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De Novo Drug Design of Shorter Chain Peptides as Potent Target for Antimalarial Activity

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ABSTRACT

De Novo drug design aims at predicting the peptide leads for anti-malarial activity from the designed set of 200 templates (Dipeptide, tripeptide, tetrapeptide and pentapeptide 50 each). Lipinski rules of 5, Molinspiration and Swiss-dock strategy was applied to identify the most potent antimalarial lead against various enzyme targets. Initially, 43 compounds were selected from 200 templates through Lipinski filters and upon subjected to molinspiration further, only 5 leads (Arg-Ser, Asn-Ser, Pro-Lys-Ser, Pro-Lys-Gly and Pro-Lys-Thr) were identified and selected as good targets for enzyme dihydrofolate Reductase (DHFR), Dihydro Orotate Dehydrogenase (DHOD) and aspartic proteinase. Among the docking results obtained with all the three enzyme targets, we found that the dipeptide Arg-Ser is the most potent lead target against malarial enzyme DHFR, aspartic proteinase and DHOD with their corresponding full fitness energy -302413.88 kcal/mol, -287460.67 kcal/mol and -453848.82 kcal/mol respectively. Dipeptide Asn-Ser was identified as the second most lead against malarial enzyme DHFR, aspartic proteinase and DHOD with their full fitness energy -285057.65 kcal/mol, -264788.72 kcal/mol and -425186.51 kcal/mol respectively. The above findings clearly shows that dipeptide Arg-Ser and Asn-Ser are potent targets against malaria and can be explored further to test in vitro, in vivo potency to validate therapeutic efficacy through structured based drug design.

Keywords: DHFR, DHOD, Aspartic proteinase, Peptides

INTRODUCTION

Drug discovery is not only a simple "synthesize and test" drudgery. Peptides basically, are the key regulators in cellular and intercellular physiological responses and possess the potential to treat various pathological conditions [1]. Malaria is a disease which occurs by the growth of the parasite *Plasmodium* in the erythrocyte. Various cellular and molecular strategies allow the parasite to evade the human immune response for many cycles of parasite multiplication. Under certain circumstances *Plasmodium* infection causes severe anemia or cerebral malaria; the expression of disease is influenced by both parasite and host factors, as exemplified by the exacerbation of disease during pregnancy [2]. Plasmodium falciparum Dihydrofolate Reductase (Pf DHFR) enzyme is one of the most important targets in the treatment of malaria using typical antifolates such as cycloguanil and pyrimethamine. The synthesis of pyrimidine in *Plasmodium* by *de novo* pathway, which does not occur in human. This step makes the enzyme a valuable target for the therapeutic agents. The drugs targeting the DHFR enzyme bind selectively to it in different species [3,4]. Thus, design and discovery of new potential Pf DHFR inhibitors, equally active against both the wild-type and mutant strains, is an urgent need. Dihydro Orotate Dehydrogenase (DHOD) is a flavoenzyme that utilizes in the oxidation of L-dihydro orotate (L-DHO) to orotate as part of the fourth and rate-limiting step of the *de novo* pyrimidine biosynthetic pathway [5]. *Plasmodium* species lack pyrimidine salvage enzymes, and unlike humans, and depend on the *de novo* pathway to acquire pyrimidines for DNA and RNA synthesis. A key step in this pathway is catalyzed by DHOD [6]. Aspartic proteinases have a role in degradation of haemoglobin in malarial food vacuole. Erythrocytic malaria parasites degrade hemoglobin in the acidic environment of food vacuole to provide amino acids for parasite protein synthesis [7,8]. The food vacuole of *P. falciparum* contains the cysteine protease falcipain and the aspartic proteinases plasmepsin I and plasmepsin II [9,10]. Each of these proteases degrades hemoglobin *in vitro* and it has been proposed that the enzymes act in a concerted manner to hydrolyze globin to small peptides or free amino acids [7,8].

Objective

Our objective is to subject various shorter chain dipeptides, tripeptides, tetrapeptides and pentapeptides and finding a suitable lead molecule with rational drug design approach through Lipinski rules, Molinspiration and Swiss Dock strategy.

MATERIALS AND METHODS

The system used in this research work is an HP pavilion Laptop with Intel® Celeron®, having CPU of 1.60 GHz, 2GB RAM, 64 bit operating system and windows 10 Pro. The various sites used in the research work to estimate different parameters are:

- Lipinski rule of 5.
- Molinspiration.
- Swiss dock.

