WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 6, 750-763. Research Article ISSN 2277–7105

MOLECULAR DOCKING STUDIES OF SOME 4*H* -1 -BENZOPYRAN-4-ONE DERIVATIVES

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Article Received on
28 Jan. 2025,

Revised on 18 Feb. 2025,
Accepted on 11 March 2025

DOI: 10.20959/wjpr20256-35958

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ABSTRACT

The synthesis and biological activity of few heterocyclic compounds derived from 2-(4-aminophenyl)- 4*H* -1 -benzopyran-4-one is reported earlier. 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: Benzopyran-4-one, Quinoline, Molecular docking, AutoDock Vina, SwissADME analysis.

INTRODUCTION

4*H* -1 -benzopyran-4-one having heterocyclic substituents at either 2 or 3- position are reported to have anticarcinogenic[1], antimicrobial activity[2,3], coronary dilatory activity[4], aldose reductase inhibitors.[5]

The inclusion of nitrogen in heterocyclic moieties plays a crucial role in influencing their biological activities by augmenting polarity and their capacity to interact with biological macromolecules. Consequently, numerous nitrogen heterocycle-induced structures have developed as useful remedies, presently deployed in treating several diseases. Previously we have reported the synthesise of few derivatives of 4*H* -1 -benzopyran-4-one such as
2-(3-Carbethoxy-4-oxo-4*H*-quinolin-6-yl)-4*H*-1- benzopyran-4-one (2),
2-(4-Methyl-2-oxo-1,2-dihydroquinolin-6-yl)-4*H*-1-benzopyran-4-one (3),
2-(4-Hydroxy-2-oxo-1,2-dihydroquinolin-6-yl)-4*H*-1-benzopyran-4-one (4) and

2-(2,4-Dichloroquinolin-6-yl)-4*H*-1-benzopyran-4- one (5) from 2-(4-Aminophenyl)-4*H*-1-benzopyran-4-one (1).[6]

Further 2-(2,4-Dichloroquinolin-6-yl)-4*H*-1-benzopyran-4- one (5) was used as a precursor to synthesize few heterocycles[7] such as

7-(4-Oxo-4*H*-1-benzopyran-2-yl) -5-chloro-1-phenyltriazolo[4,3-*a*] quinoline (6),

9-(4-Oxo-4*H*-1-benzopyran-2-yl)-7-chloro quinolino[2,1-*b*] quinazolin-1-one (7),

9-(4-Oxo-4*H*-1-benzopyran-2-yl)-7-chlorobenzimidazolo[3,2-*a*] quinoline (8) and

7-(4-Oxo-4*H*-1-benzopyran-2-yl) -5-chlorotetrazolo[4,3-*a*] quinoline (9).

These compounds (2-9) were assayed for their biological activity against a variety of microbes such as *E. coli, Staphylococcus aureus, Salmonella typhi and Bacillus subtilis*. All the compounds showed moderate activity.[6,7]

In the present paper, I have discussed 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, we have used AutoDock Vina 1.5.7, a docking tool.[11,12]

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).*[8] The molecular structure of these ligand were converted to PDB format using *Avogadro 2* app.[9]

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.[10]

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.[11,12] For this process the Grid map optimization is done. The Grid Box co-ordinates can be saved so that synthesized molecules can be dock exactly at that position. There is alternative way called as blind docking which can be use. The use of blank docking is to find out other probable sites on which ligands can be dock to the target protein molecules.

In this study blank docking processes[13] were used to find out positions as well as the highest binding energies.[14] Molecular docking applied at different stages for the drug designing/drug preparation such as to predict binding mode of known ligand, to identify novel or potent ligands, to find binding affinity. Different algorithms used to predict the biological activity of compounds by studying interactions between ligands and targeted pdb proteins of microorganisms. Molecular docking produces valuable data related to location of binding pocket, hydrogen bonding, etc. It can be compared with instrumental analysis.

Molecular docking generally used to find out virtual screening of the synthesized molecule to targeted protein of pathogenic micro-organisms. It 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

The molecular interactions can be viewed using various visualization tools such as PyMOL, BIOVIA, Discovery Studio Visualizer etc. 2D and 3D interaction plots of ligand and protein were derived. The hydrogen bond interactions were studied, visualized. The binding affinity of the ligand-protein is the resultant of all such interactions and binding energy existing between them. The various conformations of ligands viewed using visualization tools and their positional pockets on the protein.[15]

SwissADME analysis

Large number of drug candidates synthesized fails to act as drug against expected pathogenic micro-organisms. There is need to first find out possible drug candidates and their drug likeness during discovery phase. Now a days it is done by using various online computer aided tools such as SwissADME.[16] This is generally done to avoid loss of time, chemicals, manpower, expenditure etc. In this absorption, distribution, metabolism, and excretion

