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COMPUTATIONAL STUDIES OF NOVEL 1-AZETIDINONE SUBSTITUTED BENZIMIDAZOLE DERIVATIVES AS PLASMODIUM FALCIPARUM GLUTAMATE DEHYDROGENASE INHIBITORS

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ABSTRACT

Glutamate dehydrogenase is an NADP-dependent enzyme that plays a major role in maintaining a reduced state in plasmodia. Clinically effective chloroquine and mefloquine inhibit the enzyme glutamate dehydrogenase thus inhibits antioxidative enzymes like glutathione reductase and thioredoxin which induce oxidative stress. In a highly oxidized state, plasmodia fail to survive. Chloroquine and Mefloquine contain a quinoline scaffold to which the tertiary amine-containing side chain is attached. From these drug molecules as well as by the detailed study of the structure-activity relationship of quinolines, a series of molecules have been designed and developed by molecular docking. Among these all designed compounds, compound number 2(d)(-121.51 kcal/mol), 2(f)(-109.83 kcal/mol), 1(f)(-108.56 kcal/mol) and 1(d)(-103.18 kcal/mol) shows good binding affinity than other designed compounds. Molinspiration online software tool was used to predict bioavailability that shows all compounds are active on G-protein coupled receptor. SWISSADME program was used to study in silico toxicity, indicating all the compounds follow Lipinski rule of five and compounds 1(b), 1(d), 1(e), 1(f), 1(g), 2(b), 2(d), 2(e), 2(f), 2(g) do not penetrate the blood-brain barrier. The designed series of novel 1-

Azetidinone substituted benzimidazole derivatives exhibit good binding affinity with Plasmodium Falciparum glutamate dehydrogenase. The performed study contributed a better perceptive of molecular modeling necessity for maintaining or improving Plasmodium Falciparum glutamate dehydrogenase inhibitors.

Keywords: Glutathione reductase, Thioredoxin, NADP, Oxidative stress, iGEMDOCK, YASARA, SWISSADME, Molinspiration

INTRODUCTION

Glutamate dehydrogenase is an NADP dependent enzyme that found in a large number of microbes, and the mitochondria of eukaryotes. Glutamate dehydrogenase enzyme favours the synthesis of α-ketoglutarate and ammonia. Glutamate dehydrogenase that present in plasmodium falciparum is NADP dependent enzyme carry out reduction of NADP and converts it in to NADPH **[1-5]**. This reduced NADP (NADPH) provides electron source for antioxidative enzymes like glutathione reductase and thioredoxin. Glutathione reductase (GR) also termed as glutathione disulfide reductase (GSR) catalyze the reductive reaction and converts glutathione disulfide in to glutathione **[6-8]**. This glutathione resists oxidative stress and provides reduced environment to the plasmodium falciparum. Thioredoxin is oxidoreductase enzyme having molecular weight 12 kiloDalton. It possesses radical scavenging activity and plays a dominant role against oxidative stress. This produced thioredoxin and glutathione reductase suppress oxidative stress and induce reduced environment that is the primary requisite for the plasmodium falciparum to survive **[9-11]**.

Glutamate dehydrogenase inhibitors

Glutamate dehydrogenase inhibitors compete with NADP and binds with the enzyme glutamate dehydrogenase at the active site. By preventing catalysis, they will inhibit the conversation step of NADP in to NADPH. As NADPH will not be synthesized, antioxidative enzymes glutathione reductase and thioredoxin will not get electron for the reduction process. Oxidative stress will be induced and Plasmodium Falciparum fails to survive. As this glutamate dehydrogenase is absent in host erythrocyte, this can be a dominant target for the development of novel antimalarial agents **[12-15]**.

