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MOLECULAR DOCKING STUDIES OF FURANONE BEARING PYRAZOLE AS POTENTIAL INHIBITORS OF ICAM-1: DRUG TARGET FOR CEREBRAL MALARIA

Deepika Choudhary[a], Nisha Devi[b] and Sukhbir Lal Khokra[a*]

[a*]Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, 136119, Haryana, India.
[b]Dreamz College of pharmacy, Himachal Pradesh Technical University, Khilra (Sundernagar), 175036, Himachal.

Corresponding Author: Sukhbir Lal Khokra

Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, 136119, Haryana, India.

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ABSTRACT

A series of total 44 hypothetical butenolide derivatives, as shown in table 1 were designed having substituted pyrazole at α–position of butenolide ring. To pre asses their potential to be effective against cerebral malaria, these 44 hypothetical butenolide derivatives were analysed by computational analysis, particularly docking studies using programme Molegro Virtual Docker 4.0.2. In this study we considered the hypothetical compounds as ligands and suitable target bio-molecules as receptors. When ligands bind to the receptor, the course of a biochemical process is modified. The protein receptors (PDBs) used in this study PDB ID- 1IAM for cerebral malaria. The target protein receptor was found to be most suitable and actively involved as main trait for pathology of cerebral malaria. Results of docking studies revealed that almost all docked compounds have good mol dock score and showed strong interactions with the receptor in comparison to the standard drug Artesunate, main drug used to treat cerebral malaria.

KEYWORDS: Molegro virtual docker, butenolide, binding affinity, pathogenesis.

1. INTRODUCTION

Malaria is almost still the world's most important parasitic disease and which is responsible for the death of more people than any other communicable disease except tuberculosis. According to World Health Organization estimates,[1] between 300 million and 500 million people are infected with malaria every year. The disease is a public health problem in more than 90 countries, which are home to some 2,400 million people, 40% of the world's population. More than 90% of all malaria cases are in sub-Saharan Africa. Cerebral malaria (CM) is the most severe complication and the major cause of death. In some cases reported that, CM accounts for up to 10% of all cases of *Plasmodium falciparum* malaria in hospitalized persons and for 80% of fatal cases.[2]

1.1 Pathogenesis of Cerebral malaria

The mechanisms of CM pathogenesis remain incompletely understood and are the subject of a continuing debate. In case of cerebral malaria pathogenesis binding affinity other then blood cells in the modulation of pRBC.[3] The malarial parasite (pRBC) stimulated the host immune response, notably an expansion of Th1 clones, which results leading to overproduction of IFN-γ. These are also upregulating some potential receptors, such as CD36, IFN- γ which stimulates monocytes to produce soluble TNF (solTNF) and to express higher levels of the transmembrane form of the cytokine (memTNF).[4] Both forms TNF (solTNF &memTN), but particularly the memTNF via an interaction with TNFR2 expressed in increased amounts, cause an upregulation of ICAM-1 on brain endothelial cells. In case high levels of ICAM-1[5] cause platelets to adhere and fuse to brain endothelial cells, with at least two important functional consequences: an increased adhesiveness for pRBC (via CD36) and leukocytes (via LFA-1, P-selectin, etc.), are responsible for vessel obstruction, ischemia and possible neuronal dysfunction, and a potentiation of endothelial killing by TNF, which results to vessel disruption and brain haemorrhages.[6,7,8]

2. MATERIAL AND METHODS

2.1 The whole protocol followed during Molecular docking studies for cerebral malaria can be studied under following heads

- Data-set selection
- Importing a protein file, ligand file and preparation of ligands
- Protein preparation and detecting cavities of protein molecules
- Executing a docking set up through docking wizard panel
- Determination of poses of protein-ligand complex
- Calculation of Mol Dock Score and Hydrogen Bond Interaction