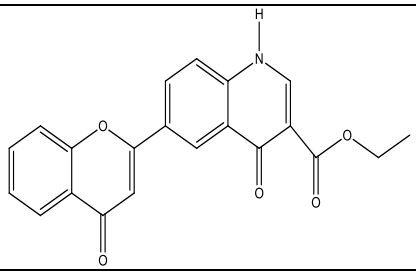
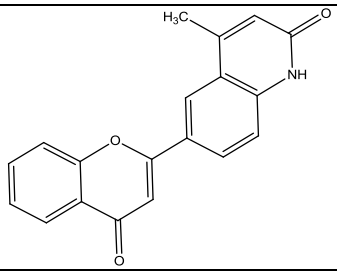
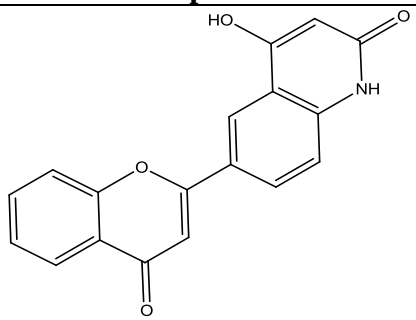
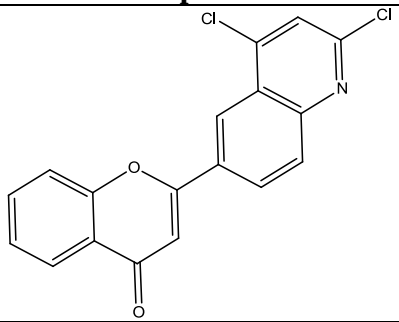
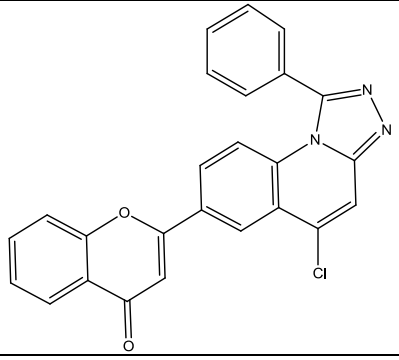
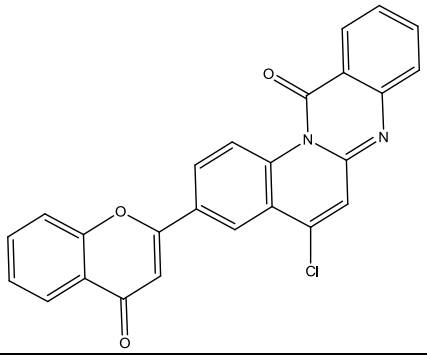
(ADME) properties are studied at the time of discovery. Pharmacokinetics allows one to study drug's ability to permeate blood brain barrier (BBB), absorption from Gastro-intestinal tract (GI) obtained from BOILED EGG model. BOILED-Egg method works by processing the polarity and lipophilicity of synthesized molecules. It is fast, reproducible, and instinctive. It also helps to predict whether drug-candidate can act as inhibitor against several protein enzymes.

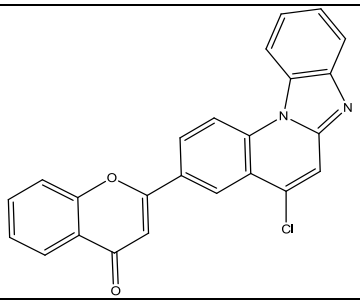
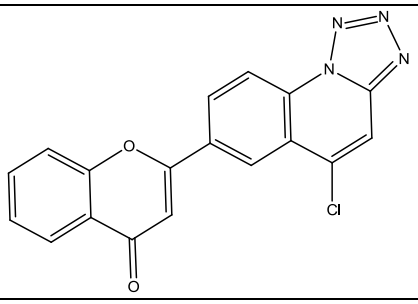
It analyzes the various points such as drugs likeness, permeation of Blood Brain, Total polar surface area[18], GI absorption analysis. The ADME analysis let know if a drug candidate is having pharmacological effect and provides specific targets for future research.

Structute of the Molecules

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

Table 1: Structure of molecules (2-9).

	
Comp. No. 2	**Comp. No. 3**
	
Comp. No. 4	**Comp. No. 5**
	
Comp. No. 6	**Comp. No. 7**

	
Comp. No. 8	**Comp. No. 9**

RESULT AND DISCUSSION

The docking results shows that all the docked ligand (2-9) have a low crucial binding energy with proteins of *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Salmonella typhi*. The most prominent docking was shown by molecule no. 8.

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 2	-10.6	-7.6	-7.3	-7.0
Molecule 3	-11.1	-7.9	-7.9	-7.1
Molecule 4	-11.6	-8.3	-8.1	-7.2
Molecule 5	-10.4	-7.9	-7.6	-6.6
Molecule 6	-11.9	-8.1	-8.0	-7.4
Molecule 7	-10.3	-8.9	-8.2	-7.6
Molecule 8	**-12.5**	**-8.9**	**-8.5**	**-8.3**
Molecule 9	-11.8	-8.1	-7.5	-7.1
Ciprofloxacin	-7.6	-8.2	-8.2	-6.5

2D and 3D interaction of some of the molecules (3,4,6 and 8) with targeted proteins are illustrated in the following figures.

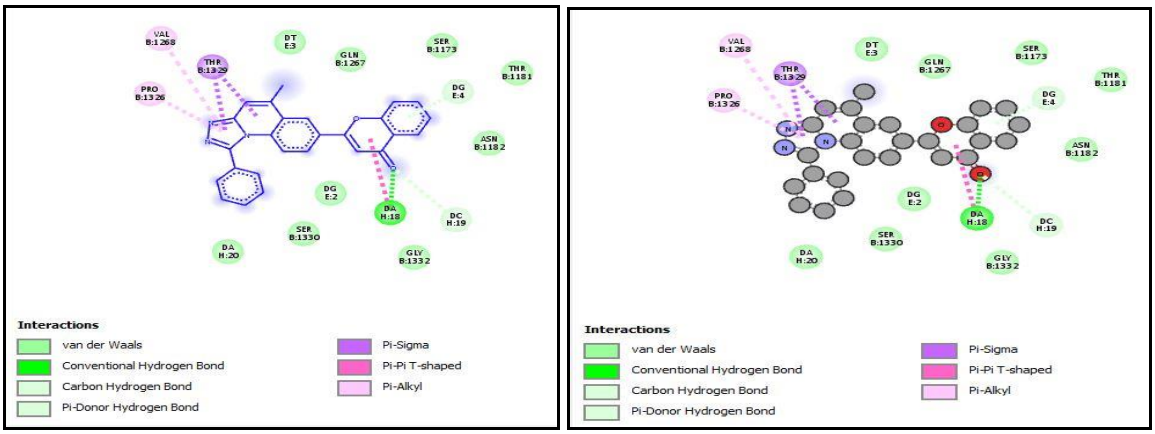


Fig. 1: 2D interaction of molecule 6 with targeted protein 2XCT.

