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MOLECULAR DOCKING STUDIES OF SOME PYRAZOL-1-YL-1, 3-THIAZOLE DERIVATIVES

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ABSTRACT

Synthesis of 4-(4-bromophenyl)-2-[4-arylhydrazono-3-methyl-5-(4-phenylthiazol-2-yl) imino- 4,5-dihydropyrazol-1-yl]-1,3-thiazole derivatives is reported. The 4-arylhydrazono derivatives have different group such as -NO_2, -Br, -Cl, -CH_3, -OCH_3 at position 4. We are hereby reporting molecular docking studies of these molecules. Structures of these molecules were docked to the target protein molecules of disease producing pathogens using AutoDock Vina, a docking tool. SwissADME studies were carried out to test the gastro-intestinal absorption and brain permeation.

KEYWORDS: Pyrazole, Thiazole, Molecular docking, SwissADME analysis.

INTRODUCTION

Pyrazole plays a vital role in many biological activities such as anti-bacterial and antifungal.[1,2] analgesic, anti-inflammatory and anti -microbial.[3]

Thiazole possess various biological activities such as antibacterial.[4,5,6] antifungal.[4] antitubercular.[5] and antioxidant activities.[6]

Earlier we have reported synthesis and biological activity of 4-(4-bromophenyl)-2-[4-arylhydrazono-3-methyl-5-(4-phenylthiazol-2-yl) imino-4,5-dihydropyrazol-1-yl]-1,3-thiazole derivatives.[7]

These heterocycles having different substituents such as -NO_2, -Br, -Cl, -CH_3, -OCH_3 group at position 4 in the arylhydrazono group 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 were found to be inactive.[7]

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.

MATERIALS AND METHOD

In this study, AutoDock Vina 1.5.7, a docking tool.[10,11] 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).*[8] The molecular structure of these ligands 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.

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.[10,11] 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.

In this study blank docking processes[12] were used to find out positions as well as the highest binding energies.[13] 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 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.[14]

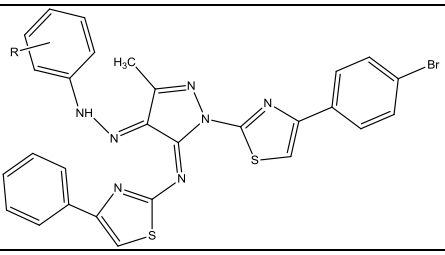
SwissADME Analysis

SwissADME help to first find out possible drug candidates and their drug likeness,[15] which is generally done during discovery phase to avoid loss of time, chemicals, manpower, expenditure etc. wherein the 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.[16] 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 compounds 1(a-e).



1(a-e), R = a) 4-NO_2, b) 4-Br, c) 4-Cl, d) 4-CH_3, e) 4-OCH_3

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 1a	-10.4	**-8.7**	-7.3	**-7.7**
Molecule 1b	**-10.7**	-7.1	-6.9	-7.4
Molecule 1c	-10.3	-8.3	-7.5	-7.2
Molecule 1d	-8.9	-7.6	**-7.7**	-6.3
Molecule 1e	-9.9	-8.3	-7.0	-7.2

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

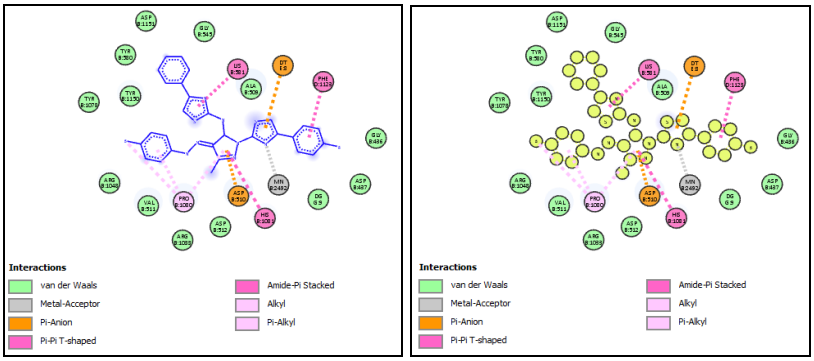


Fig. 1: 2D interaction of protein 2XCT with molecule 1b.

