WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 10, 995-1004. Research Article ISSN 2277–7105

MOLECULAR DOCKING STUDIES OF FEW PYRAZOL-1-YL QUINOLINE DERIVATIVES

Satish M. Bhalekar*

Department of Chemistry, S.I.W.S. College, Wadala, Mumbai - 400031, India.

Article Received on
25 March 2025,

Revised on 15 April 2025,
Accepted on 05 May 2025

DOI: 10.20959/wjpr202510-36639

***Corresponding Author**
Dr. Satish M. Bhalekar
Department of Chemistry,
S.I.W.S. College, Wadala,
Mumbai - 400031, India.

ABSTRACT

Earlier we have reported the synthesis of few novel substituted quinolines and heterocyclic substituted quinolones (1-5). In the present paper the molecular docking studies of these molecules is reported. Structures of the synthesized molecules were docked to the target protein molecules of disease producing pathogens using AutoDock Vina, a docking tool. The molecular docking showed good score of bioavailability. SwissADME studies were carried out to test the gastro-intestinal absorption and brain permeation.

KEYWORDS: Quinoline, Pyrazole**,** Benzimidazole, Benzthiazole, Benzoxazole, Molecular docking, AutoDock Vina, SwissADME analysis.

INTRODUCTION

Quinoline is considered an important biological active moiety with numerous biological properties such as antimalarial,[1,2] anticancer,[3] anti-inflammatory,[4] anti-fungal,[5] antihypertensive,[6] anti-convulsant,[6] anesthetic[7] and anti-arrhythmic activity.[7]

Pyrazole plays a vital role in many biological activities such as anti-bacterial and antifungal[8,9] analgesic, anti-inflammatory and anti –microbial.[10]

Some pyrazole analogues showed good oral bioavailability and could be used for the potential treatment of IBS and other GI disorders.[11]

Previously we have reported the synthesis of few novel substituted quinolines[12] such as3-(Benzimidazol-2-yl)-6-(3,5-dimethyl-1H-pyrazol-1-yl) quinoline (1), 3- (Benzthiazol-2-yl)-6-(3,5-dimethyl-1H-pyrazol-1-yl) quinoline (2), 3- (Benzoxazol-2-yl)-6-(3,5-dimethyl-1H-

pyrazol-1-yl) quinoline (3) and synthesis of 6-(3,5-dimethylpyrazol-1-yl)-3- carbethoxy-1H-quinolin-4-one (4) and 6-(3,5-dimethylpyrazol-1-yl)-3- carboxy-1H-quinolin-4-one (5).[13]

These compounds 1-5 were assayed for their biological activity against a variety of microbes such as *E. coli, Staphylococcus aureus, Salmonella typhi and Bacillus subtilis*. Compound 2 was found to be moderately active against *S. aureus* only. Rest all the compounds were found to be inactive.[12,13]

The present paper describes the Computational study of these compounds which was carried out with the help of various computer applications available such as AutoDock Vina and SwissADME. (Absorption, Distribution, Metabolism and Excretion).

MATERIALS AND METHOD

In this study, AutoDock Vina 1.5.7, a docking tool[16,17] was used.

SwissADME online platform and the visualization is done with the help of biovia discovery software.

Ligand preparation

The synthesized compounds were used for the computational study against proteins of various disease producing pathogens such gram +ve bacteria (*Staphylococcus aureus, Bacillus subtilis*) and gram -ve bacteria (*Escherichia coli, Salmonella typhi).*[14] The molecular structure of these ligands were converted to PDB format using *Avogadro 2* app.[15]

Preparation of target protein

The proteins of gram +ve bacteria (*Staphylococcus aureus* (PDB ID:2XCT), *Bacillus subtilis* (PDB ID:1BAG)) and gram -ve bacteria (*Escherichia coli* (PDB ID:1KZN), *Salmonella typhi* (PDB ID: 1QFE) were referred and downloaded from rcsb.org site, which is repository of protein data, in PDB format. The protein receptor further prepared by removal of water molecule, adding polar hydrogen atoms, adding charges and atoms, then converted into PDBQT form using Auto Dock Tool -1.5.7.