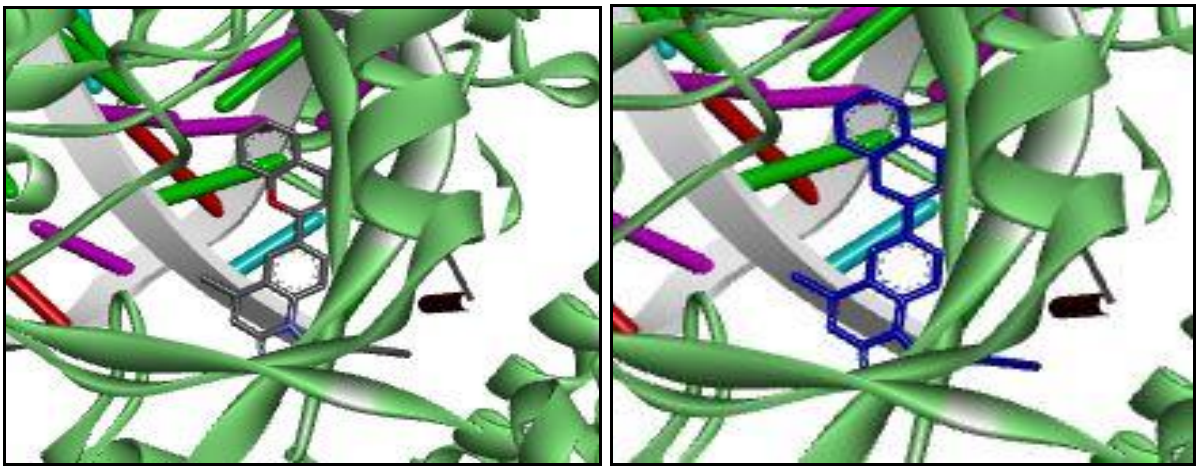


Fig.2: 3D interaction of molecule 6 with targeted protein 2XCT.

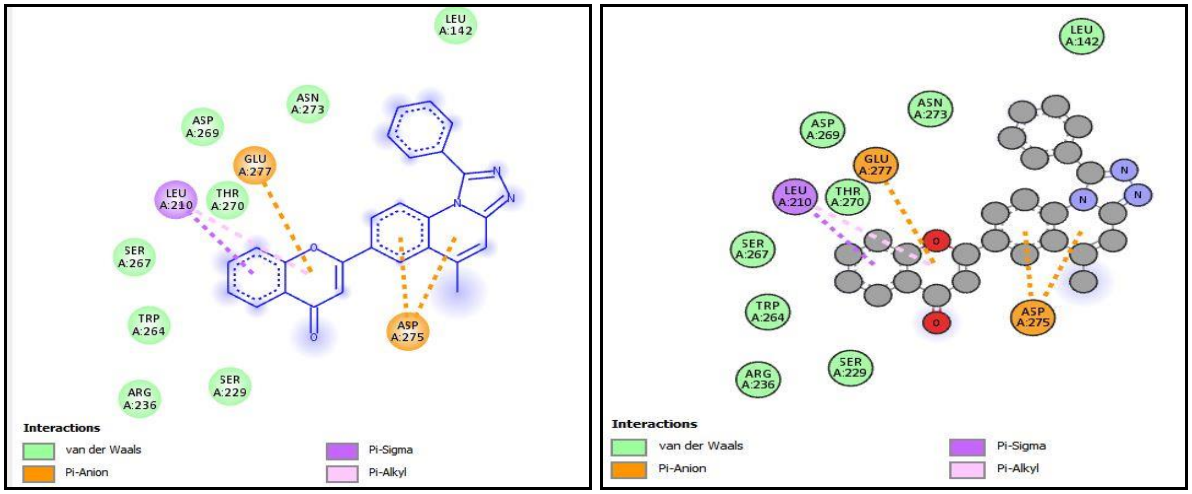


Fig. 3: 2D interaction of molecule 6 with targeted protein 1BAG.

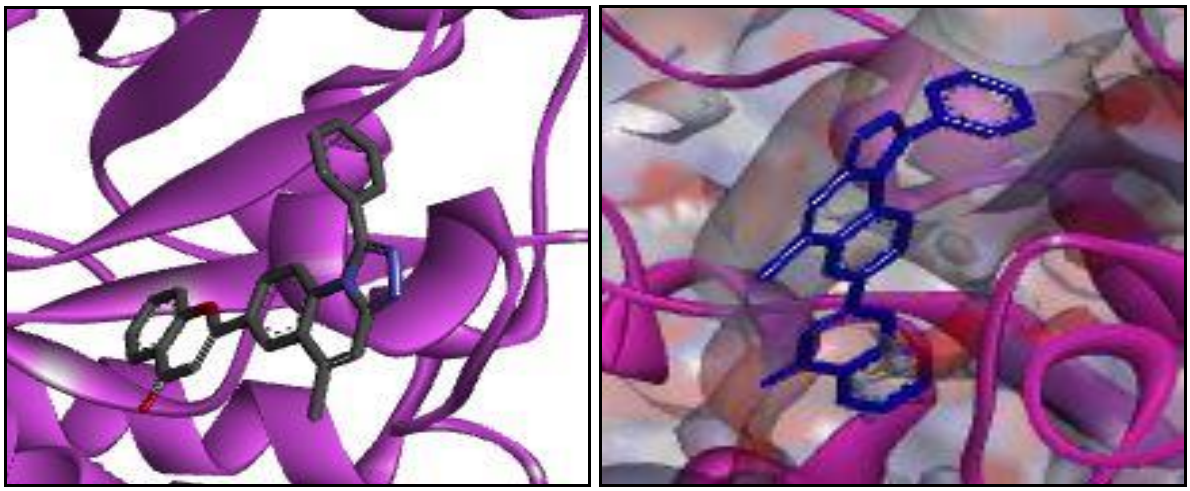


Fig. 4: 3D interaction of molecule 6 with targeted protein 1BAG.