Methodology

We have short-listed some amino acids which were having the potential antimalarial activity according to the literature review, which is mandatory in all the combinations and the rest of amino acids in combination were selected by hit and trial approach for the study. In total 200 combinations of the peptides were subjected to Lipinski rules of 5 initially in which 50 dipeptides, 50 tripeptides, 50 tetrapeptides and 50 pentapeptides are chosen for the study as given in Table 1 of results section. Six amino acids (namely lysine, glycine, arginine, asparaginine, proline and serine) were being kept as compulsory amino acid in all the combinations of dipeptides, tripeptides, tetrapeptides and pentapeptides as from past and recent literature surveys. Remaining amino acids present in the combinations of di, tri, tetra and pentapeptides were randomly placed and subjected for the present study.

Lipinski rule

In drug discovery, an increase in the lipophilicity and molecular weight are often observed in order to improve the affinity and selectivity of the drug candidate. The rule of five includes the following parameters: Molecular weight-Should be less than 500, log P (the logarithm of the partition coefficient between water and 1-octanol)-Should be less than 5. Number of groups in the molecule that can donate hydrogen to hydrogen bonds-Should be less than 5. Number of groups that can accept hydrogen atoms to form hydrogen bond-Should be less than 10. The rules, based on the 90-percentile values of the drugs proper distributions, apply only to absorption by passive diffusion compounds through cell membrane; compounds that are active transported through cell membranes by transporter proteins are exceptions to the rule [11].

Molinspiration

Molinspiration is web based software used to obtain parameter such as Moriguchi's logP (MLogP), Topological Polar Surface Area (TPSA), drug likeness. Mi log P parameter determines the permeability across the cell membrane. Partition coefficient or Log P is an important parameter used in rational drug design to measure molecular hydrophobicity. Hydrophilic/Lipophilic nature of drug molecule affects drug absorption, bioavailability, drug-receptor interactions, metabolism of molecules, as well as their toxicity. TPSA is calculated based as a sum of fragment contributions of O- and N- centered polar fragments. TPSA is closely related to the hydrogen bonding potential of a molecule and is a very good predictor of drug transport properties such as intestinal absorption, bioavailability, Blood Brain Barrier (BBB) penetration etc., calculation of volume developed at Molinspiration is based on group contributors. Number of rotatable bonds measures molecular flexibility. It is a very good descriptor of absorption and bioavailability of drugs. Through drug likeness data of molecule, it can be checked molecular properties and structure feature in respect to known drugs [12].

The Swiss Dock web server

A large interest for docking web servers has emerged recently, as can be seen through the growing list of similar web services currently available, such as [13]:

- Blaster [14].
- DockingAtUTMB (http://docking.utmb.edu/).
- Pardock (http://www.scfbio-iitd.res.in/dock/pardock.jsp).
- PatchDock (http://bioinfo3d.cs.tau.ac.il/PatchDock/).
- MetaDock (http://dock.bioinfo.pl/).
- PPDock (http://140.112.135.49/ppdock/index.html).
- MEDock (http://medock.ee.ncku.edu.tw/).
- With the Swiss Dock web site aims at extending the use of protein-small molecule docking software far beyond experts in the field by providing convenient answers to many of the difficulties. Initially, manually curated protein structures can be downloaded from the web site and original PDB files can be prepared through ad hoc scripts [14]. Second, the docking software is easily accessible through either a web browser or a programmatic interface. Third, predicted Binding Modes (BMs) can be viewed online with a simple embedded applet or analyzed in more details thanks to a seamless integration with the UCSF Chimera molecular viewer [15], with the help of the online documentation and the user community.

Swiss dock

SwissDock is a docking web server. The structure of the target protein, as well as that of the ligand, can be automatically prepared for docking. All calculations are performed on the server side, so that docking runs do not require any computational power from the user. The interpretation of docking results and their integration into existing research pipelines is greatly facilitated by the seamless visualization of docking predictions in the UCSF Chimera molecular viewer, which can be launched directly from the web browser.

Web interface

Inputs

Only 3 steps are required to start a docking assay through the web interface of Swiss Dock: users must define a protein structure, one or several putative ligands and docking parameters. They are guided throughout this short and simple submission process by a comprehensive contextual help.

Target selection

A target protein structure can be determined either by specifying its Protein Data Bank code [16] or by uploading structure files. The first option allows users who are not familiar with 3D structure files to start a docking assay with only a PDB code. If several PDB records are available for the same target, those with a high resolution and a ligand similar to the one that will be docked should be considered first.