Molecular docking

All the synthesized drug molecule structures were docked to the target protein molecules of disease producing pathogens using AutoDock Vina 1.5.7, a docking tool.[16,17] For this process the Grid map optimization is done.

In this study blank docking processes[18] were used to find out positions as well as the highest binding energies.[19]

Molecular docking is useful to determine binding affinities by following various steps such as preparing PDBQT files for proteins and ligands, Grid Box optimization, etc. The proteins in this study were kept rigid and ligands flexible.

Visualization and Molecular interactions

2D and 3D interaction plots of ligand and protein were derived. The hydrogen bond interactions were studied, visualized. The various conformations of ligands viewed using visualization tools and their positional pockets on the protein.[20]

SwissADME analysis

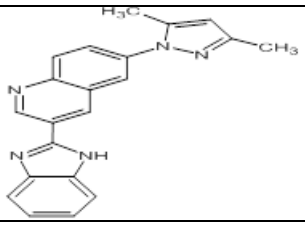
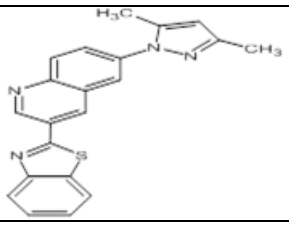
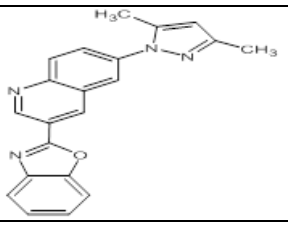
SwissADME help to first find out possible drug candidates and their drug likeness.[21]

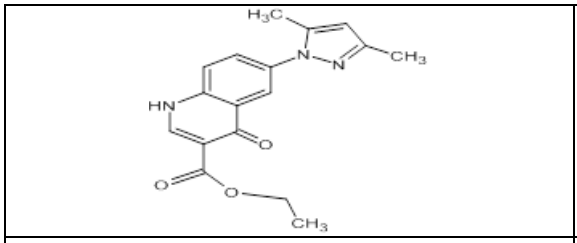
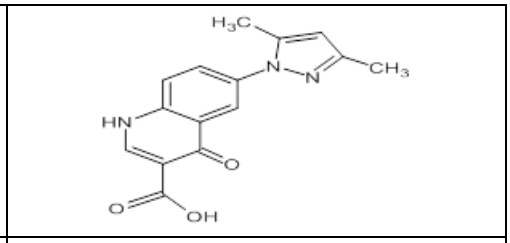
This is generally done during discovery phase to avoid loss of time, chemicals, manpower, expenditure etc. In this absorption, distribution, metabolism and excretion (ADME) properties are studied at the time of discovery. Pharmacokinetics allows one to study drug's ability to permeate blood brain barrier (BBB), absorption from Gastro-intestinal tract (GI) obtained from BOILED EGG model. BOILED-Egg method works by processing the polarity and lipophilicity of synthesized molecules. It also helps to predict whether drug-candidate can act as inhibitor against several protein enzymes.

It analyzes the various points such as drugs likeness, permeation of Blood Brain, Total polar surface area,[22] GI absorption analysis. The ADME analysis let know if a drug candidate is having pharmacological effect and provides specific targets for future research.

The structure of the molecules under investigation are depicted in the table no. 1.

Table 1: Structure of the molecules.

		
1	**2**	**3**

	
4	**5**

RESULT AND DISCUSSION

The docking results shows that the docked ligand have a low crucial binding energy with proteins of *Staphylococcus aureus.*

Table 2: Docking scores for antibacterial target selected for docking.

Binding Energy (kcal/mol)				
Compound	**Gram- positive**		**Gram-negative**	
	S.aureus	***B.subtilis***	***E.coli***	***S.typhi***
	2XCT	**1BAG**	**1KZN**	**1QFE**
Molecule 1	**-10.8**	**-7.8**	-7.3	**-6.9**
Molecule 2	-10.4	-7.6	-7.2	-6.9
Molecule 3	-10.4	-7.8	**-7.5**	-6.7
Molecule 4	-9.2	-6.9	-6.0	-6.1
Molecule 5	-9.6	-7.2	-6.8	-5.9

The 2D and 3D interaction of some of the molecules with targeted proteins are illustrated in the following figures.