2.2 Molecular docking on Molegro Virtual Docker 4.0.2

Molecular modelling for antimalarial and cerebral malaria activity on programme Molegro Virtual Docker 4.0.2- Methods for predicting modes of small organic molecules to protein receptors are widely used within drug discovery efforts. Ligand docking is typically achieved by generating a number of orientations (or poses) of a ligand within the active site, and scoring of poses to identify one or more that closely approximate the bioactive conformation determined by X-ray crystallography.[9] Docking algorithms are also used for identifying putative binders from virtual chemical databases and for estimating the binding affinity of protein-ligand complex.[10] Docking study has been performed with a set of 44 hypothetical butenolide derivatives using Molegro Virtual docker MVD 2010.4.2 for cerebral malaria on 1CAM-1 using (PDB ID: 1IAM)[11] The X-ray structures of which were accessed from the protein data bank (PDB).

2.2.1 Data-set selection- A series of total 44 hypothetical butenolide derivatives on the basis of literature explored, as shown in table 1 were designed, among these 44 compounds were having substituted quinolines at α–position of butenolide ring and 44 of them were having substituted pyrazole moieties at the same position of butenolide ring. General structures of hypothetical compounds are shown in fig.1

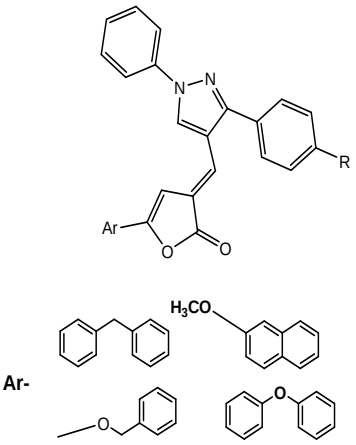
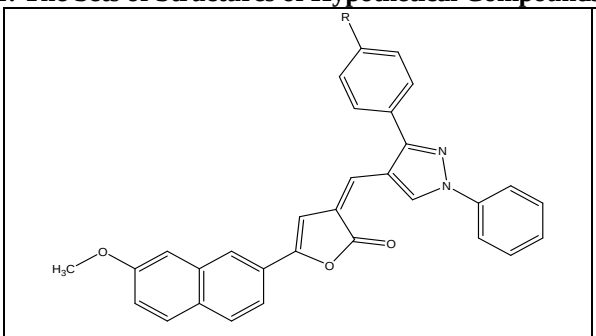
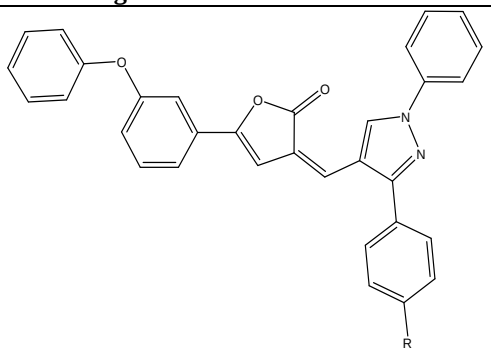


Fig- 1 General structure for hypothetical compounds.

Table 1: The Sets of Structures of Hypothetical Compounds for docking studies



5(a-k)



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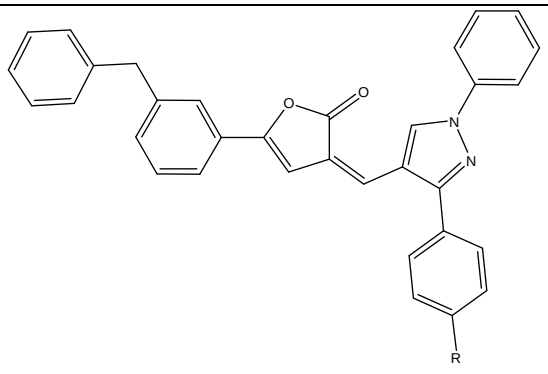
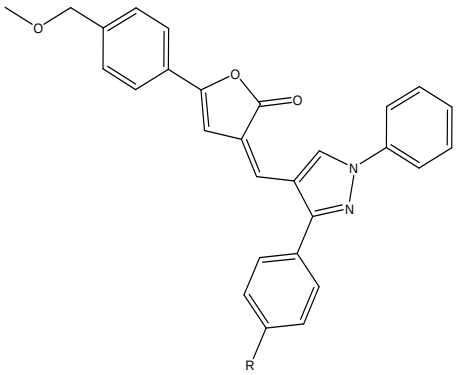