Chloroquine and chloroquine phosphate are 4-amino Quinoline derivatives that can be well useful in the treatment as well as prophylaxis of malaria. The exact mechanism of this drug is unknown yet. However, it

forms complex with the compound heme (Ferriprotoporphyrin IX, toxic to malaria parasite). This complex is known as chloroquine-heme complex. As, due to formation of this complex heme cannot be converted in to hemozoin (nontoxic compound to malaria parasite). So, malaria parasite fails to survive as a formation of chloroquine-Heme complex. Chloroquine has much more side effects like nausea, vomiting, blurred vision, abdominal cramp, headache, diarrhoea, loss of appetite, hearing loss, change in skin color, hair loss, weight loss, seizures. Further this drug cannot be given to the pregnant lady. Mefloquine, the newest 4-aminoquinoline derivative that available in the market as R, S-isomer. This drug differs from the other agents in a manner that at 2 and 8 positions, it contains trifluromethyl moieties. Also it does not contain any electronegative substituent as that present in chloroquine. It increases pH in vesicles of malaria parasite and interfere with the processing of heme. Mefloquine can cause exacerbate mental disorders so it is not given to the patient suffering from active depression, psychosis, anxiety, schizophrenia and convulsions **[16-22]**.

A detailed Structure Activity Relationship of quinoline derivative reveals that quinoline ring shows better activity. At 4^{th} position of quinoline nucleus, a side chain having 2 to 5 carbon atom must be attached between two nitrogen atoms and at terminal end tertiary amino nitrogen must be present for maximum activity. In the side chain, presence of aromatic nucleus shows increased activity and presence of heterocyclic ring in the side chain reduce the toxicity. This all parameters have been considered for the designing of new molecules. **Figure 1** shows a general designed novel 1-Azetidinone substituted benzimidazole ligand that fulfills all the requirements. One such attempt has been made of replacement of quinoline with benzimidazole nucleus. It contains two carbon atoms side chain between two nitrogen atoms, one phenyl ring on the azetidine ring, outside the chain and terminal tertiary nitrogen in the form of azetidine ring **[23-27]**.

As there has been no any successive compound prepared that can inhibit the action of glutamate dehydrogenase as well as glutathione reductase till date. Further both glutamate dehydrogenase and glutathione reductase that present in plasmodium falciparum have different fold than that present in the mammals. So these enzymes can be a better target to design and develop some novel antimalarial agents.