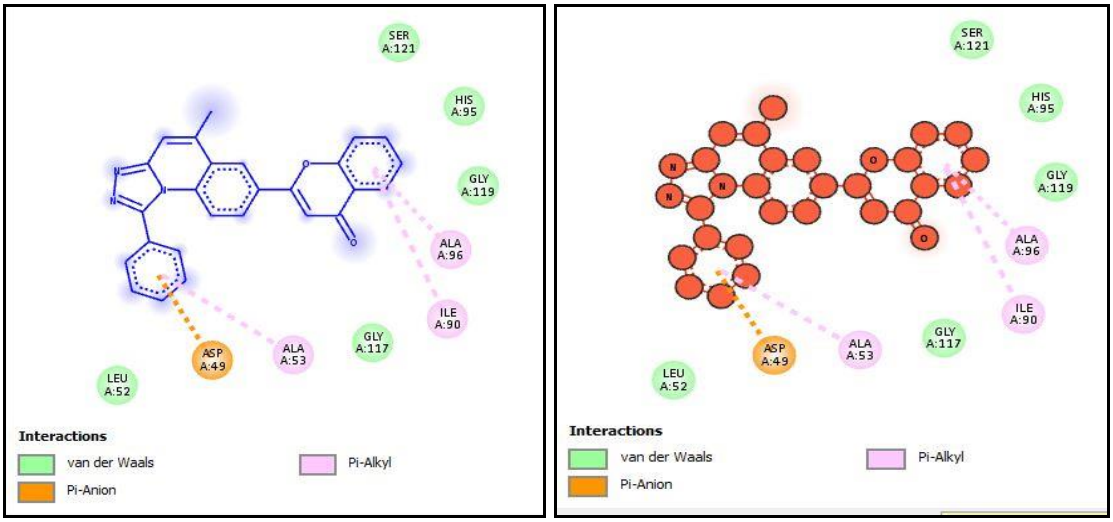


Fig. 5: 2D interaction of molecule 6 with targeted protein 1KZN.

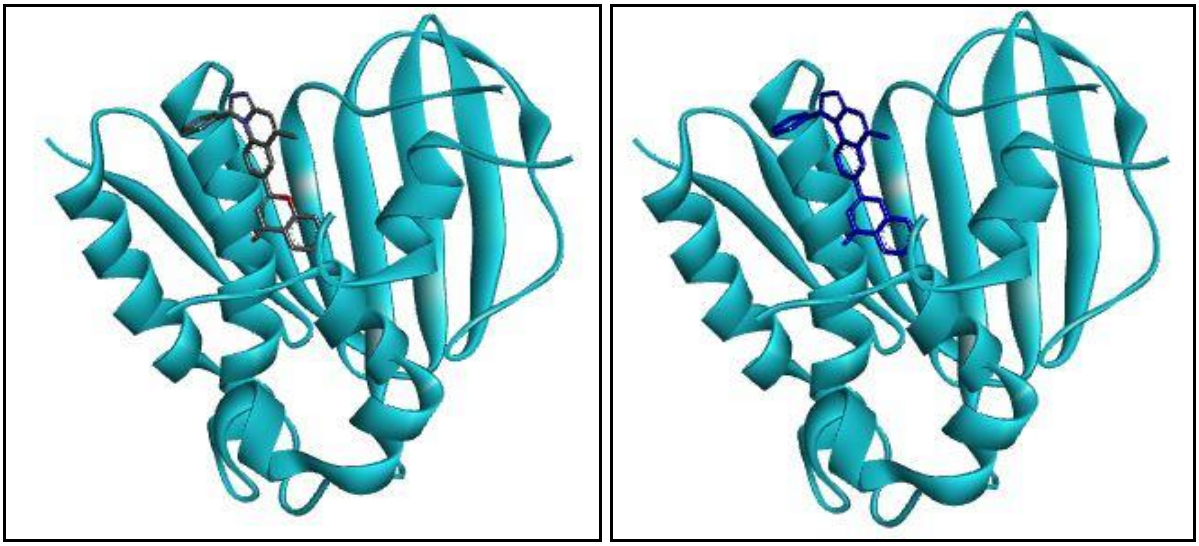


Fig. 6: 3D interaction of molecule 6 with targeted protein 1KZN.