7(a-k)



8(a-k)

where	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**
R	H	CH_3	OH	2,4-diOH	OCH_3	Cl	Br	F	NO_2	NH_2	2-OH-5-OCH_3

2.2.2 Ligand preparation- The molecules were built in MarvinSketch 5.11.4.MarvinSketch is a robust collection of tools designed to prepare high quality, all-atom 3D structures for large numbers of drug like molecules, starting with the 2D structures in Marvin format. Before converting the 2D molecules into 3D; all hydrogen's in the structure were added. After converting the 2D molecules into 3D, the conformational energy of molecules was minimized. The resulting structures was saved in MarvinSketch as MDL Molfile (*.mol). The simplest use of MarvinSketch produces a single, low energy with 3D structure. Finally, the prepared 3D structures of molecules were imported by dragging or dropping a molecule structure file in the workspace.

2.3.3 Protein preparation and detecting cavities of protein molecules

The target selected for cerebral malaria target was inter cellular adhesion molecule- 1 (1CAM-1) (PDB ID-1IAM).[12, 13] The corresponding X-ray structure for the protein targets were accessed from the protein data bank (PDB) and imported. The protein structures were prepared using the protein preparation wizard in MVD. In this step, bond order were assigned, all hydrogen's in the structure were added, and bonds to metals were deleted and adjust the formal charge on the metal and the neighbouring atoms and deleted waters that were more than 5Å specific distance. The energy of imported molecules was minimized using Ligand Energy inspector. The energy minimization supports in stability of molecules to be imported. In next, the protein surface was created using protein preparation. This step helps to inspect and change the protonation state for the residues. In order to determine the potential binding sites, a cavity prediction algorithm was performed.[14]

2.2.4 Executing a docking set up through docking wizard panel

Molegro searches for suitable interaction between one or more ligand molecules and the receptor. In next, all ligands were selected and docking was performed through the docking wizard panel. After then docking result were imported. Various orientation (or poses) of docked compounds were analysed by determination of Mol Dock Score and H-bond interaction. Compounds were arranged according to their Mol Dock scores and were visualized inside the pocket to view their fitting and closure to main residues. Molecular docking studies were revealed further insight into the nature of interactions between the compounds and the active site amino acids to rationalize the obtained biological results.

3. RESULTS AND DISCUSSION

Results of in *silico* analysis for cerebral malaria on receptor for ICAM (PDB-1IAM) are shown in table 2 and it was observed that almost every derivative has better mol dock score than the standard drug Artesunate, having mol dock score -89.284 and it forms four interactions (H bond) with receptor 1IAM as shown in as shown in fig 5. The compounds **1j, 2d, 2j, 2k, 3d, 3i, 3k, 4d** and **4g** were found best with mol dock score > -102 and docking score > -106 and form > 4 no. of H-bond interactions with the receptor as shown in table 2. Binding mode of compound 3i and 4d with protein receptor 1IAM for cerebral malaria were shown in fig 2 and fig 3 respectively.

