-0.02	-0.21	-0.33	0.23	0.01	0.25
48	D48	-0.13	-0.36	-0.36	-0.26	-0.01	0.20
49	D49	-0.01	-0.21	-0.35	0.12	-0.01	0.25
50	D50	-0.08	-0.77	-1.08	0.06	-0.27	0.15
51	D51	-0.13	-0.38	-0.48	0.10	-0.13	0.18
52	D52	-0.06	-0.20	-0.43	0.10	0.01	0.27
53	D53	-0.02	-0.36	-0.40	0.12	-0.02	0.18
54	D54	-0.12	-0.35	-0.46	0.13	-0.12	0.19
55	D55	-0.06	-0.37	-0.44	0.12	-0.14	0.22
56	D56	0.14	-0.08	-0.18	0.12	0.10	0.40
57	D57	-0.06	-0.35	-0.36	0.14	-0.03	0.27
58	D58	-0.09	-0.36	-0.43	0.13	-0.06	0.22
59	D59	-0.13	-0.42	-0.52	0.12	-0.18	0.18
60	D60	-0.13	-0.44	-0.37	-0.28	-0.17	0.24
61	D61	-0.06	-0.14	-0.44	0.04	0.01	0.29
62	D62	-0.10	-0.35	-0.38	0.12	-0.10	0.23
63	D63	-0.06	-0.28	-0.43	0.15	-0.01	0.27
64	D64	-0.07	-0.33	-0.33	0.17	-0.08	0.21
65	D65	-0.05	-0.34	-0.32	0.15	-0.01	0.27
66	D66	-0.39	-0.54	-0.48	-0.51	-0.38	0.09
67	D67	-0.12	-0.35	-0.55	-0.05	-0.07	0.26
68	D68	-0.14	-0.21	-0.47	0.03	-0.05	0.22
69	D69	-0.23	-0.45	-0.52	-0.04	-0.23	0.17
70	D70	-0.04	-0.34	-0.58	-0.07	-0.03	0.12
71	D71	-0.10	-0.23	-0.34	0.05	-0.09	0.25
72	D72	-0.04	-0.22	-0.28	0.14	-0.08	0.27
73	D73	-0.00	-0.17	-0.25	0.15	-0.01	0.28
74	D74	-0.01	-0.20	-0.36	0.03	-0.08	0.29
75	D75	-0.03	-0.19	-0.30	0.11	-0.02	0.28
76	D76	-0.04	-0.22	-0.34	0.13	-0.03	0.27
77	D77	-0.15	-0.21	-0.40	0.02	-0.13	0.18
78	D78	0.03	-0.19	-0.26	0.12	-0.03	0.26
79	D79	-0.01	-0.16	-0.32	0.13	-0.02	0.29
80	D80	-0.12	-0.18	-0.37	0.12	-0.11	0.27

5. PreADMET

5.1 Druglikeness

- **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 druglikeness are described below in table no. 5.

Table-5: Results of Druglikeness.

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, D42, D43, D44, D45, D46, D47, D49, D50, D51, D52, D54, D55, D56, D57, D58, D59, D60, D61, D62, D64, D65, D66, D67, D68, D69, D70, D71, D72, D73, D74, D75, D76, D77, D78, D79, D80
	Drug like	D1, D3, D7, D10, D11, D15, D18, D20, D31, D37, D41, D48, D53, D63
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, D41, D42, D43, D44, D45, D46, D47, D48, D49, D50, D51, D52, D55, D56, D57, D58, D59, D60, D61, D62, D63, D64, D65, D66, D67, D68, D71, D72, D73, D74, D75, D76, D77, D78, D79, D80
	Violated	D7, D15, D18, D19, D22, D27, D37, D53, D54, D69,D70.