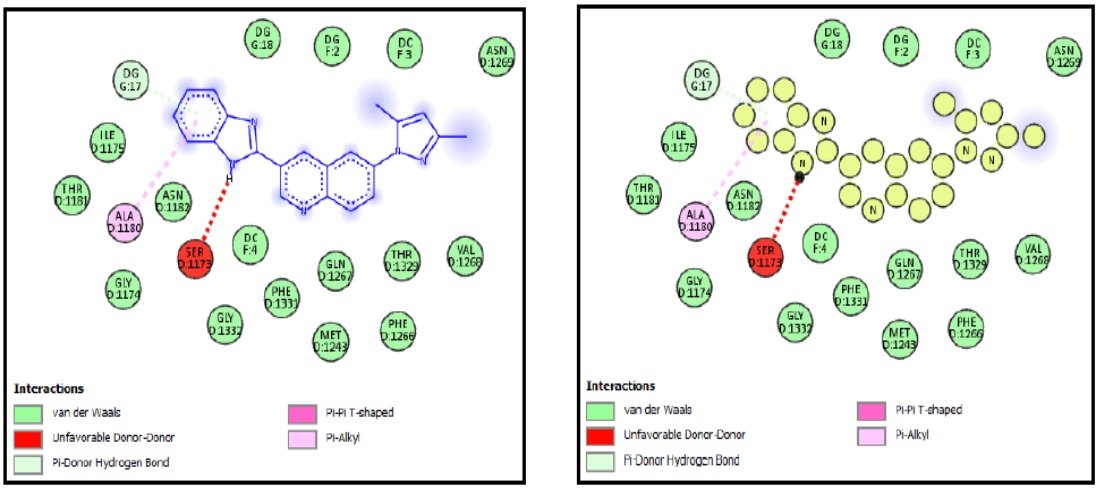


Fig. 1: 2D interaction of ligand 1 with 2XCT.

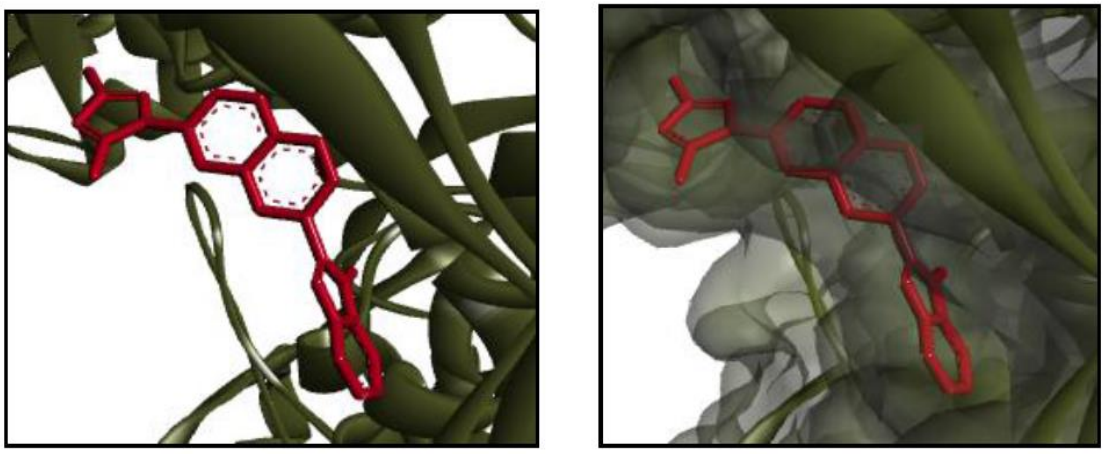


Fig. 2: 3D interaction of ligand 1 with 2XCT.