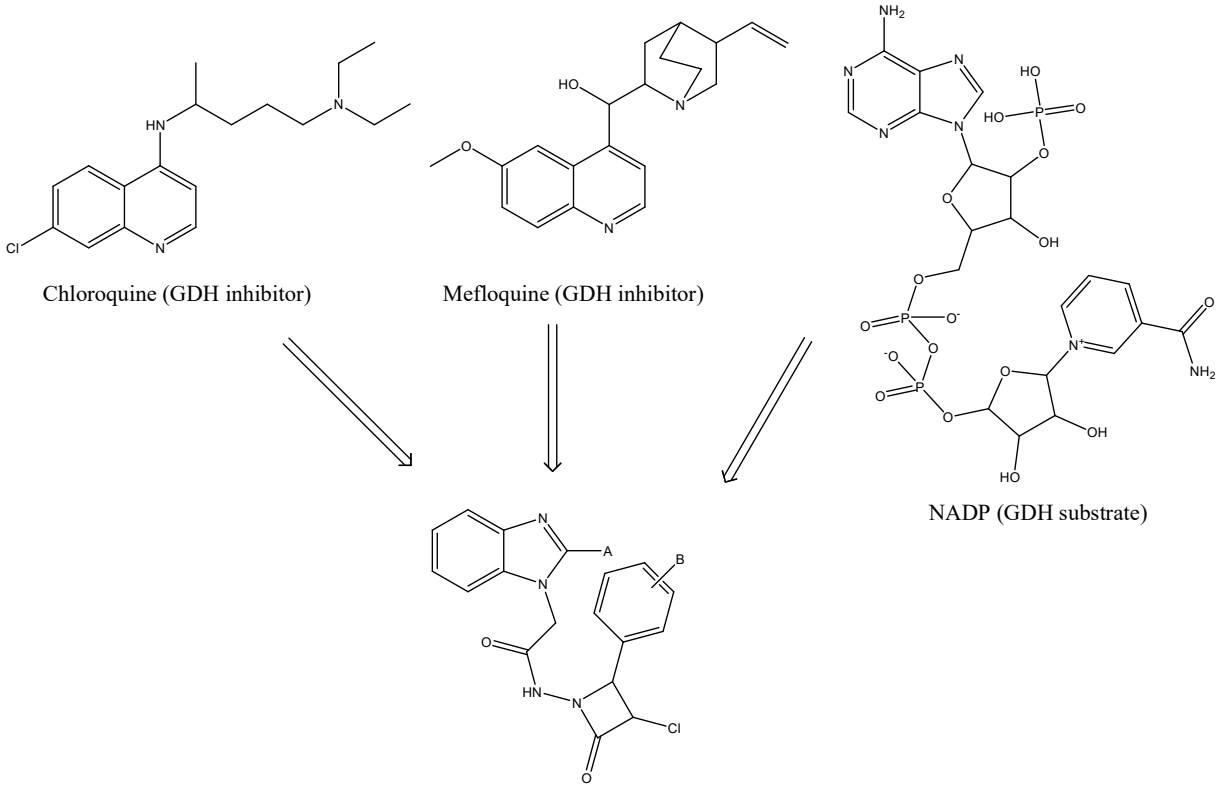


Figure 1: Design of novel 1-Azetidinone substituted benzimidazole derivatives as Plasmodium Falciparum Glutamate Dehydrogenase Inhibitors

MATERIALS AND METHODS

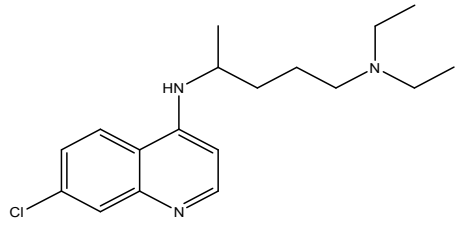
Protein Preparation

Crystallographic structures of the target protein (PDB ID: 2BMA) was prepared and saved in standard 3D coordinate format[28]. The conformations and the energy states with added hydrogens were fixed and corrected by energy minimization by using YASARA energy minimization server.

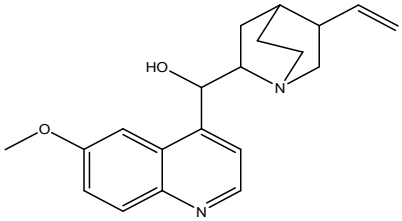
Molecular Docking

Molecular docking is a computational technique that evaluates the preferred orientation of one molecule to the binding site of target protein. Evaluation can be done on the basis when they bound with each other to form a stable complex. Docking was performed with iGEMDOCK version 2.1-1 between protein (enzyme) and inhibitor (ligand) that gives binding orientation in kcal/mol. Total 200 population size and number of generations 2 were taken for the generation of accurate settings in docking process. The binding energies were compared with the docking score of the standard ligand Chloroquine and Mefloquine. **Table 1** shows the binding affinity of selected novel Plasmodium Falciparum Glutamate Dehydrogenase inhibitors **[29-32]**.

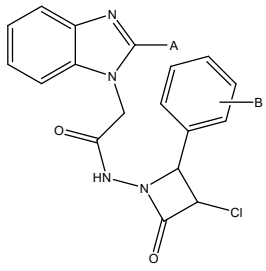
Table 1: Binding affinity of the designed novel Plasmodium Falciparum glutamate dehydrogenase inhibitors. [#Chq= Chloroquine (Standard compound 1), #Mfq= Mefloquine (Standard compound 2)]



Chloroquine (01) (Standard compound 1)



Mefloquine (02) (Standard compound 2)



Compound Code	A	B
1(a)	H	H
1(b)	H	4-OCH_3
1(c)	H	2-Cl
1(d)	H	3-NO_2
1(e)	H	2-OH
1(f)	H	2-NO_2
1(g)	H	2-OCH_3
1(h)	H	4-Cl
1(i)	H	2-Br
1(j)	H	4-Br