5.2 ADME

- **BBB-** All the compounds are the CNS inactive compounds except D7, D18, D56 andD72.
- **CaCO2-** All the compounds have moderately permeability.
- **HIA-** All the compounds have higher absorption.
- **MDCK-** All the compounds have lower absorption except D72 have higher absorption.
- **PPB-** All the compounds are strongly bounded except D2, D17, D19, D27, D33 andD66.
- **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
41	D41	0.139	52.085	98.697	0.044	90.061	-3.129
42	D42	0.139	34.268	98.543	0.051	97.491	-2.702
43	D43	0.124	53.131	98.886	0.051	92.397	-2.578
44	D44	0.111	52.800	98.886	0.048	92.313	-2.534
45	D45	0.109	52.800	98.886	0.049	92.063	-2.511
46	D46	0.068	49.954	97.832	0.043	92.480	-2.515
47	D47	0.082	37.944	98.883	0.048	92.585	-1.816
48	D48	0.504	47.434	99.364	0.591	99.62	-3.630
49	D49	0.199	32.784	97.940	0.044	95.356	-2.970
50	D50	0.015	9.869	84.983	0.055	91.676	-4.045
51	D51	0.155	34.265	98.546	0.055	97.492	-2.699
52	D52	0.201	32.719	97.940	0.043	96.153	-2.934
53	D53	0.174	54.961	97.631	2.343	96.171	-1.126
54	D54	0.232	35.621	97.846	0.044	100	-2.684
55	D55	0.136	34.313	97.975	0.047	100	-2.699
56	D56	2.619	36.296	93.639	0.047	90.078	-3.186
57	D57	0.067	50.352	98.818	0.063	93.129	-2.995
58	D58	0.111	52.290	98.886	0.057	92.058	-2.533
59	D59	0.220	35.515	98.393	0.046	96.605	-2.678
60	D60	0.462	44.498	97.620	0.072	90.407	-3.792
61	D61	0.373	29.511	95.402	0.076	91.713	-3.635
62	D62	0.085	32.924	98.677	0.063	100	-2.711
63	D63	0.095	52.564	98.886	0.260	93.118	-2.391
64	D64	0.119	34.393	98.668	0.048	100	-3.116
65	D65	0.119	50.196	98.825	0.047	95.312	-3.276
66	D66	0.160	5.964	78.513	0.060	88.098	-3.731

67	D67	0.099	48.722	97.605	0.160	93.576	-2.973
68	D68	0.031	11.403	93.166	0.046	90.902	-2.607
69	D69	0.270	32.984	97.513	0.018	100	-2.330
70	D70	0.154	25.629	99.442	0.043	91.071	-3.698
71	D71	0.162	39.400	97.475	0.025	100	-2.429
72	D72	1.499	22.281	100	204.401	100	-1.866
73	D73	0.369	51.947	97.629	0.053	92.124	-2.948
74	D74	0.097	54.680	98.126	17.577	95.483	-3.101
75	D75	0.148	51.963	98.151	0.099	96.527	-2.733
76	D76	0.639	55.327	97.740	0.286	96.477	-2.328
77	D77	0.014	31.977	95.453	0.047	95.453	-2.760
78	D78	0.322	54.389	97.629	0.082	92.380	-2.932
79	D79	0.811	44.710	97.494	0.234	100	-2.603
80	D80	0.073	51.365	98.876	0.100	92.322	-2.555

5.3 Toxicity

- **Ames test-** The compounds D21, D24, D35, D37, D61, D66, D67, D68, D69, D71,D73, D74, D75, D77, D78 are in the range of mutagen are changing the DNA and show the gene mutation. And the non-mutagen compounds did not affect the DNA.
- **Carcino mouse-** The compounds which are positive D15, D26, D55, D57, D63, D71, D72 and D75 can cause cancer in carcino mouse and the compounds which are negative are safe.
- **Carcino rat-** The compounds D2, D13, D17, D24, D27, D28, D33, D34, D38, D50,D60, D61, D65, D66, D67, D73, D74, D75 and D78 can cause cancer in carcino rats and the compounds which are negative are safe.
- **hERG inhibition-** The compounds D6, D15, D17, D19, D27, D28, D33, D38, D39, D46, D53, D56, D60 and D66 are have medium risk2 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, D61, D66, D67, D68, D69, D71, D73, D74, D75, D77, D78.
	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,D41, D42, D43, D44, D45, D46, D47, D48, D49, D50, D51, D52, D53, D54, D55, D56, D57, D58, D59, D60, D62, D63, D64, D65, D70, D72, D76, D79, D80.
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, D41, D42, D43, D44, D45, D46, D47, D48, D49, D50, D51, D52, D53, D54, D56, D58, D59, D60, D61, D62, D64, D65, D66, D67, D68, D69, D70, D73, D74, D76, D77, D78. D79, D80.
	Positive	D15, D26, D55, D57, D63, D71, D72, D75.
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, D40, D41, D42, D43, D44, D45, D46, D47, D48, D49, D51, D52, D53, D54, D55, D56, D57, D58, D59, D62, D63, D64, D68, D69, D70, D71, D72, D76, D77, D79, D80.

	Positive	D2, D13, D17, D24, D27, D28, D33, D34, D38, D50, D60, D61, D65, D66, D67, D73, D74, D75, D78.
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, D41, D42, D43, D44, D45, D47, D48, D49, D50, D51, D54, D55, D57, D58, D59, D61, D62, D63, D64, D65, D67, D68, D69, D70, D71, D72, D73, D74, D75, D76, D77, D78, D79, D80.
	MediumRisk	D6, D15, D17, D19, D27, D28, D33, D38, D39, D46, D53, D56, D60, D66.