Ligand selection

A ligand can be uploaded in the mol2 format or by specifying its identifier from the ZINC database [17]. The latter allows uploading several ligands at once or uploading ligands that are not present in the ZINC database.

Outputs

After a docking assay has been submitted, it can be tracked by the URL provided on the submission confirmation page. If an (optional) email address has been specified in the submission form, the URL will also be sent to the user by email, as well as a link to the docking result web page once the docking is completed.

RESULTS AND DISCUSSION

The designed 200 peptides were subjected to Lipinski rules of 5 using the software online on the website of IIT Delhi bio-informatics and its results are tabulated in Table 1 [18,19].

Table 1: Results of Lipinski rules of 5 for the designed peptides

Dipeptide molecule						
S. No.	**Molecule**	**Mass**	**Hydrogen bond donor**	**Hydrogen bond acceptor**	**Log P**	**Molar refractivity**
1	Lys-Ile	248	2	6	-0.28	67.14
2	Lys-Ser	223	4	7	-2.06	54.05
3	Lys-Arg	293	7	9	-1.26	78.63
4	Lys-Lys	265	5	7	-0.19	71.62
5	Lys-Phe	286	4	6	-0.01	78.35
6	Lys-Asn	269	6	8	-1.49	69.53
7	Lys-Pro	240	4	6	0.01	63.99
8	Lys-Glu	269	4	8	-2.25	63.32
9	Lys-Gly	198	4	6	-1.15	50.14
10	Lys-Tyr	302	6	7	-1.25	79.44
11	Arg-Ile	280	6	8	-0.89	75.52
12	Arg-Ser	251	6	9	-3.14	61.05
13	Arg-Lys	291	7	9	-1.48	78.53
14	Arg-Leu	280	6	8	-0.89	75.52
15	Arg-Phe	312	6	8	-0.59	83.94
16	Arg-Asn	283	10	10	-3.91	68.99
17	Arg-Pro	268	6	8	-1.06	70.99
18	Arg-Glu	297	6	10	-3.37	70.33
19	Arg-Arg	321	10	11	-2.69	84.80
20	Arg-Tyr	330	7	9	-1.76	86.51
21	Leu-Ile	237	3	5	0.32	65.31
22	Leu-Ser	210	3	6	-1.69	50.94
23	Leu-Glu	252	4	6	0.17	68.51
24	Leu-Gln	254	5	7	-1.37	64.31
25	Leu-Leu	237	3	5	0.32	65.31
26	Leu-Phe	273	3	5	0.35	75.24
27	Leu-Asn	240	5	7	-1.76	59.69
28	Leu-Pro	227	2	5	0.32	60.84
29	Leu-Gly	183	2	5	-1.16	45.17
30	Leu-Tyr	289	4	6	-0.32	76.40
31	Asn-Ile	240	5	7	-1.76	59.69
32	Asn-Ser	213	5	8	-3.78	45.32
33	Asn-Lys	253	7	8	-2.70	62.72
34	Asn-Glu	259	6	9	-4.54	54.52
35	Asn-Gln	257	7	9	-3.46	58.69
36	Asn-Phe	276	5	7	-1.73	69.62
37	Asn-Asn	243	8	9	-4.42	54
38	Asn-Gly	186	4	7	-3.25	39.55
39	Asn-Tyr	292	7	8	-2.97	70.71
40	Asn-His	266	6	9	-2.86	64.59
41	Pro-Ile	221	3	4	-0.01	58.27
42	Pro-Ser	194	3	5	-2.03	43.89