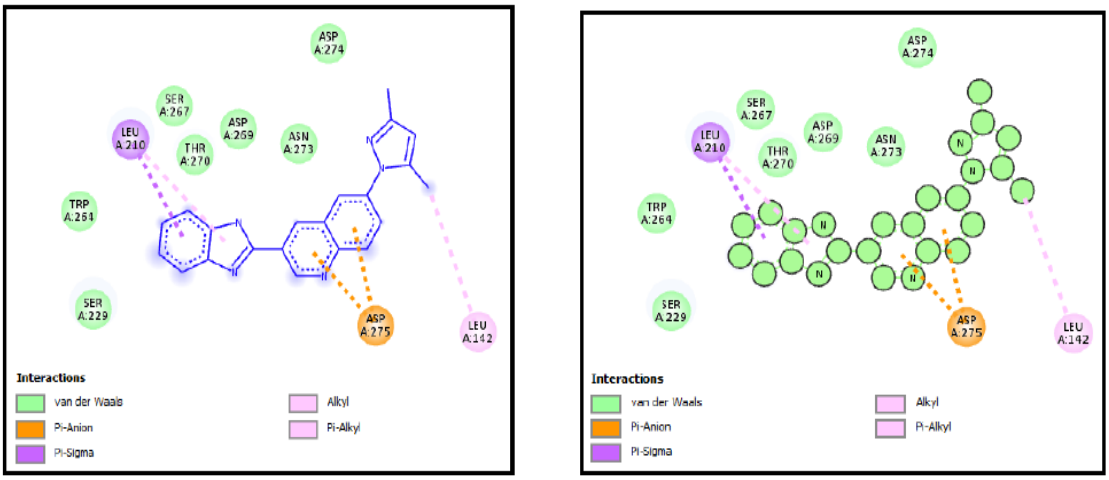


Fig. 3: 2D interaction of ligand 1 with 1BAG.

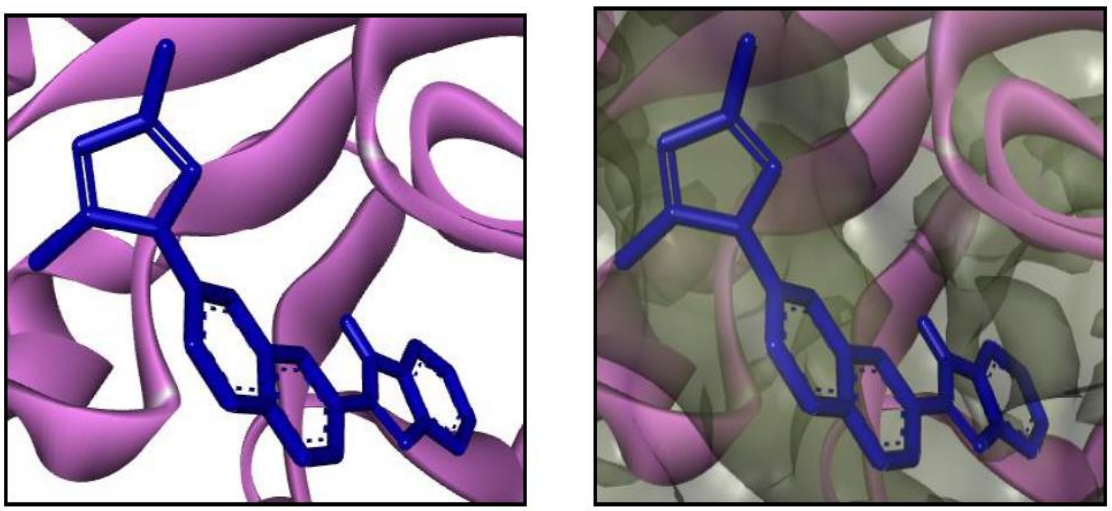


Fig. 4: 3D interaction of ligand 1 with 1BAG.