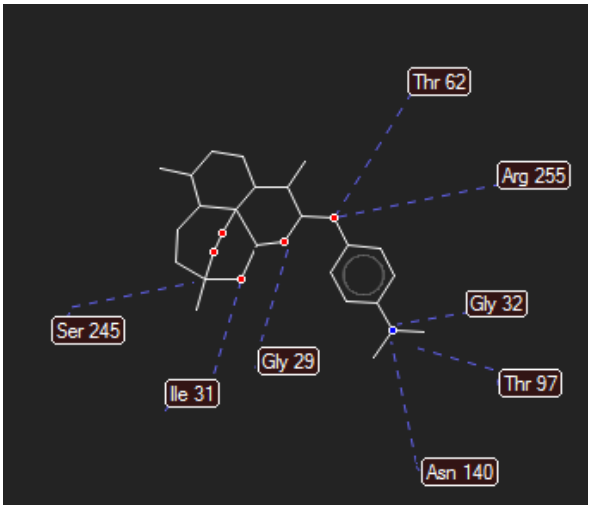
6. Docking study

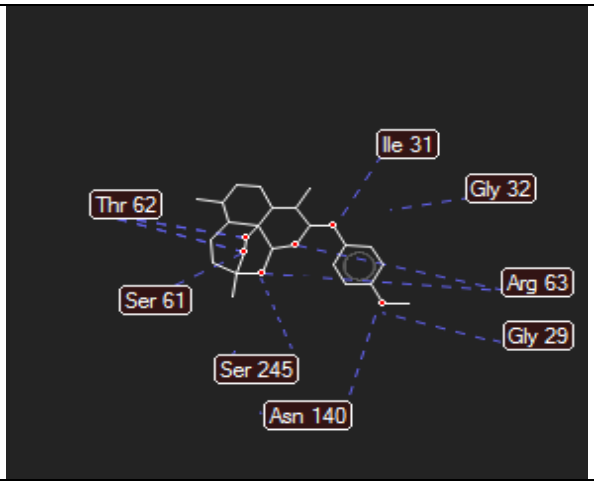
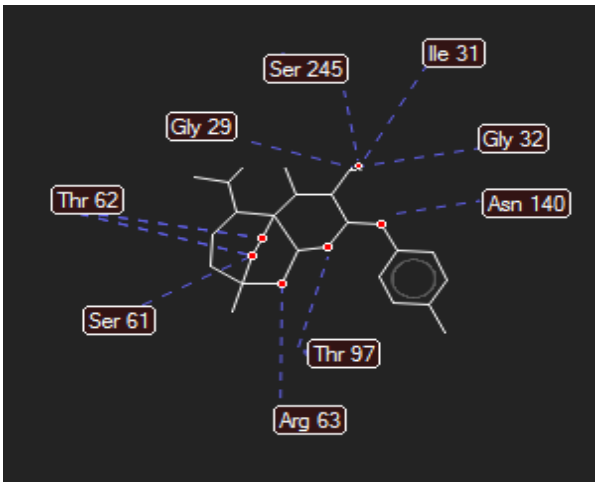
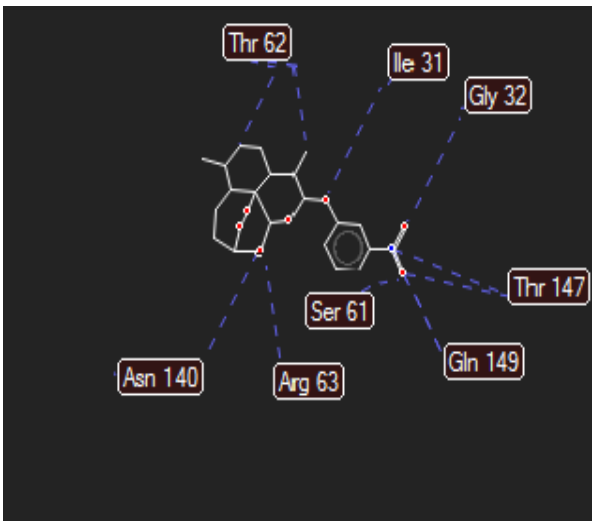
Working with Molegro, molecular docking studies were conducted to obtain insights into the inhibitors' binding affinities and interaction patterns. Table no .8 and 9.