43	Pro-Glu	243	6	6	-0.36	58.36
44	Pro-Gln	238	5	6	-1.71	57.26
45	Pro-Val	209	3	4	-0.18	53.74
46	Pro-Phe	257	3	4	0.01	68.20
47	Pro-Asn	224	5	6	-2.10	52.65
48	Pro-Pro	209	3	4	-0.38	55.12
49	Pro-Gly	167	2	4	-1.50	38.13
50	Pro-Tyr	273	4	5	-0.66	69.36
Tripeptide molecules						
S. No.	**Molecule**	**Mass**	**Hydrogen bond donor**	**Hydrogen bond acceptor**	**Log P**	**Molar refractivity**
51	Lys-Arg-Ile	404	10	11	-1.01	110.94
52	Lys-Arg-Ser	377	11	12	-3.60	96.50
53	Lys-Arg-Lys	417	12	12	-1.95	113.98
54	Lys-Arg-Leu	417	11	12	-1.38	114.05
55	Lys-Arg-Phe	438	10	11	-1.58	118.69
56	Lys-Arg-Asn	407	12	13	-3.31	106.08
57	Lys-Arg-Pro	394	10	11	-1.71	107.27
58	Lys-Arg-Glu	423	11	13	-3.71	105.77
59	Lys-Arg-Gly	352	10	11	-2.13	92.66
60	Lys-Arg-Thr	392	10	12	-2.69	101.67
61	Arg-Leu-Ile	391	9	10	-0.63	107.65
62	Arg-Leu-Ser	363	8	11	-1.57	93.21
63	Arg-Leu-Lys	411	12	11	0.74	117.00
64	Arg-Leu-Phe	427	9	10	-0.82	118.52
65	Arg-Leu-Asn	392	10	12	-2.60	102.95
66	Arg-Leu-Pro	383	9	10	-0.68	107.76
67	Arg-Leu-Glu	408	8	12	-2.72	103.46
68	Arg-Leu-Gly	335	6	10	-1.70	88.19
69	Arg-Leu-Thr	379	10	11	-2.67	97.73
70	Arg-Leu-Tyr	441	9	11	-1.16	119.66
71	Leu-Asn-Ile	349	6	9	-1.25	91.47
72	Leu-Asn-Ser	324	7	10	-3.81	78.46
73	Leu-Asn-Lys	364	8	10	-1.53	95.95
74	Leu-Asn-Phe	387	7	9	-1.12	102.77
75	Leu-Asn-Pro	341	7	9	-1.10	88.41
76	Leu-Asn-Glu	370	7	11	-2.33	88.56
77	Leu-Asn-Gly	297	6	9	-2.64	72.70
78	Leu-Asn-Thr	341	8	10	-1.83	85.27
79	Leu-Asn-Tyr	403	8	10	-1.80	103.73
80	Leu-Asn-Leu	351	7	9	-1.16	92.84
81	Asn-Pro-Ile	341	7	9	-1.10	88.41
82	Asn-Pro-Ser	314	7	10	-3.12	74.04
83	Asn-Pro-Lys	352	8	10	0	0
84	Asn-Pro-Phe	377	7	9	-1.06	98.34
85	Asn-Pro-Glu	360	7	11	-3.31	83.31
86	Asn-Pro-Gly	287	6	9	-2.59	68.27
87	Asn-Pro-Thr	331	8	10	-1.71	80.84
88	Asn-Pro-Tyr	393	8	10	-1.74	99.50
89	Asn-Pro-Leu	337	7	9	-1.57	86.20
90	Asn-Pro-Gln	354	8	11	-3.05	58.20
91	Pro-Lys-Ile	349	7	7	-2.67	93.68
92	Pro-Lys-Ser	318	6	8	-4.64	78.92
93	Pro-Lys-Phe	383	7	7	-2.86	103.51
94	Pro-Lys-Glu	366	7	9	-5.10	88.49
95	Pro-Lys-Gly	293	6	7	-4.38	73.44
96	Pro-Lys-Thr	337	8	8	-3.56	86.01
97	Pro-Lys-Tyr	399	8	8	-3.54	104.67
98	Pro-Lys-Leu	347	7	7	-2.89	93.58
99	Pro-Lys-Gln	360	7	10	-2.19	90.06
100	Pro-Lys-Val	335	7	7	-3.06	89.06
Tetrapeptide molecule						
S. No.	**Molecule**	**Mass**	**Hydrogen bond donor**	**Hydrogen bond acceptor**	**Log P**	**Molar refractivity**
101	Asn-Arg-Leu-Ile	505	13	14	-2.13	135.36
102	Asn-Arg-Leu-Ser	478	12	15	-3.79	121.82
103	Asn-Arg-Leu-Asn	508	14	16	-3.86	130.57
104	Asn-Arg-Leu-Gln	522	15	16	-3.83	134.36
105	Asn-Arg-Leu-Phe	541	13	14	-2.10	145.29
106	Asn-Arg-Leu-Arg	548	15	17	-2.99	146.40
107	Asn-Arg-Leu-Pro	495	13	14	-2.67	130.93
108	Asn-Arg-Leu-Glu	524	12	16	-3.99	131.10
109	Asn-Arg-Leu-Gly	451	12	14	-3.62	115.22
110	Asn-Arg-Leu-Thr	495	13	15	-2.44	128.63
111	Arg-Leu-Asn-Ile	503	12	14	-1.84	133.41