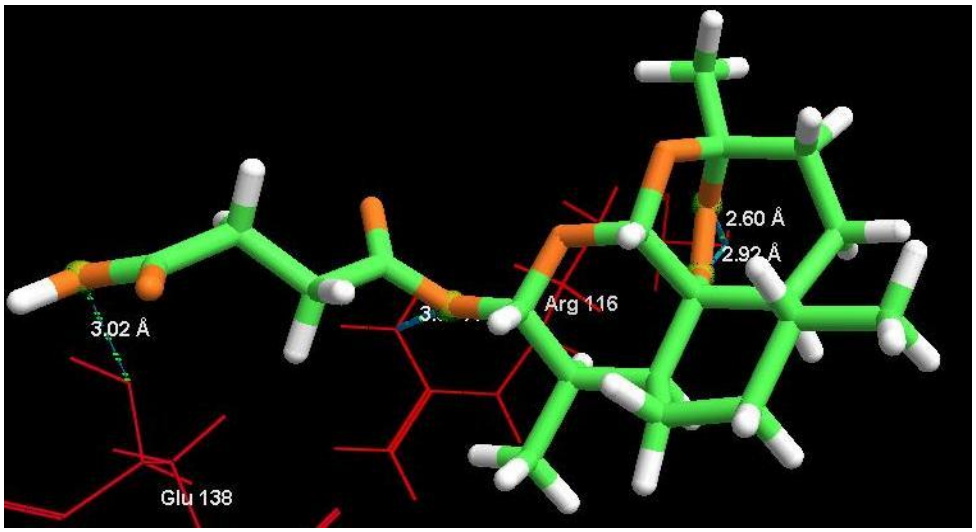


Fig. 1- Binding mode of Artesunate with 1IAM for Cerebral Malaria

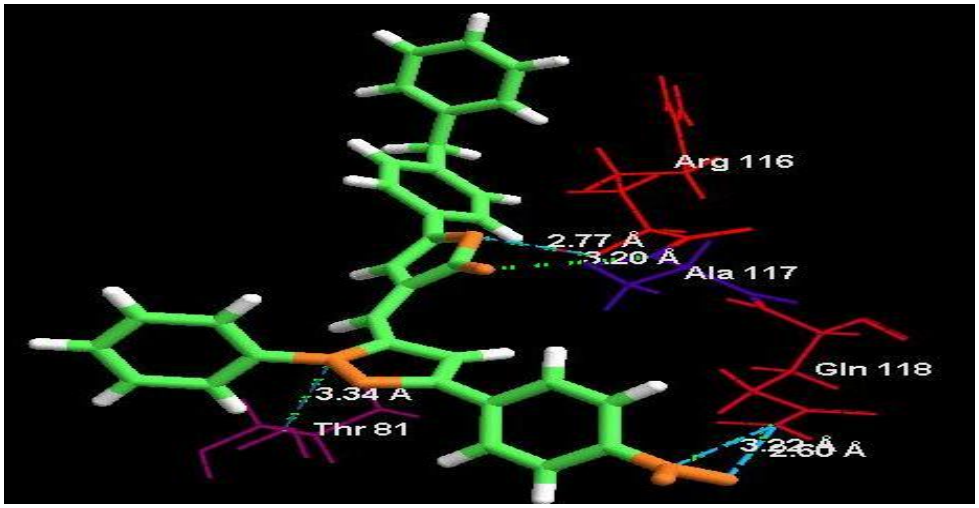


Fig. 2- Binding mode of 3i with 1IAM for Cerebral Malaria

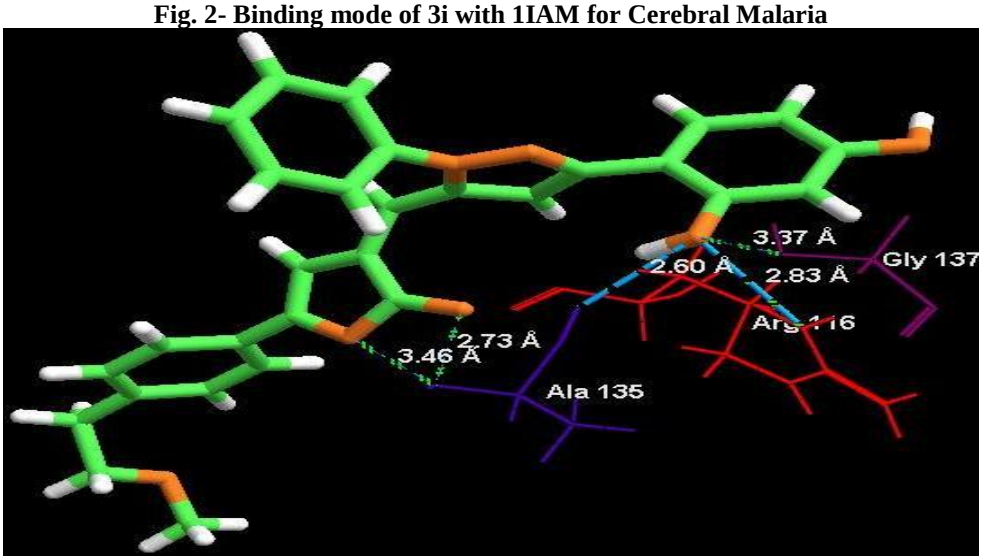


Fig. 3- Binding mode of 4d with receptor1IAM for Cerebral Malaria

TABLE- 2- docking results for cerebral malaria on Molegro (PDB ID- 1IAM)

Compound	Mol dock score	No. of H-bonds	H-bond distance (A°)	Amino acid involved	Structural feature involved
Artesunate (standard)	-89.284	**4**	2.60 2.92 3.06 3.02	Arg116 Arg116 Arg116 Glu138	Cycloheptane-O-N Cycloheptane-O-N side chain-CO-N HO-N
1a	-118.471	**4**	3.36 2.82 3.20 3.45	Ala117 Arg116 Thr81 Thr81	Furan O-N Furan O-N pyrazole N- O pyrazole N- O
1b	-120.229	3	3.23 3.46 3.04	Arg116 Arg116 Arg116	pyrazoleN-N pyrazoleN-N pyrazole N- N
1d	-124.76	3	3.24 2.60 2.86	Gln118 Thr120 Leu119	HO-O HO-O HO-O
1f	-127.376	3	3.55 3.57 2.97	Thr81 Arg116 Arg116	CH_3O-O Furan O-N C=O-N
1g	-120.408	**4**	3.33 2.72 3.15	Ala117 Arg116 Thr81	Furan O-N furan O-N pyrazoleN-O

			3.37	Thr81	pyrazoleN-O
1i	-131.145	**4**	3.13 2.60 3.35 2.76	Gln118 Gln118 Ala117 Arg116	O_2N-N N_2O- N C=O-N Furan O-N