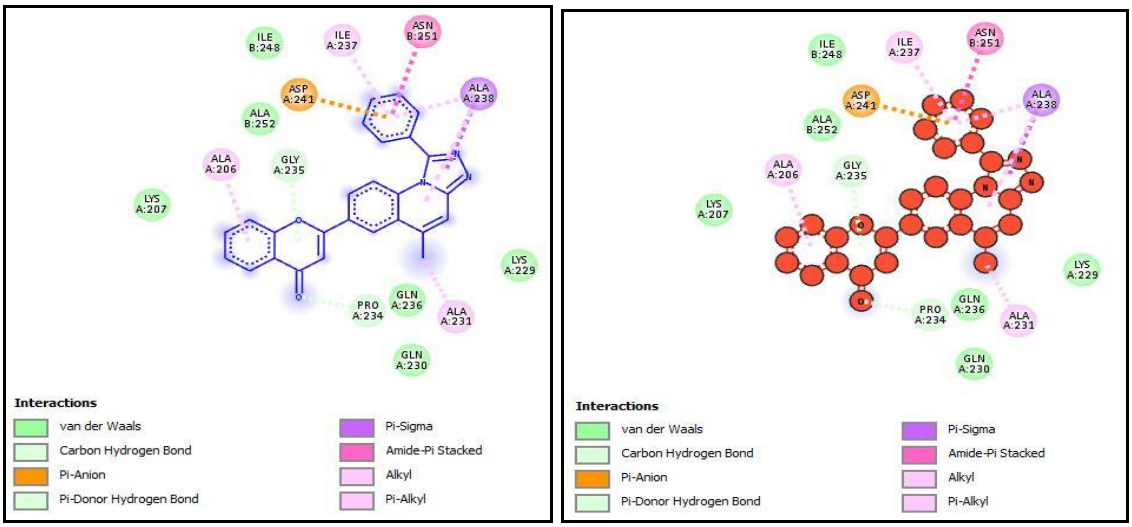


Fig. 7: 2D interaction of molecule 6 with targeted protein 1QFE.

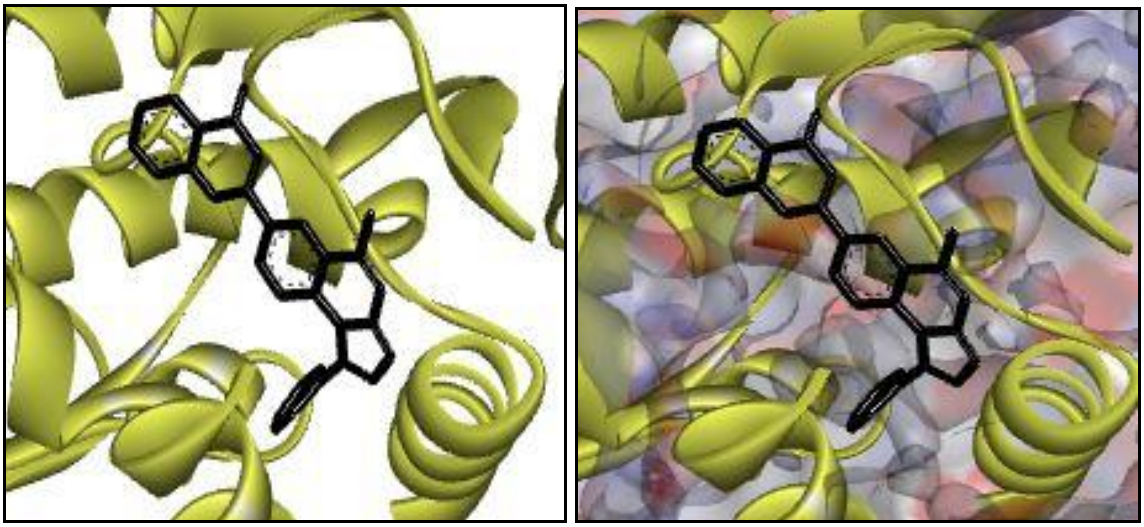


Fig. 8: 3D interaction of molecule 6 with targeted protein 1QFE.

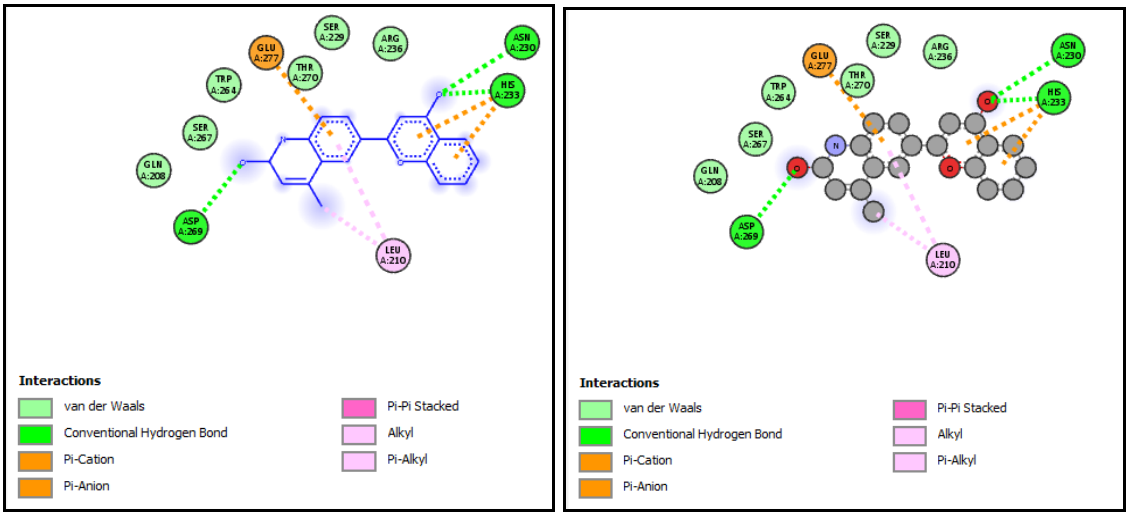


Fig. 9: 2D interaction of molecule 3 with targeted protein 1BAG.