112	Arg-Leu-Asn-Ser	476	12	15	-4.08	119.98
113	Arg-Leu-Asn-Lys	518	14	15	-2.78	137.48
114	Arg-Leu-Asn-Leu	503	12	14	-2.06	134.35
115	Arg-Leu-Asn-Pro	539	12	14	-2.03	144.28
116	Arg-Leu-Asn-Gln	520	14	16	-3.76	133.33
117	Arg-Leu-Asn-Pro	539	12	14	-2.03	144.28
118	Arg-Leu-Asn-Glu	522	12	16	-4.27	129.26
119	Arg-Leu-Asn-Gly	449	11	14	-3.55	114.21
120	Arg-Leu-Asn-Thr	493	13	15	-2.73	126.78
121	Asn-Leu-Pro-Ile	452	9	11	-0.49	121.56
122	Leu-Asn-Pro-Ser	425	9	12	-2.51	107.18
123	Leu-Asn-Pro-Lys	467	11	12	-1.21	124.69
124	Leu-Asn-Pro-Leu	452	9	11	-0.49	121.56
125	Leu-Asn-Pro-Phe	488	9	11	-0.46	131.49
126	Leu-Asn-Pro-Asn	455	11	13	-2.58	115.94
127	Leu-Asn-Pro-Gln	469	11	13	-2.21	120.55
128	Leu-Asn-Pro-Glu	471	9	13	-2.71	116.46
129	Leu-Asn-Pro-Gly	398	8	11	-1.98	101.42
130	Leu-Asn-Asn-Thr	453	11	14	-4.10	110.34
131	Lys-Pro-Asn-Ile	465	11	12	-1.43	124.59
132	Lys-Pro-Asn-Ser	438	11	13	-3.45	110.22
133	Lys-Pro-Asn-Gln	482	12	14	-2.59	123.66
134	Lys-Pro-Asn-Leu	465	11	12	-1.43	124.59
135	Lys-Pro-Asn-Phe	501	10	12	-0.83	134.60
136	Lys-Pro-Asn-Asn	468	13	14	-3.52	118.97
137	Lys-Pro-Asn-Pro	455	11	12	-1.37	120.16
138	Lys-Pro-Asn-Gly	411	10	12	-2.92	104.45
139	Lys-Pro-Asn-Glu	484	11	14	-3.64	119.50
140	Lys-Pro-Asn-Thr	455	12	13	-2.10	117.02
141	Pro-Lys-Arg-Ile	499	12	13	-0.75	137.05
142	Pro-Lys-Arg-Ser	472	12	13	-2.78	122.68
143	Pro-Lys-Arg-Lys	512	13	13	-1.12	140.16
144	Pro-Lys-Arg-Leu	499	12	12	-0.75	137.05
145	Pro-Lys-Arg-Phe	535	11	12	-0.36	147.81
146	Pro-Lys-Arg-Asn	502	14	14	-2.85	131.43
147	Pro-Lys-Arg-Pro	489	12	12	-0.70	132.62
148	Pro-Lys-Arg-Glu	518	12	14	-2.97	131.95
149	Pro-Ly-sArg-Gly	447	11	12	-1.51	119.60
150	Pro-Lys-Arg-Thr	489	13	13	-1.42	129.48
Pentapeptide molecule						
S. No.	**Molecule**	**Mass**	**Hydrogen bond donor**	**Hydrogen bond acceptor**	**Log P**	**Molar refractivity**
151	Lys-Arg-Leu-Asn-Pro	579	14	16	-2.35	152.19
152	Lys-Arg-Leu-Asn-Pro	535	14	16	-4.46	136.41
153	Lys-Arg-Leu-Asn-Ala	549	14	16	-3.35	142.87
154	Lys-Arg-Leu-Asn-Ser	562	15	17	-5.00	142.18
155	Lys-Arg-Leu-Asn-Thr	579	16	17	-3.65	148.98
156	Lys-Arg-Leu-Asn-Leu	589	14	16	-2.41	156.62
157	Lys-Arg-Leu-Asn-Ile	589	14	16	-2.41	156.60
158	Lys-Arg-Leu-Asn-Val	577	15	16	-3.14	152.03
159	Lys-Arg-Leu-Asn-Phe	625	14	16	-2.38	166.56
160	Lys-Arg-Leu-Asn-Tyr	641	15	17	-3.06	167.71
161	Arg-Leu-Asn-Pro-Lys	619	15	17	-2.24	167.94
162	Arg-Leu-Asn-Pro-Asn	681	14	17	-0.89	187.91
163	Arg-Leu-Asn-Pro-Pro	594	14	16	-1.28	160.39
164	Arg-Leu-Asn-Pro-Leu	596	14	16	-2.02	158.99
165	Arg-Leu-Asn-Pro-Met	623	14	16	-1.31	167.82
166	Arg-Leu-Asn-Pro-Asp	607	14	18	-4.16	155.01
167	Arg-Leu-Asn-Pro-Asn	607	16	18	-3.43	159.72