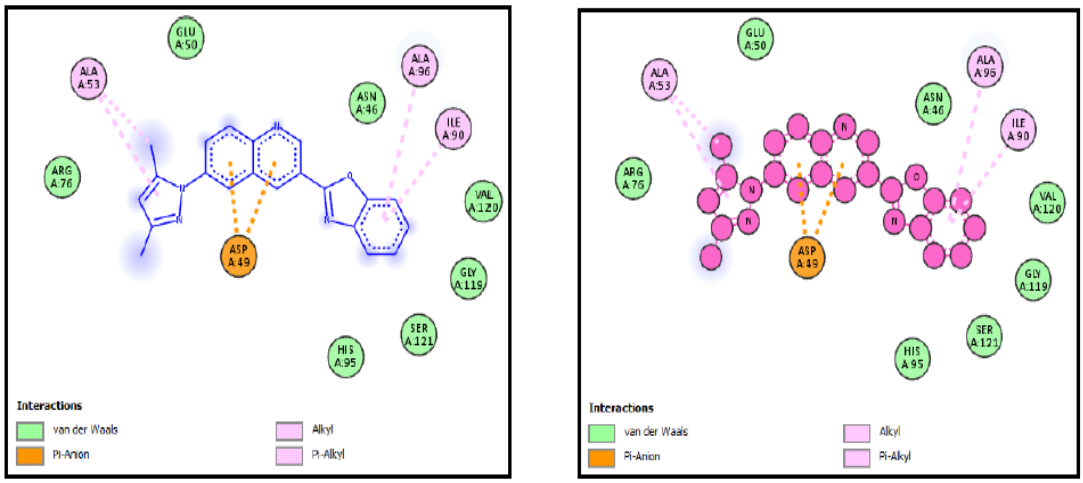


Fig. 5: 2D interaction of ligand 3 with 1KZN.

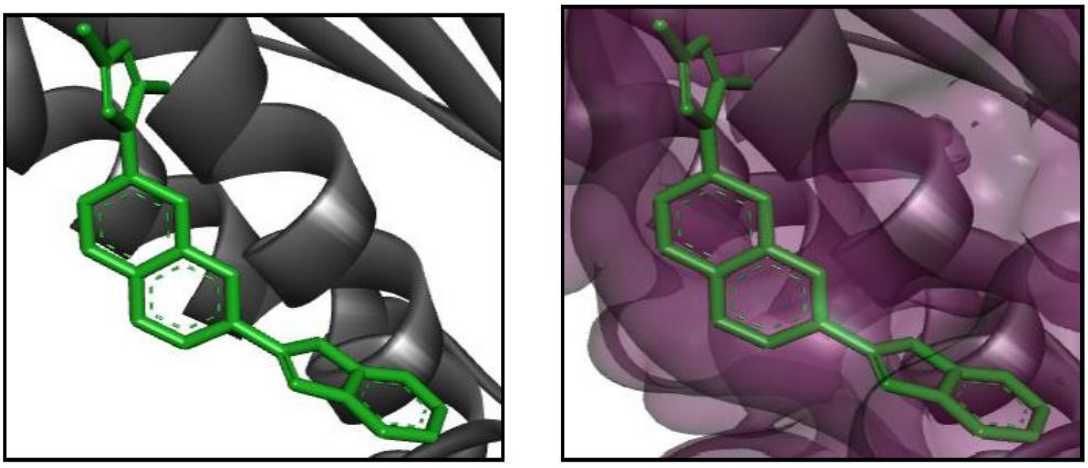


Fig. 6: 3D interaction of ligand 3 with 1KZN.