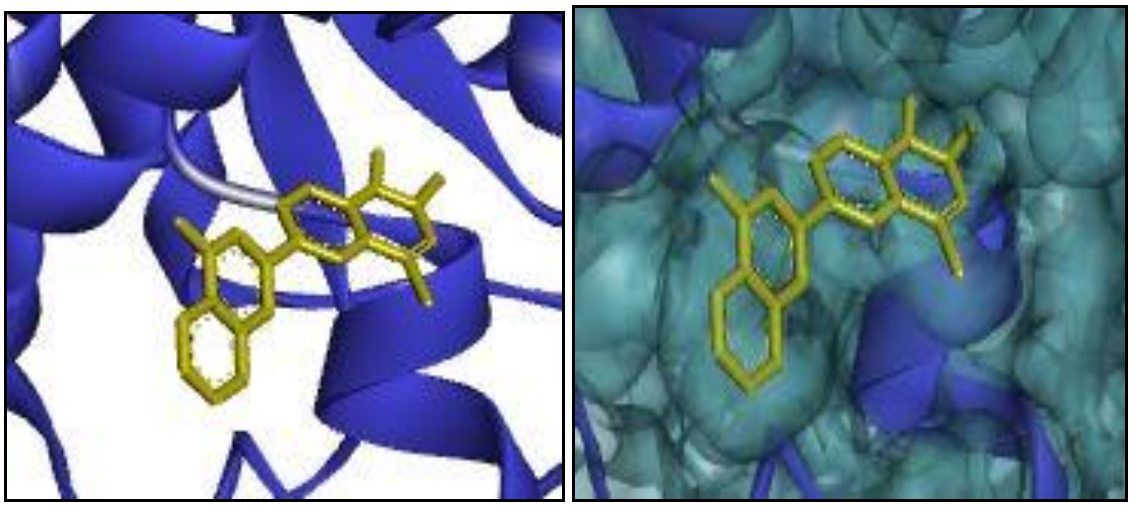


Fig. 10: 3D interaction of molecule 3 with targeted protein 1BAG.

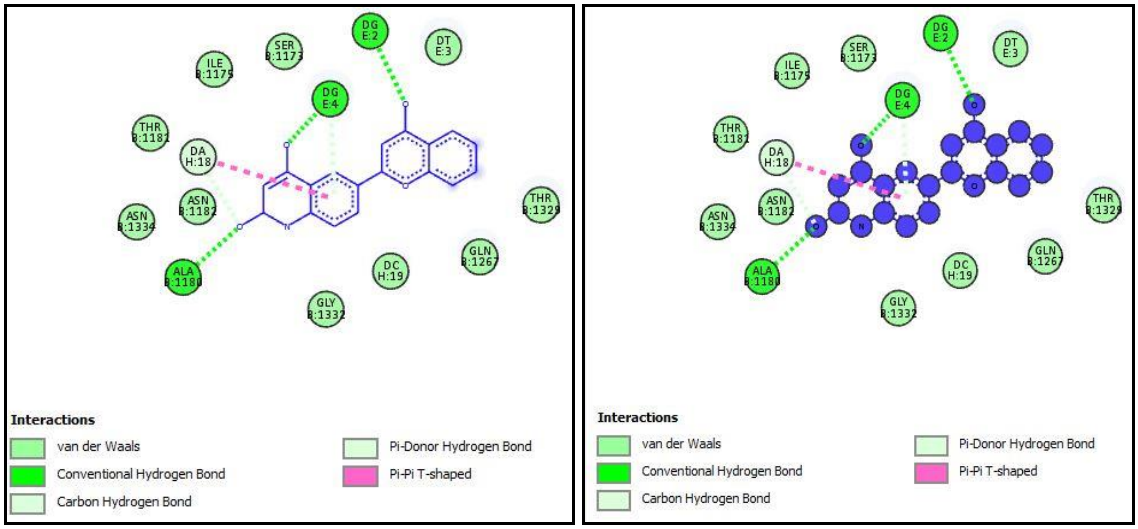


Fig. 11: 2D interaction of molecule 4 with targeted protein 2XCT.

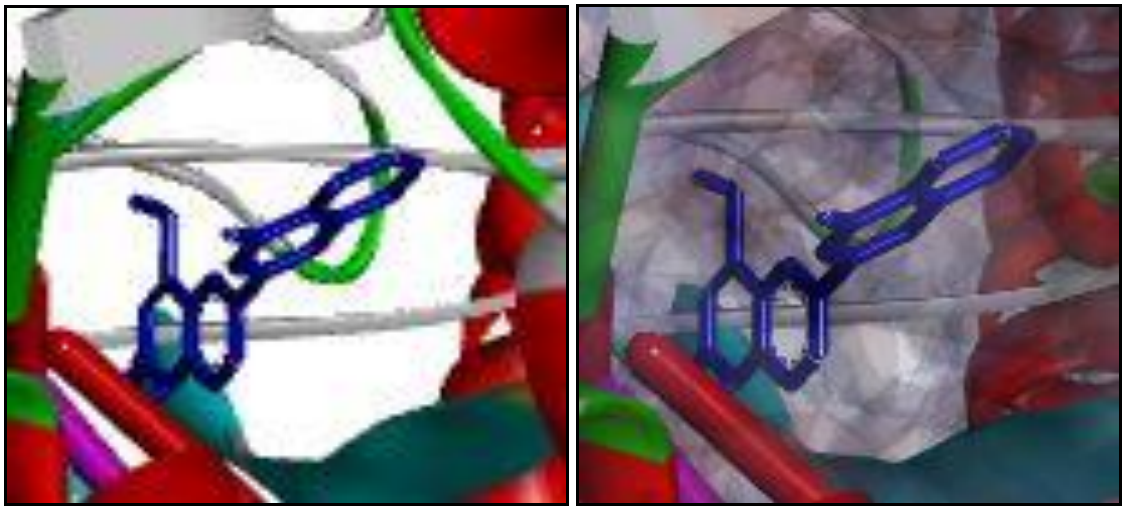


Fig. 12: 3D interaction of molecule 4 with targeted protein 2XCT.