168	Arg-Leu-Asn-Pro-Glu	623	14	18	-3.55	159.72
169	Arg-Leu-Asn-Pro-Gln	621	16	18	-3.04	163.82
170	Arg-Leu-Asn-Pro-Arg	647	18	19	-2.91	174.20
171	Leu-Asn-Pro-Lys-Arg	619	15	16	-2.41	165.76
172	Leu-Asn-Pro-Lys-Lys	591	14	15	-0.97	160.95
173	Leu-Asn-Pro-Lys-Met	595	12	14	-0.31	160.82
174	Leu-Asn-Pro-Lys-His	602	13	16	-1.36	162.71
175	Leu-Asn-Pro-Lys-Gly	522	11	14	-1.75	137.68
176	Leu-Asn-Pro-Lys-Ala	536	11	13	-2.31	140.61
177	Leu-Asn-Pro-Lys-Ser	549	12	15	-2.28	143.44
178	Leu-Asn-Pro-Lys-Thr	566	13	15	-0.93	150.25
179	Leu-Asn-Pro-Lys-Leu	576	12	14	-0.26	157.81
180	Leu-Asn-Pro-Lys-Ile	576	12	14	-0.26	157.81
181	Asn-Pro-Lys-Arg-Leu	621	16	16	-2.89	166.61
182	Asn-Pro-Lys-Arg-Phe	655	16	16	-3.08	176.44
183	Asn-Pro-Lys-Arg-Thr	609	18	17	-4.14	158.11
184	Asn-Pro-Lys-Arg-Gly	507	15	16	-4.38	146.47
185	Asn-Pro-Lys-Arg-Pro	609	17	16	-3.42	161.25
186	Asn-Pro-Asn-Pro-Asn	559	15	16	-2.86	138.96
187	Asn-Pro-Asn-Pro-Lys	569	15	16	-2.86	147.69
188	Asn-Pro-Asn-Pro-Leu	556	14	15	-2.49	144.58
189	Asn-Pro-Asn-Leu-Ile	566	13	14	-3.58	146.90
190	Asn-Pro-Lys-Asn-Pro	571	16	16	-3.20	147.71
191	Pro-Lys-Arg-Leu-Asn	615	16	16	-2.23	165.43
192	Pro-Lys-Arg-Leu-Arg	655	18	17	-1.72	180.43
193	Pro-Lys-Arg-Leu-His	638	14	16	-0.67	176.02
194	Pro-Lys-Arg-Leu-Lys	627	15	15	-0.28	174.26
195	Pro-Lys-Lys-Lys-Pro	585	12	14	-0.06	159.15
196	Pro-Asn-Pro-Asn-Pro	540	12	13	-3.30	135.50
197	Pro-Asn-Lys-Pro-Asn	563	13	14	-3.73	143.04
198	Pro-Asn-Leu-Ile-Pro	549	10	11	-1.04	145.60
199	Pro-Asn-Leu-Pro-Ile	545	9	11	-1.36	144.18
200	Pro-Asn-Leu-Thr-Ser	520	11	13	-4.02	128.04

From the observations from Table 1, only 43 lead compounds were identified which were further subjected to Molinspiration (Table 2).

Out of these 43 peptides, only 5 compounds were found and selected as potent lead compounds (Arg-Ser, Asn-Ser, Pro-Lys-Ser, Pro-Lys-Gly, Pro-Lys-Thr) which were further subjected to Swiss Dock procedure. Targets selected for binding and inhibiting activity of selected peptides: DHFR [20], DHOD [21] and aspartic proteinase [22]. All the 5 leads were subjected to binding with each enzyme and their respective results were tabulated in Table 3.

It is clearly found that out of 5 lead compounds selected against DHFR, aspartic proteinase and DHOD the most potent lead compound is Arg-Ser with their corresponding full fitness energy as -302413.88 kcal/mol, -287460.67 kcal/mol and -453848.82 kcal/mol respectively. Dipeptide Asn-Ser was identified as the second most lead against malarial enzyme DHFR, aspartic proteinase and DHOD with their full fitness energy -285057.65 kcal/mol, -264788.72 kcal/mol and -425186.51 kcal/mol respectively.