Compound Code	A	B
2(a)	CH_3	H
2(b)	CH_3	4-OCH_3
2(c)	CH_3	2-Cl
2(d)	CH_3	3-NO_2
2(e)	CH_3	2-OH
2(f)	CH_3	2-NO_2
2(g)	CH_3	2-OCH_3
2(h)	CH_3	4-Cl
2(i)	CH_3	2-Br
2(j)	CH_3	4-Br

Sr. No.	Compound Code	Chemical name of designed compounds	Binding energy score (Kcal/mol)
1	01 (#Chq)	7-Chloro-N-(5-(diethylamino)pentan-2-yl)quinolin-4-amine	-86.26
2	02 (#Mfq)	(2,8-Bis(trifluromethyl)quinolin-4-yl)(piperidin-2-yl)methanol	-93.19
3	1(a)	2-(1-*H*-Benzo[d]imidazol-1-yl)-N-(3-chloro-2-oxo-4-phenylazetidin-1-yl)acetamide	-91.61
4	1(b)	2-(1-*H*-Benzo[d]imidazol-1-yl)-N-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)acetamide	-88.55
5	1(c)	2-(1-*H*-Benzo[d]imidazol-1-yl)-N-(3-chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-yl)acetamide	-95.01
6	1(d)	2-(1-*H*-Benzo[d]imidazol-1-yl)-N-(3-chloro-2-(3-nitrophenyl)-4-oxoazetidin-1-yl)acetamide	-103.18
7	1(e)	2-(1-*H*-Benzo[d]imidazol-1-yl)-N-(3-chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)acetamide	-93.9
8	1(f)	2-(1-*H*-Benzo[d]imidazol-1-yl)-N-(3-chloro-2-(2-nitrophenyl)-4-oxoazetidin-1-yl)acetamide	-108.56
9	1(g)	2-(1-*H*-Benzo[d]imidazol-1-yl)-N-(3-chloro-2-(2-methoxyphenyl)-4-oxoazetidin-1-yl)acetamide	-94.39
10	1(h)	2-(1-*H*-Benzo[d]imidazol-1-yl)-N-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)acetamide	-92.74
11	1(i)	2-(1-*H*-Benzo[d]imidazol-1-yl)-N-(2-(2-bromophenyl)- 3-chloro-4-oxoazetidin-1-yl)acetamide	-89.02
12	1(j)	2-(1-*H*-Benzo[d]imidazol-1-yl)-N-(2-(4-bromophenyl)- 3-chloro-4-oxoazetidin-1-yl)acetamide	-92.71
13	2(a)	N-(3-Chloro-2-oxo-4-phenylazetidin-1-yl)-2-(2-methyl-1-*H*-benzo[d]imidazol-1-yl)acetamide	-100.16
14	2(b)	N-(3-Chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)-2-(2-methyl-1-*H*-benzo[d]imidazol-1-yl)acetamide	-96.08
15	2(c)	N-(3-Chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-yl)-2-(2-methyl-1-*H*-benzo[d]imidazol-1-yl)acetamide	-87.42
16	2(d)	N-(3-Chloro-2-(3-nitrophenyl)-4-oxoazetidin-1-yl)-2-(2-methyl-1-*H*-benzo[d]imidazol-1-yl)acetamide	-121.51
17	2(e)	N-(3-Chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)-2-(2-methyl-1-*H*-benzo[d]imidazol-1-yl)acetamide	-93.3
18	2(f)	N-(3-Chloro-2-(2-nitrophenyl)-4-oxoazetidin-1-yl)-2-(2-methyl-1-*H*-benzo[d]imidazol-1-yl)acetamide	-109.83
19	2(g)	N-(3-Chloro-2-(2-methoxyphenyl)-4-oxoazetidin-1-yl)-2-(2-methyl-1-*H*-benzo[d]imidazol-1-yl)acetamide	-88.78
20	2(h)	N-(3-Chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)-2-(2-methyl-1-*H*-benzo[d]imidazol-1-yl)acetamide	-88.53
21	2(i)	N-(2-(2-Bromophenyl)3-Chloro-4-oxoazetidin-1-yl)-2-(2-methyl-1-*H*-benzo[d]imidazol-1-yl)acetamide	-89.54
22	2(j)	N-(2-(4-Bromophenyl)3-Chloro-4-oxoazetidin-1-yl)-2-(2-methyl-1-*H*-benzo[d]imidazol-1-yl)acetamide	-87.94