1j	-119.535	**5**	3.13 3.14 3.33 3.38 2.68	Gln168 Thr81 Thr81 Ala117 Arg116	H_2N-O pyrazole N- O pyrazole N- O Furan O-N Furan O-N
1k	-138.017	3	3.10 3.21 2.67	Gln168 Ala117 Arg116	OH-O C=O-N Furan O-N
2d	-139.619	**10**	2.82 2.95 2.82 3.02 3.38 2.83 2.60 2.79 2.59 3.38	Arg116 Asp164 Glu162 Gln118 Thr120 Thr120 Thr120 Thr120 Thr120 Ala135	HO-N OH-O OH-O OH-O OH-N OH-O pyrazoleN-O pyrazoleN-O C=O-O furanO-N
2e	-119.414	3	3.10 3.14 3.44	Gln118 Arg116 Thr86	CH_3O-N CH_3O-N pyrazoleN-O
2f	120.909	3	3.13 3.15 3.52	Arg116 Arg116 Arg116	furanO-N pyrazoleN-N pyrazoleN-N
2j	-121.894	**7**	2.79 3.11 2.76 3.46 3.14 3.59 2.46	Thr120 Thr120 Thr120 Ala135 Ala135 Asp164 Glu162	pyrazoleN-O pyrazoleN-O C=O-O C=O-N furanO-N H_2N-O H_2N-O
2k	-126.008	**7**	3.25 3.08 2.38 3.02 3.45 3.24 3.59	Leu119 Arg132 Thr120 Glu162 Thr120 Thr120 Thr120	furanO-N pyrazoleN-N furanO-O HO-O HO-O pyrazoleN-O pyrazoleN-O
3b	-121.011	3	3.01 3.16 3.56	Arg116 Arg116 Arg116	furanO-N pyr-N-N pyrN-N
3c	-128.469	**4**	3.27 3.41 3.58 2.77	Gln58 Arg13 Asp60 Arg116	HO-O HO-N PyrN-N furanO-N
3d	-128.588	**9**	2.61 2.64 2.68 3.10 3.41 2.83 3.29 2.75 3.18	Thr120 Thr120 Thr120 Thr120 Arg132 Glu162 Asp164 Arg166 Gln118	C=O-N PyrN-O PyrN-O HO-O Pyr-N-N HO-O HO-O HO-N HO-O
3e	-119.473	**4**	3.59	Ala117	furanO-N