Table 2: Biological significance of enzyme and receptor targets of subjected peptide leads by Molinspiration

S. No.	Molecule	Mi-log P	TPSA	N - violation	GPCR Ligand	ICM	KI	NRL	PI	EI
1	Lys-Ile	-2.47	118.44	1	0.4	0.45	-0.19	-0.32	0.87	0.52
2	Lys-Ser	-4.54	138.67	1	0.48	0.55	-0.11	-0.31	0.86	0.65
3	Lys-Phe	-2.29	118.44	1	0.66	0.47	0.1	0.08	0.95	0.53
4	Lys-Pro	-3.34	109.65	0	0.65	0.59	-0.05	-0.11	1.03	0.6
5	Lys-Glu	-4.26	155.74	1	0.58	0.49	-0.02	0.04	0.87	0.63
6	Lys-Gly	-3.53	118.44	1	0.2	0.38	-0.39	-0.46	0.66	0.42
7	Arg-Ser	-4.78	174.55	1	0.77	0.7	-0.1	-0.58	1.24	0.71
8	Arg-Asn	-4.27	197.42	1	0.72	0.53	-0.06	-0.37	1.25	0.6
9	Arg-Glu	-4.56	191.62	1	0.79	0.60	-0.05	-0.25	1.18	0.65
10	Leu-Ile	-0.66	92.42	0	0.18	0.34	-0.45	-0.40	0.73	0.37
11	Leu-Ser	-2.92	112.65	0	0.23	0.39	-0.48	-0.38	0.76	0.46
12	Leu-Leu	-0.64	92.42	0	0.26	0.38	-0.4	-0.12	0.71	0.40
43	Leu-Phe	-0.48	92.42	0	0.5	0.38	-0.14	0.07	0.89	0.42
14	Leu-Pro	-1.64	83.63	0	0.44	0.47	-0.38	-0.16	0.96	0.43
15	Leu-Gly	-1.73	92.42	0	-0.08	0.2	-0.82	-0.55	0.55	0.18
16	Asn-Ser	-4.30	155.74	1	0.17	0.21	-0.34	-0.47	0.66	0.43
17	Asn-Glu	-3.93	174.81	1	0.36	0.23	-0.20	-0.07	0.74	0.48
18	Asn-Phe	-1.91	135.51	1	0.45	0.24	-0.04	0	0.82	0.40
19	Asn-Asn	-3.49	178.61	1	0.21	0.22	-0.28	-0.21	0.62	0.37
20	Pro-Ile	-1.00	78.42	0	0.17	0.39	-0.51	-0.63	0.64	0.30
21	Pro-Ser	-3.26	98.65	0	0.24	0.45	-0.46	-0.66	0.6	0.39
22	Pro-Val	-1.51	78.42	0	0.14	0.36	-0.53	-0.64	0.59	0.23
23	Pro-Phe	-0.83	78.42	0	0.52	0.45	-0.10	-0.11	0.78	0.39
24	Pro-Pro	-1.98	69.44	0	0.36	0.45	-0.40	-0.48	0.73	0.34
25	Pro-Gly	-2.07	78.42	0	-0.11	0.23	-0.83	-0.87	0.36	0.08
26	Lys-Pro-Ser	-4.68	158.98	1	0.83	0.52	0.21	0.19	1.25	0.64
27	Lys-Arg-Pro	-4.67	200	2	0.90	0.62	0.17	-0.12	1.37	0.61
28	Lys-Arg-Gly	-4.71	209.44	2	0.77	0.54	0.13	-0.15	1.25	0.57
29	Lys-Arg-Thr	-5.05	229.67	2	0.73	0.47	0.06	-0.12	1.12	0.57
30	Arg-Leu-Ser	-4.35	203	2	0.75	0.54	0.04	-0.16	1.25	0.57
31	Arg-Leu-Asn	-3.57	226.51	2	0.66	0.43	-0.01	-0.12	1.18	0.47
32	Arg-Leu-Gly	-3.24	183.42	1	0.72	0.49	-0.03	-0.14	1.29	0.50
33	Arg-Leu-Thr	-4.06	203.65	2	0.68	0.42	-0.07	-0.12	1.16	0.52
34	Leu-Asn-Ser	-3.60	184.84	1	0.49	0.25	0.04	0.11	0.99	0.45
35	Leu-Asn-Gly	-2.41	164.61	1	0.39	0.16	-0.07	0.10	0.96	0.36
36	Leu-Asn-Thr	-3.24	184.84	1	0.43	0.12	-0.08	0.16	0.92	0.40
37	Asn-Pro-Ser	-4.47	176.05	1	0.68	0.32	0.11	0.13	1.17	0.53
38	Asn-Pro-Lys	-4.12	181.85	1	0.72	0.40	0.14	0.22	1.20	0.53
39	Asn-Pro-Thr	-4.22	176.05	1	0.61	0.18	-0.02	0.11	1.08	0.43
40	Pro-Lys-Ser	-4.28	153.77	1	0.72	0.53	0.26	0.02	1.09	0.46
41	Pro-Lys-Glu	-3.40	170.84	1	0.66	0.47	0.16	0.11	0.97	0.53
42	Pro-Lys-Gly	-3.13	133.54	1	0.63	.046	0.01	1.05	1.05	0.52
43	Pro-Lys-Thr	-3.96	153.77	1	0.65	0.39	0.12	0.08	1.01	0.53