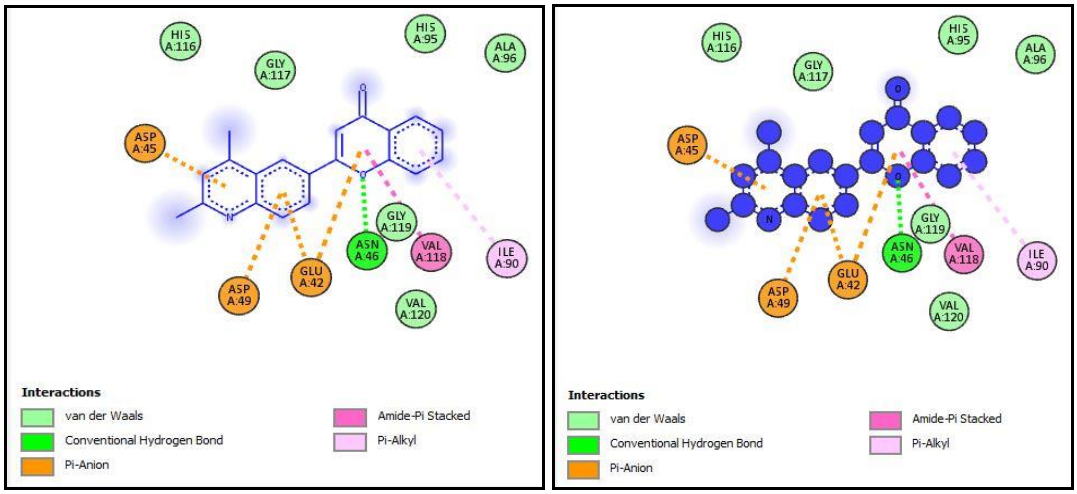


Fig. 13: 2D interaction of molecule 4 with targeted protein 1KZN.

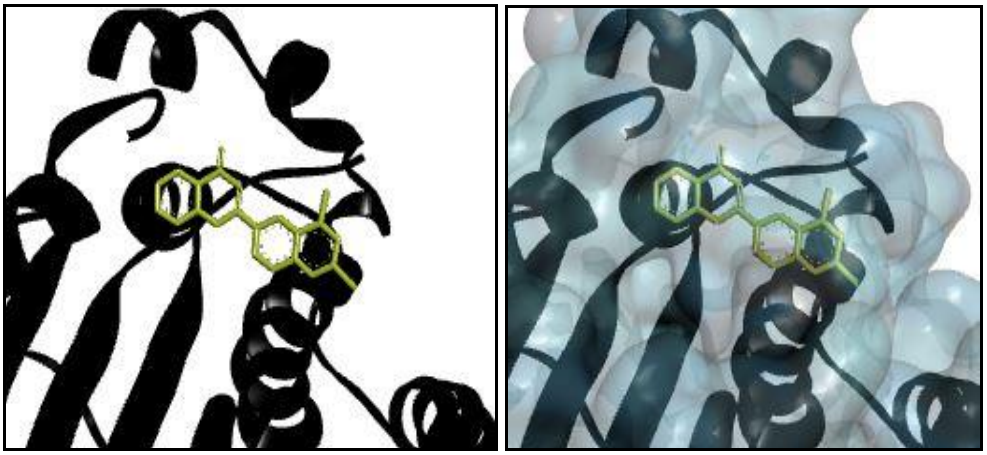


Fig. 14: 3D interaction of molecule 4 with targeted protein 1KZN.

Most docking interaction

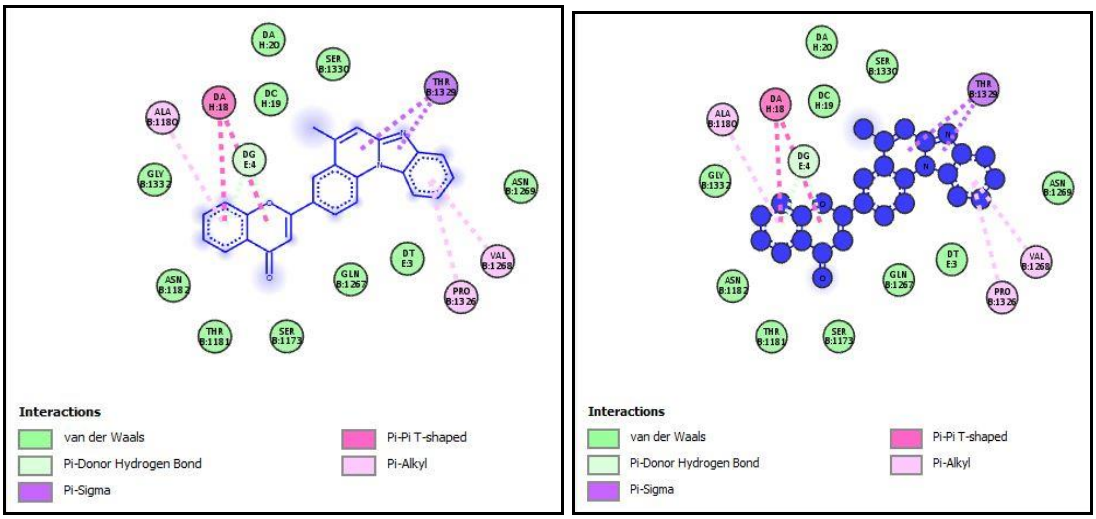


Fig. 15: 2D interaction of molecule 8 with targeted protein 2XCT.