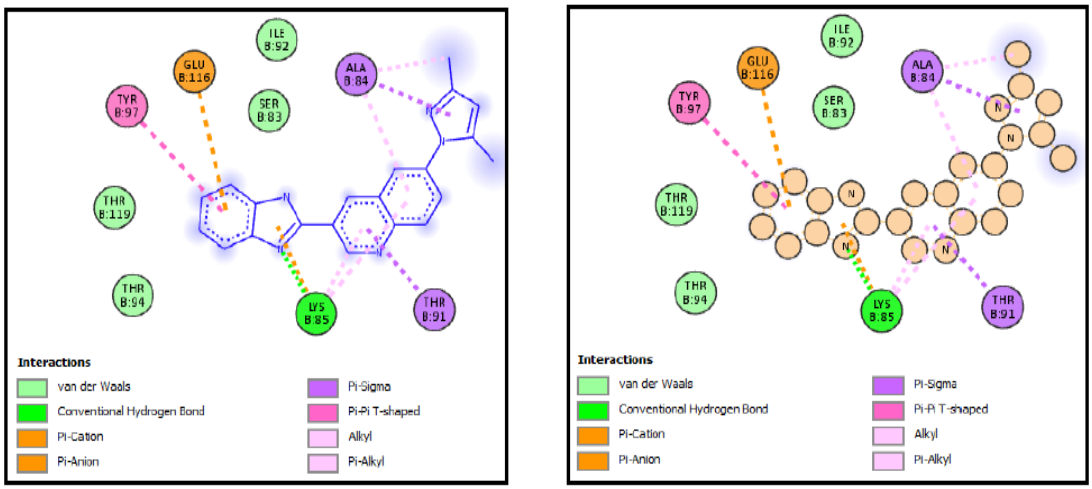


Fig. 7: 2D interaction of ligand 1 with 1QFE.

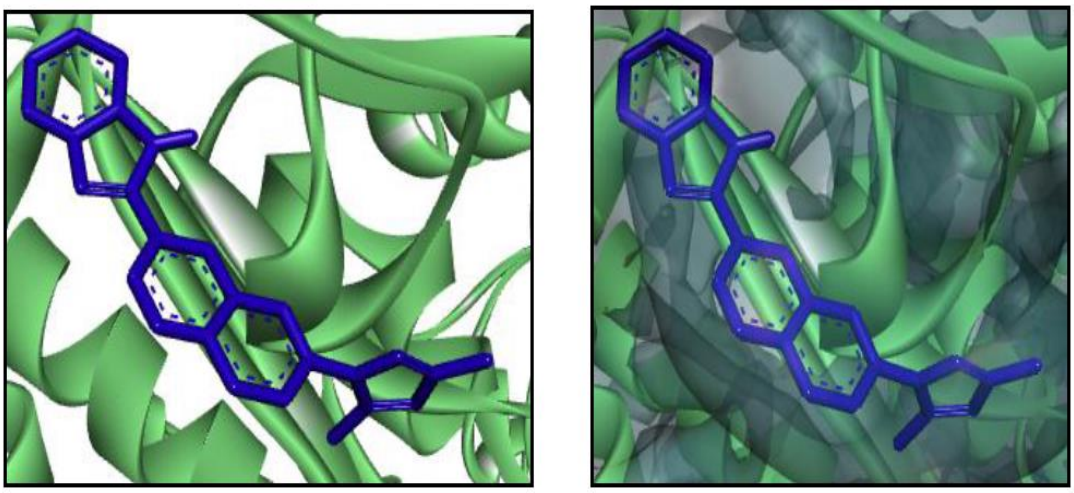


Fig. 8: 3D interaction of ligand 1 with 1QFE.

All the molecules showed high GI absorption, three molecule (1,3 and 4) showed blood brain barrier permeation and 2 and 5 did not permeate the brain.

A bioavailability score of ≥ 0.55 suggest that the compound exhibits excellent absorption by the body.[23]

The molecular docking showed good score of bioavailability. Metabolism is predicted based on the CYP models for substrate and are indicated in the following table (Table 3). Molecules 1,2 and 3 were recognized by the P-glycoprotein (P-gp).

According to the Lipinski rule, one of the most important chemical descriptors that correlate well with PK (Pharmacokinetic) properties is the topological polar surface area (TPSA), and the TPSA of a good drug should be less than 140 $Å^2$. In the present study, all the molecules have TPSA less than 90 $Å^2$ and thus all the molecules satisfied the Lipinski rule.

Table 3: Pharmacokinetic profile, Lipophilicity and Physiochemical property profile of the compounds.

Molecule	**1**	**2**	**3**	**4**	**5**
GI absorption	High	High	High	High	High
BBB permeant	Yes	No	Yes	Yes	No
CYP1A2 inhibitor	No	Yes	Yes	Yes	Yes
CYP2C19 inhibitor	Yes	Yes	Yes	No	No
CYP2C9 inhibitor	Yes	Yes	Yes	Yes	No
CYP2D6 inhibitor	Yes	No	Yes	No	No
CYP3A4 inhibitor	Yes	Yes	Yes	No	No
P-gp Substrate	Yes	Yes	Yes	No	No
Lipinski # violations	No	No	No	No	No
WLOGP	3.11	5.31	4.85	2.51	2.03

TPSA	54.77	71.84	56.74	76.98	87.98
Bioavailability Score	0.55	0.55	0.55	0.55	0.56

The BOILED-Egg model generally indicates the BBB and HIA evaluation where the Blue dots (PGP+) shows the molecules to be effluated. The Red dots (PGP-) addresses the molecules not to be effluated by the P-glycoprotein from central nervous system. The Yellow (yolk) region indicates high likelihood of brain penetration. The White region shows the region having passive gastrointestinal absorption.