In Silico ADME/T properties

The selected designed compounds were checked for *in silico* toxicity study by using SWISSADME program. For a drug candidate, to be effective, it must reach with proper concentration at the target inside the body. Also it should remain in the body for enough time so that normal biological events can be proceeding as usual. Drug design and development particularly involves appraisal of absorption, distribution, metabolism and excretion (ADME) at earlier increasingly but at a stage compounds are numerous and access to the physical samples are limited. In that situation, the computer models and softwares play a major role as an alternative to this approach. **Table 2** indicates *in silico* toxicity studies of novel Plasmodium Falciparum Glutamate Dehydrogenase inhibitors.

Table 2: *In silico* toxicity studies of designed compounds [#Chq= Chloroquine (Reference compound 1), #Mfq= Mefloquine (Reference compound 2)]

Sr. No.	Sample Code	H-Bond Donor	H-Bond Acceptor	Log P*o/w* (iLOGP)	MW (g/mol)	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	BBB Penetration
1	1(#Chq)	1	2	3.95	319.87	Yes	No	No	Yes	Yes	Yes
2	2(#Mfq)	2	9	2.78	378.31	No	No	No	Yes	Yes	No
3	1(a)	1	3	1.84	354.79	No	Yes	Yes	No	No	Yes
4	1(b)	1	4	2.29	384.82	No	Yes	Yes	Yes	Yes	No
5	1(c)	1	3	1.97	389.24	No	Yes	Yes	Yes	No	Yes
6	1(d)	2	5	-4.00	400.80	No	Yes	No	No	No	No
7	1(e)	2	4	1.67	370.79	No	No	No	No	No	No
8	1(f)	2	5	-4.49	400.80	No	Yes	No	No	No	No
9	1(g)	1	4	2.04	384.82	No	Yes	Yes	Yes	Yes	No
10	1(h)	1	3	2.09	389.24	No	Yes	Yes	Yes	No	Yes
11	1(i)	1	3	2.27	433.69	No	Yes	Yes	Yes	No	Yes
12	1(j)	1	3	2.16	433.69	No	Yes	Yes	Yes	No	Yes
13	2(a)	1	3	2.06	368.82	No	Yes	Yes	Yes	Yes	Yes
14	2(b)	1	4	2.30	398.84	No	Yes	Yes	Yes	Yes	No
15	2(c)	1	3	2.24	403.26	No	Yes	Yes	Yes	Yes	Yes
16	2(d)	2	5	-3.86	414.82	No	Yes	No	No	No	No
17	2(e)	2	4	1.70	384.82	No	Yes	No	No	No	No
18	2(f)	2	5	-3.35	414.82	No	Yes	No	No	No	No
19	2(g)	1	4	2.23	398.84	No	Yes	Yes	Yes	Yes	No
20	2(h)	1	3	2.17	403.26	No	Yes	Yes	Yes	Yes	Yes
21	2(i)	1	3	2.09	447.71	No	Yes	Yes	Yes	Yes	Yes
22	2(j)	1	3	2.38	447.71	No	Yes	Yes	Yes	Yes	Yes

Bioactivity Prediction

Another computational approach to predict biological activity is bioactivity score. Bioactivity prediction of all designed compounds was done using a Molinspiration online software tool. If the bioactivity score is >0 then the drug candidate is active. If in between -5.0 to 0 then moderately active and if <-5 then the drug candidate is inactive. **Table 3** indicates bioactivity scores of designed compounds **[33-35]**.