			2.43 2.64 2.95	Ala117 Arg116 Gly137	C=O-N C=O-N CH_3O –N
3i	-123.358	**5**	3.22 2.60 2.77 3.34 3.20	Gln118 Gln118 Arg116 Thr81 Arg117	O_2 N -N N_2O-N furanO-N pyr-N-O C=O-N
3k	-123.562	**7**	3.19 2.68 2.70 2.60 3.15 2.76 3.10	Arg132 Thr120 Thr120 Thr120 Thr120 Glu162 Gln118	pyrN-N pyrN-O pyrN-O C=O-O HO-O HO-O HO-O
4b	-118.542	**4**	3.44 2.92 3.52 3.21	Ala117 Arg116 Thr81 Thr81	Furan O-N Furan O-N pyrazole N- O pyrazole N- O
4c	-128.223	**4**	3.10 3.53 2.95 3.10	Lys8 Ala117 Arg116 Gln113	Furan O-N Furan O-N CH_3O –N HO-O
4d	-129.364	**5**	3.37 2.83 2.60 2.73 3.40	Gly137 Arg116 Ala135 Ala135 Ala135	HO-N HO-N HO-O C=O-N Furan O-N
4e	-118.655	**4**	3.18 3.44 3.35 3.10	Ala117 Ala117 Arg116 Arg13	pyrazole N- N pyrazole N- N pyrazole N- N CH_3O –N
4g	-115.511	**5**	2.82 3.48 3.01 3.43 3.18	Arg116 Ala117 Arg116 Thr81 Thr81	CH_3O-O Furan O-N Furan O-N pyrazole N- O pyrazole N- O
4i	-110.477	**4**	2.69 3.20 2.60 2.96	Thr120 Thr120 Arg116 Gly137	N_2O- N O_2N-N Furan O-N Furan O-N
4j	-120.421	3	2.94 3.40 2.94	Arg116 Asp60 Gln58	Furan O-N pyrazole N- N H_2N-O
4k	-121.79	**4**	2.71 3.57 3.11 3.00	Ala135 Leu119 Thr120 Arg132	C=O-N Furan O-N CH_3O –O CH_3O –N

4. CONCLUSION

In present study, an approach of virtual screening based on docking study is applied to evaluate a set of designed hypothetical butenolides against receptor ICAM-1, main target involved in the pathogenesis of cerebral malaria. From *In silico* analysis, it was concluded that among the 44 designed analogues, almost all compounds may be considered as potent and active derivatives, against Cerebral malaria. In each series, compounds with R-group like 2,4-DiOH (1d, 2d, 3d, 4d, $-NO_2$ (1i, 2i, 3i, 4i) $-NH_2$ (1j, 2j, 3j, 4j) showed very good binding affinities with protein receptors ICAM-1, for cerebral malaria. Hence should be explored as template to design some new potent hits and can be subjected to *in vivo* studies for further confirmation of their potential.

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