In the BOILED-Egg model of Brain penetration (BBB), three molecules 1, 3 and 4 showed blood brain barrier permeation whereas 2 and 5 did not permeate the brain.

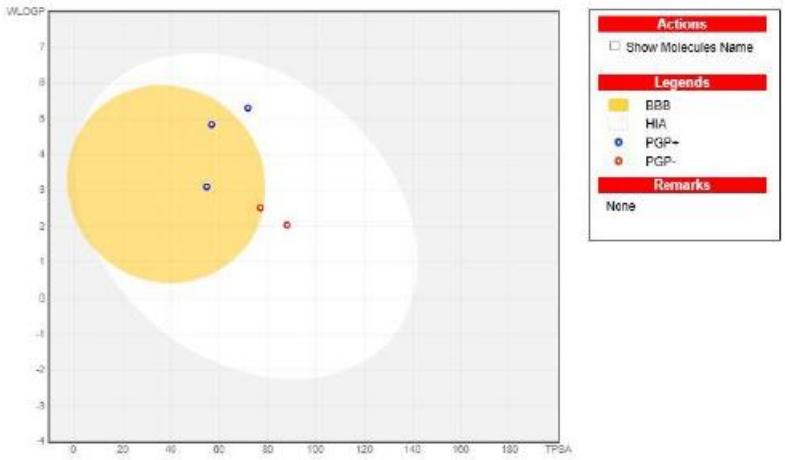


Fig. 9: Brain Permeation and Passive gastrointestinal absorption, (BOILED-Egg) of synthesized.

CONCLUSION

The computational study analysis showed that all the synthesized molecules could bind with the receptor proteins. The antibacterial activity was suggested by the synthesized molecules in docking studies with good negative values of binding affinity with *S.aureus*. The molecular docking showed good score of bioavailability.

REFERENCES

1. Delarue-Cochin S, Grellier P, Maes L, Mouray E, Sergheraert C, Melnyk P. Synthesis and antimalarial activity of carbamate and amide derivatives of 4-anilinoquinoline. Eur. J. Med. Chem., 2008; 43(10): 2045-55.