Table 3: Bioavailability score of designed compounds

Sr. No.	Compound Code	GPCR Ligand	Ion Channel Modulator	Kinase Inhibitor	Nuclear Receptor Ligand	Protease Inhibitor	Glutamate Dehydrogenase Inhibitor
1	Chloroquine (Standard 1)	0.32	0.32	0.38	-0.19	0.05	0.11
2	Mefloquine (Standard 2)	0.45	0.21	-0.05	0.30	0.36	0.21
3	1(a)	-0.38	-0.34	-0.18	-0.44	0.02	-0.19
4	1(b)	-0.12	-0.39	-0.20	-0.43	-0.04	-0.23
5	1(c)	-0.27	-0.71	-0.51	-0.66	-0.32	-0.42
6	1(d)	-0.22	-0.37	-0.29	-0.49	-0.12	-0.29
7	1(e)	-0.08	-0.32	-0.18	-0.34	0.01	-0.15
8	1(f)	-0.19	-0.32	-0.38	-0.46	-0.15	-0.28
9	1(g)	-0.13	-0.38	-0.24	-0.43	-0.06	-0.23
10	1(h)	-0.08	-0.34	-0.19	-0.45	-0.01	-0.21
11	1(i)	-0.18	-0.47	-0.29	-0.50	-0.17	-0.26
12	1(j)	-0.17	-0.40	-0.22	-0.54	-0.09	-0.26
13	2(a)	-0.12	-0.38	-0.36	-0.59	-0.07	-0.32
14	2(b)	-0.15	-0.42	-0.37	-0.57	-0.12	-0.34
15	2(c)	-0.13	-0.40	-0.46	-0.56	-0.16	-0.38
16	2(d)	-0.25	-0.40	-0.45	-0.63	-0.20	-0.40
17	2(e)	-0.12	-0.35	-0.36	-0.48	-0.08	-0.28
18	2(f)	-0.23	-0.35	-0.54	-0.59	-0.23	-0.39
19	2(g)	-0.16	-0.41	-0.41	-0.57	-0.15	-0.35
20	2(h)	-0.11	-0.37	-0.37	-0.59	-0.10	-0.34
21	2(i)	-0.21	-0.50	-0.47	-0.64	-0.25	-0.39
22	2(j)	-0.20	-0.43	-0.40	-0.68	-0.18	-0.38

RESULTS AND DISCUSSION

Palsmodia cannot survive in oxidative stress. Plasmodium Falciparum glutamate dehydrogenase is NADP dependent enzyme that responsible for development of NADPH in the parasite. This produced NADPH serves as electron source for antioxidative enzymes like glutathione reductase and thioredoxin reductase. This leads to suppression of oxidized state in plasmodia make them difficult to survive. Further glutamate dehydrogenase is absent in the host erythrocyte so it is an interesting target for design of some newer potential antimalarial drug molecules. After the docking studies of novel 1-azetidinone substituted benzimidazole derivatives scaffold plays a significant effect on plasmodium falciparum glutamate dehydrogenase enzyme. Among all designed compounds, sample code 1(e) number compound containing Hydroxy group at ortho position of benzene ring on the azetidine nucleus is having enzyme inhibitor activity -0.15 shows most significant activity. It binds at ARG-75, ASN-99, SER-101, LYS-13, PHE-77, ASN-99, LEU-100, LEU-100, LEU-14, LEU-14, PRO-16 amino acids. This compound does not show CYP450 oxidase enzyme inhibitory activity and cannot penetrate BBB. So, this compound will be devoid of CNS side effects. Whereas, sample code 1(c) number compound containing chloro group at ortho position of benzene ring on the azetidinone

nucleus is having enzyme inhibitor activity -0.42 shows less significant activity. It binds at ASN-17, GLU-20, ASN-17, GLN-18, GLN-18, GLN-18, ASN-99, ASP-15, ASP-15, PRO-16, ASN-17, GLN-18 amino acids. **Figure 2** indicates binding of compound 1(e) and 1(c) with the enzyme glutamate dehydrogenase. After the bioactivity prediction, it can be concluded that all the designed compounds are moderately active (activity between -5.0 to 0). Bioactivity of designed compounds in decreasing order is as under:

Mefloquine (Standard 2) > Chloroquine (Standard 1) > 1(e) > 1(a) > 1(h) > 1(b), 1(g) > 1(i), 1(j) > 1(f), 2(e) > 1(d) > 2(a) > 2(b), 2(h) > 2(g) > 2(c), 2(j) > 2(f), 2(i) > 2(d) > 1(c)

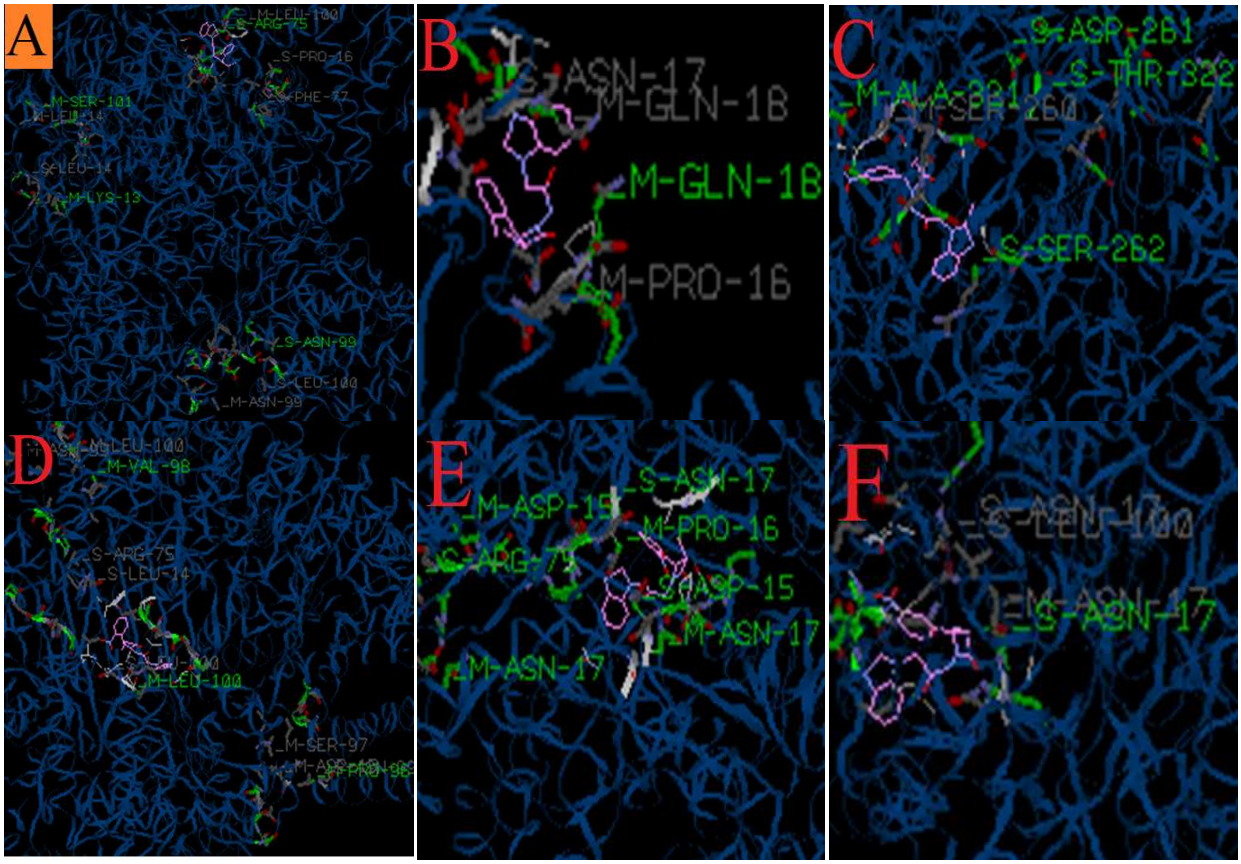


Figure 2: Superimposed docked in to binding pocket of Plasmodium Falciparum glutamate dehydrogenase. Green color indicates selected glutamate dehydrogenase residues. (A) Binding orientation of compound 1(e) with the glutamate dehydrogenase pocket with H-S-ARG-75, H-S-ASN-99, H-M-SER-101, H-M-LYS-13, V-S-PHE-77, V-M-ASN-99, V-M-LEU-100, V-S-LEU-100, V-M-LEU-14, V-S-LEU-14, V-S-PRO-16 amino acid binding site. (B) Binding orientation of compound 1(c) with the glutamate dehydrogenase pocket with H-M-ASN-17, H-S-GLU-20, H-M-ASN-17, H-M-GLN-18, V-M-GLN-18, V-S-GLN-18, V-S-ASN-99, V-M-ASP-15, V-S-ASP-15, V-M-PRO-16, V-S-ASN-17, V-S-GLN-18 amino acid binding site. (C) Binding orientation of compound 2(d) with glutamate dehydrogenase pocket with H-M-SER-238, H-S-ASP-261, H-M-SER-262, H-S-SER-262, H-M-GLY-289, H-S-THR-322, H-S-ASP-325, V-M-GLY-237, V-M-SER-238, V-M-SER-260, V-M-ASP-261, V-S-ASP-261, V-M-SER-262, V-S-SER-262, V-S-ARG-290, V-M-ALA-321, V-S-ASP-325 amino acid binding site. (D) Binding orientation of compound 2(f) with glutamate dehydrogenase pocket with H-M-PRO-96, H-M-VAL-98, H-M-LEU-100, V-S-ARG-75, V-M-SER-97, V-M-ASN-99, V-S-ASN-99, V-M-LEU-100, V-S-LEU-100, V-S-LEU-14, V-M-ASP-15 amino acid binding site. (E) Binding orientation of compound 1(f) with glutamate dehydrogenase pocket with H-S-ARG-75, H-S-ASP-15, H-M-PRO-16, H-S-GLN-18, V-M-ASN-17, V-S-ASN-17, V-M-ASP-15, V-M-ASN-17, V-S-ASN-17, V-S-GLN-18 amino