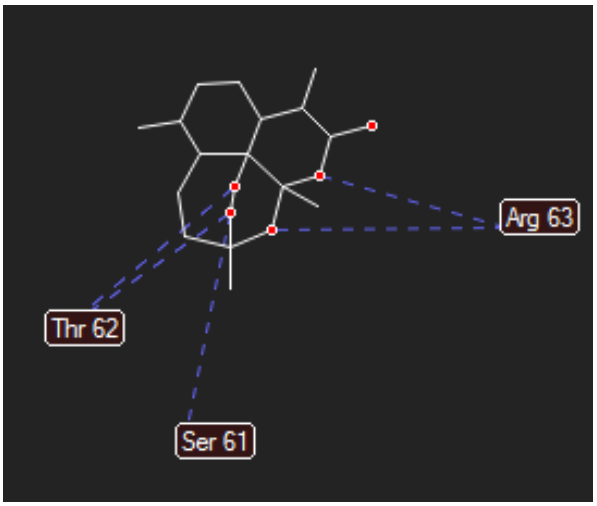
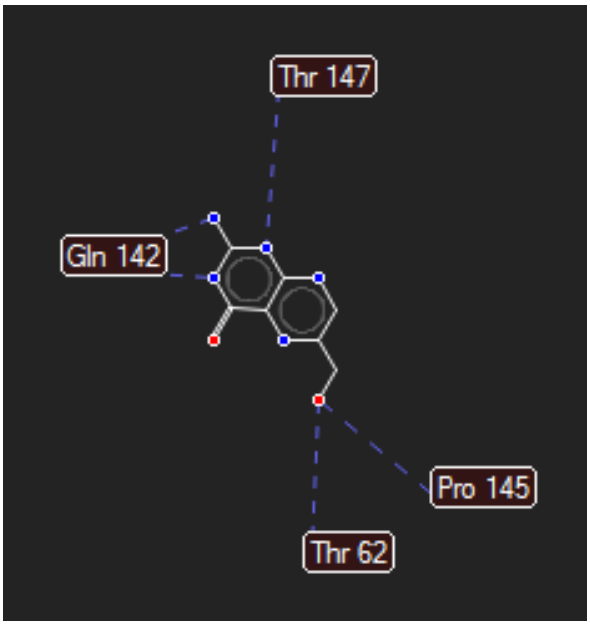
Table-8: Results of docking study.

S. No.	Code	MolDock Score	HBond	Hydrogen Bond Interaction	Steric Interaction
1.	D74	-204.1319	-16.9698	Arg109, Thr101, Asn140	Gly32, Thr97, Phe100, Gly99, Thr101, Gly29, Met30, leu112, Asn140, Ser245, Ile31
2.	D75	-198.5608	-13.80715	Ile31, Gly32, Arg63, Gly29, Asn140, Ser245, Ser61, Thr62	Phe100, Gly99, Thr101, Gly32, Thr97,Gly29, Met30, Asn140, Ser245, Val138, Ile31,
3.	D76	199.1346	-10.412953	Ile31, Gly32, Arg63, Gly29, Asn140, Ser245, Ser61, Thr62, Thr97	Asn140, Ser245, Phe100, Gly99, Thr101, Thr97, Gly29,Met30, leu112, Val138,Ile31
4.	D77	-199.2446	-14.77291	Thr62, Ile31, Gly32, Thr147,Gln149, Ser61, Arg63, Asn140.	leu112, Ser245, Val138, Ile31, Phe100, Gly99, Thr101, Gly32, Thr97, Gly29, Met30

Table-9: Hydrogen bond interaction.

S. No.	Code	H-Bond Interaction
1.	D74	

2.	D75	
3.	D76	
4.	D77	

5.	Standard Artemisinin	
6.	Co-Crystal	

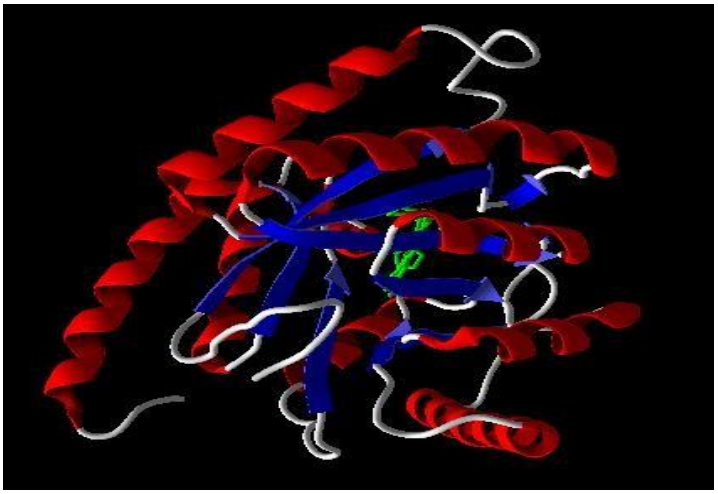


Figure-4: Proposed binding mode of ligands in the active site.

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 80 different compounds were designed and analysed through molecular docking. Compound D73, D74, D75, D76 and D77 have a good interaction with amino acids of PDB: 1AJ0 and also having good hydrogen interaction.

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