2. Hwang JY, Kawasuji T, Lowes DJ, Clark, JA, Connelly MC, Zhu F, Guiguemde WA, Sigal MS, Wilson EB, DeRisi JL, Guy RK. Synthesis and Evaluation of 7- Substituted 4-Aminoquinoline Analogues for Antimalarial Activity. J. Med. Chem., 2011; 54, 7084–7093.
3. Venkatarao V, Kumar L, Jha A, Sridhar G. Synthesis and Biological Evaluation of Chalcone Fused Quinoline Derivatives as Anticancer Agents. Chem. Data Collect. 2019; 22: 100236.
4. El-Feky SAH, Abd El-Samii ZK, Osman NA, Lashine J, Kamel MA, Thabet H. Synthesis, Molecular Docking and Anti-Inflammatory Screening of Novel Quinoline Incorporated Pyrazole Derivatives Using the Pfitzinger Reaction II. Bioorg. Chem., 2015; 58: 104–116.
5. Eteghwia CM, Ojaikre E, Onoabedje EA, Eze CC, Adomi PO. 7-Chloroquinoline Sulphonamide Derivatives: Synthesis, Characterization, Biological and Drug-likeness Evaluation. Communication in physical sciences, 2024; 12(1): 141-148.
6. Muruganantham, N, Sivakumar, R, Anbalagan N, Gunasekaran V, Leonard JT. Synthesis, Anticonvulsant and Antihypertensive Activities of 8-Substituted Quinoline Derivatives. Biol. Pharm. Bull, 2004; 27: 1683–1687.
7. Goda FE, Abdel-Aziz AAM, Ghoneim HA. Synthesis and Biological Evaluation of Novel 6-nitro-5- substituted Aminoquinolines as Local Anesthetic and Anti-arrhythmic Agents: Molecular Modeling Study. Bioorg. Med. Chem., 2005; 13: 3175–3183..
8. Satheesha Rai N, Balakrishna K. A novel series of nitrofuran containing 1,3,4,5- tetra substituted pyrazole via 1,3 dipolar addition reaction. Indian j of chem., 2007; 46B: 375-8.
9. Mari SK, Bantwal S, Holla, Nalilu S. Synthesis and antimicrobial studies on novel chloro-fluorine containing hydroxyl pyrazolines. European Journal of Medicinal Chemistry, 2007; 42: 30-36.
10. Sahu SK, Banerjee M, Samantray A, Behera C, Azaml MA. Synthesis, Analgesic, Anti-inflammatory and Antimicrobial Activities of Some Novel Pyrazoline Derivatives. Tropical Journal of Pharmaceutical Research, 2008; 7(2): 961-8.
11. Gomez L, Hack MD, McClure K, Sehon C, Huang L, Morton M, Li L, Barrett TD, Shankley N, Breitenbucher JG. SAR studies of 1, 5-diarylpyrazole- based CCK receptor antagonists. Bio-org & Med Chem Letters, 2007; 17: 6493-98.
12. Bhalekar SM, Fernandes PS. Synthesis and biological activity of few novel substituted quinolines. Research J. of Chemistry and Environment, 2001; 5(1): 29-30.

13. Bhalekar SM, Filmwala ZA, Singh B,Fernandes PS. Synthesis and biological activity of heterocyclic substituted quinolones. Indian J. of Heterocyclic Chemistry, 2001; 10: 229-230.
14. Aazam ES, Zaki M. Synthesis and characterization of Ni (II)/Zn (II) metal complexes derived from Schiff base and ortho-phenylenediamine: in vitro DNA binding, molecular modeling and RBC hemolysis. ChemistrySelect, 2020; 16, 5(2): 610-8.
15. Allinger NL, Geise HJ, Pyckhout W, Paquette LA, Gallucci JC. Structures of norbornane and dodecahedrane by molecular mechanics calculations (MM3), X-ray crystallography, and electron diffraction. Journal of the American Chemical Society, 1989; 111(3): 1106-14.
16. Rawal K, Khurana T, Sharma H, Verma S, Gupta S, Kubba C, Strych U, Hotez PJ, Bottazzi ME. An extensive survey of molecular docking tools and their applications using text mining and deep curation strategies. PeerJ Preprints, 2019; 15, 7: e27538v1.
17. Vieira TF, Sousa SF. Comparing AutoDock and Vina in ligand/decoy discrimination for virtual screening. Applied Sciences, 2019; 25, 9(21): 4538.
18. Ou-Yang SS, Lu JY, Kong XQ, Liang ZJ, Luo C, Jiang H. Computational drug discovery. Acta Pharmacologica Sinica, 2012; 33(9): 1131-40.
19. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific reports, 2017; 3, 7(1): 1-3.
20. Hassan AS, Askar AA, Naglah AM, Almehizia AA, Ragab A. Discovery of new schiff bases tethered pyrazole moiety: design, synthesis, biological evaluation, and molecular docking study as dual targeting DHFR/DNA gyrase inhibitors with immunomodulatory activity. Molecules, 2020; 25(11): 2593.
21. Daina A, Zoete V. Application of the SwissDrugDesign online resources in virtual screening. International journal of molecular sciences, 2019; 18, 20(18): 4612.
22. Wen H, Jung H, Li X. Drug delivery approaches in addressing clinical pharmacology-related issues: opportunities and challenges. The AAPS journal, 2015; 17(6): 1327-40.
23. Madanagopal P, Ramprabhu N, Jagadeesan R. In silico prediction and structure-based multitargeted molecular docking analysis of selected bioactive compounds against mucormycosis. Bulletin of the National Research Centre, 2022; 46(1): 1-21.