acid binding site. (F) Binding orientation of compound 1(d) with glutamate dehydrogenase pocket with H-S-ASN-17, H-M-ASN-17, H-S-ARG-75, V-S-PRO-16, V-S-ASN-17, V-S-GLN-18, V-M-ASN-17, V-S-GLN-18, V-S-ASN-99, V-M-LEU-100, V-S-LEU-100 amino acid binding site

CONCLUSION

Glutamate dehydrogenase enzyme is a potential target for the design and development of some newer antimalarial agents. Molecular modeling, molecular docking and virtual screening play a major role in drug discovery as well as drug development. 1-Azetidinone substituted benzimidazole scaffold is a putative pharmacophore for inhibition of NADP dependent Plasmodium Falciparum glutamate dehydrogenase enzyme. All the designed compounds show moderate activity. All the compounds follow Lipinski rule of five without any violation, so, in future, it can be possible to prepare orally bioavailable drug from this.

List of Abbreviations

NADP = Nicotinamide adenine nucleotide phosphate

NADPH = Reduced Nicotinamide adenine nucleotide phosphate

GDH = Glutamate dehydrogenase

GR = Glutathione reductase

GSR = Glutathione disulfide reductase

PDB = Protein Drug Binding

ADME/T = Absorption, Distribution, Metabolism, Excretion, Toxicity

BBB = Blood brain barrier

CNS = Central Nervous System

MW = Molecular weight

GPCR = G-Protein couple receptor

RMSD = Root mean square deviation

ARG = Arginine

ASN = Asparagine

SER = Serine

LYS = Lysine

PHE = Phenylalanine

LEU = Leucine

PRO = Proline

GLU = Glutamine

GLN = Glycine

ASP = Aspartic acid

Conflict of Interest

The authors have no conflicts of interest regarding this research work.

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