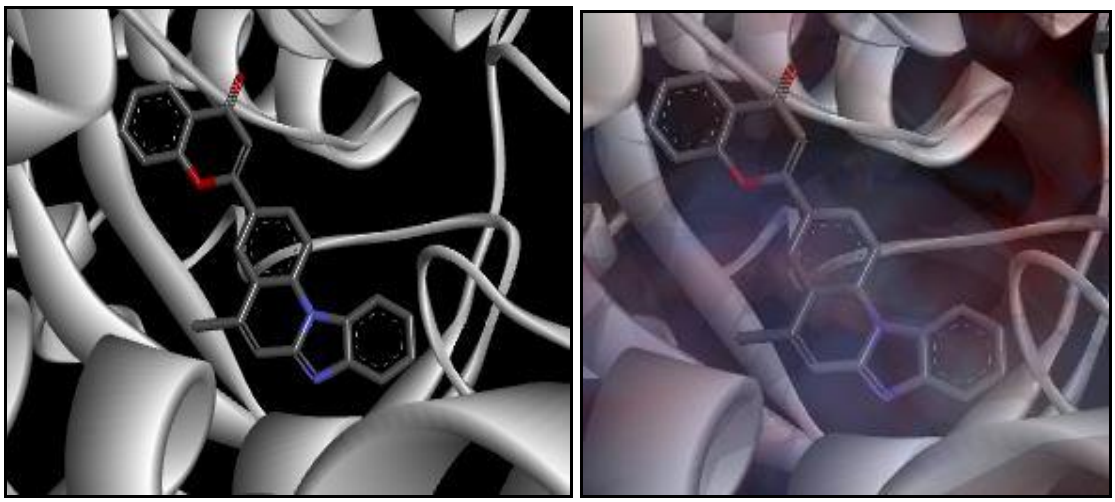


Fig. 16: 3D interaction of molecule 8 with targeted protein 2XCT.

All the molecules (2-9) showed high GI absorption, three molecules (3,5 and 9) showed blood brain barrier permeation and rest of the molecules did not permeate the brain. The molecular docking showed good score of bioavailability of 0.55.[19] Metabolism is predicted based on the CYP models for substrate and are indicated in the following table (Table 3). None of the molecules (2-9) were recognized by the P-glycoprotein (P-gp) (Table 4).

Table 3: Pharmacokinetic profile of the compounds.

Molecule	GI absorption	BBB permeant	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
Molecule 2	High	No	Yes	Yes	Yes	No	Yes
Molecule 3	High	Yes	Yes	No	No	No	Yes
Molecule 4	High	No	Yes	No	No	Yes	No
Molecule 5	High	Yes	Yes	Yes	Yes	No	No
Molecule 6	High	No	No	Yes	No	No	No
Molecule 7	High	No	Yes	No	No	No	No
Molecule 8	High	No	Yes	Yes	No	No	No
Molecule 9	High	Yes	Yes	No	No	No	No

Table 4: Pharmacokinetic profile of the compounds.

Molecule	P-gp Substrate	Lipinski # violations
Molecule 2	No	0
Molecule 3	No	0
Molecule 4	No	0
Molecule 5	No	0
Molecule 6	No	1
Molecule 7	No	1
Molecule 8	No	0
Molecule 9	No	0

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 $Å^2$ (Table 5) and this satisfies the Lipinski rule.

Table 5: Lipophilicity and Physiochemical property profile.[17]

Molecule	2	3	4	5	6	7	8	9
WLOGP	3.48	3.61	3.01	5.32	5.98	5.43	6.07	3.70
TPSA	89.37	63.07	83.30	43.10	60.80	64.58	47.51	73.29
Bioavailability Score	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55

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 (3,5 and 9) showed blood brain barrier permeation and rest of the molecules did not permeate the brain.

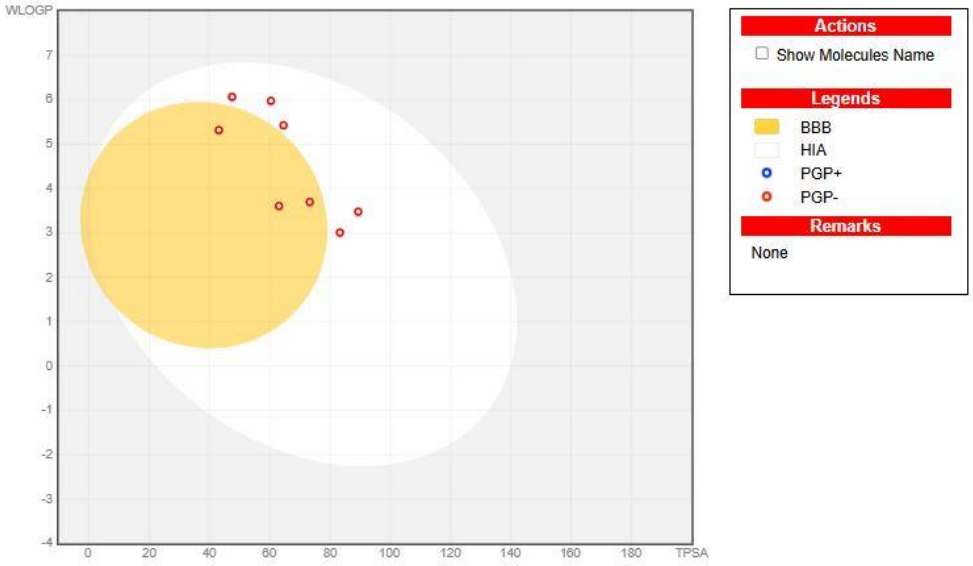


Fig. 17: Brain permeation and passive gastrointestinal absorption (BOILED-Egg) of synthesized molecules.

CONCLUSION

The computational study analysis showed that 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. The molecular docking showed good score of bioavailability of 0.55[19]. Molecule 8 can be a good candidate for further research and drug development process.

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