ICM-Ion Channel Modulator; KI-Kinase Inhibitor; NRL-Nuclear Receptor Ligand; EI-Enzyme Inhibitor; PI-Protease Inhibitor

CONCLUSION

Peptides are designed as the anti-malarial agents, as they have the potential role in the treatment of malaria. After analyzing all the results of Swiss Dock against DHFR enzyme, it was found that a particular dipeptide (Arg-Ser) was identified as the best lead having the full-fitness energy as -302413.88 kcal/mol and the second most potent lead is (Asn-Ser) having the full-fitness energy as -285057.65 kcal/mol. These peptides are observed as the best lead compounds against DHFR enzyme which can be utilized as the potent anti-malarial agent and have to be further explored for its pre-clinical and clinical studies.

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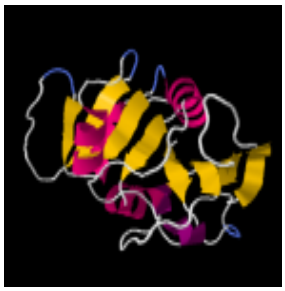
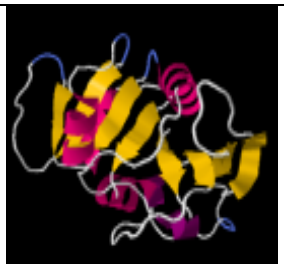
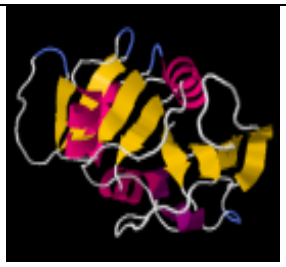
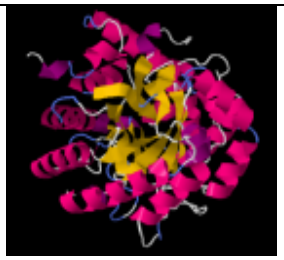
Table 3: Estimation of the free energy when the lead peptide is subjected for docking against various enzymes

S. No.	Peptide	Target	Full fitness (kcal/mol)	Estimated GΔ (Kcal/mol)	Image
1	Arg-Ser	DHFR	-302413.88	-1755.29	
2	Asn-Ser	DHFR	-285057.65	-1605.36	
3	Pro-Lys-Ser	DHFR	-276927.66	-1883.92	
4	Pro-Lys-Gly	DHFR	-278541.72	-1779	
5	Pro-Lys-Thr	DHFR	-276785.15	-1931.83	
6	Arg-Ser	Aspartic proteinase	-287460.67	-1538.48	

7	Asn-Ser	Aspartic proteinase	-264788.72	-1458.76	
8	Pro-Lys-Ser	Aspartic proteinase	-254636.9	-1488.75	
9	Pro-Lys-Gly	Aspartic proteinase	-257094.32	-1489.27	
10	Pro-Lys-Thr	Aspartic proteinase	-254630.86	-1531.05	
11	Arg-Ser	DHOD	-453848.82	-1792.65	
12	Asn-Ser	DHOD	-425186.51	-1630.14	

13	Pro-Lys-Ser	DHOD	-423771.2	-1885.66	
14	Pro-Lys-Gly	DHOD	-422701.66	-1851.43	
15	Pro-Lys-Thr	DHOD	-418708.23	-1887.44	

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