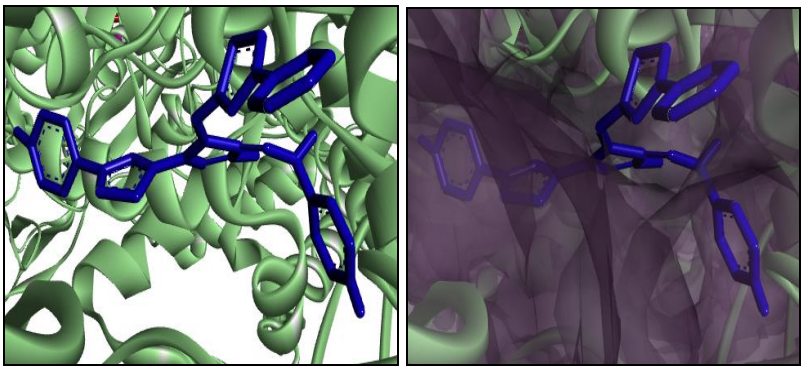


Fig. 2: 3D interaction of protein 2XCT with molecule 1b.

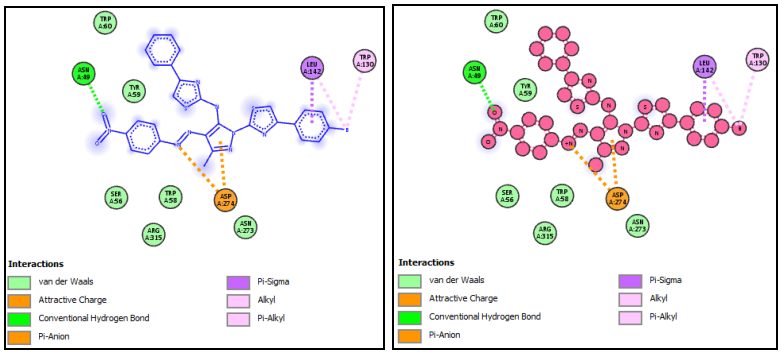


Fig. 3: 2D interaction of protein 1BAG with molecule 1a.

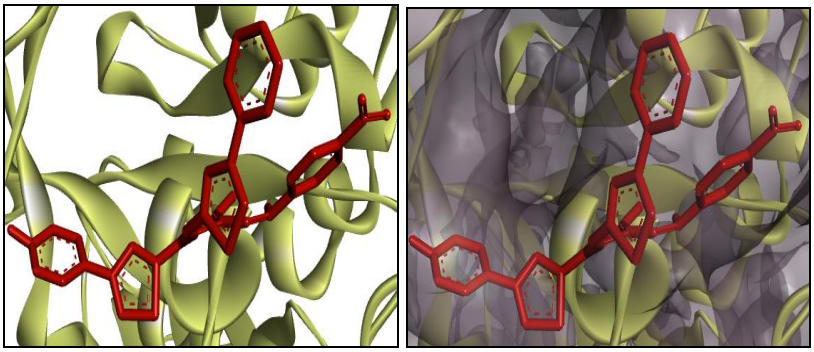


Fig. 4: 3D interaction of protein 1BAG with molecule 1a.

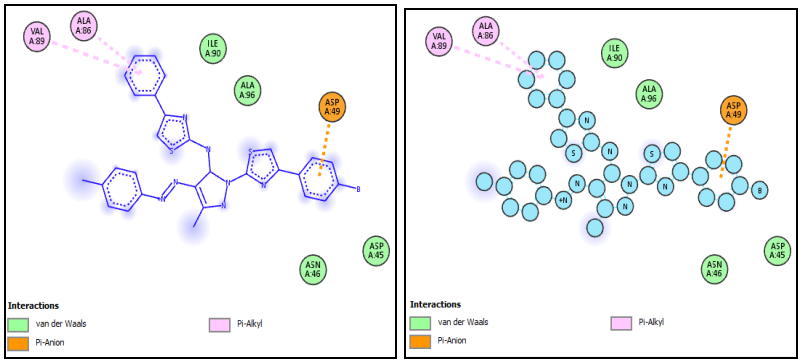


Fig. 5: 2D interaction of protein 1KZN with molecule 1d.

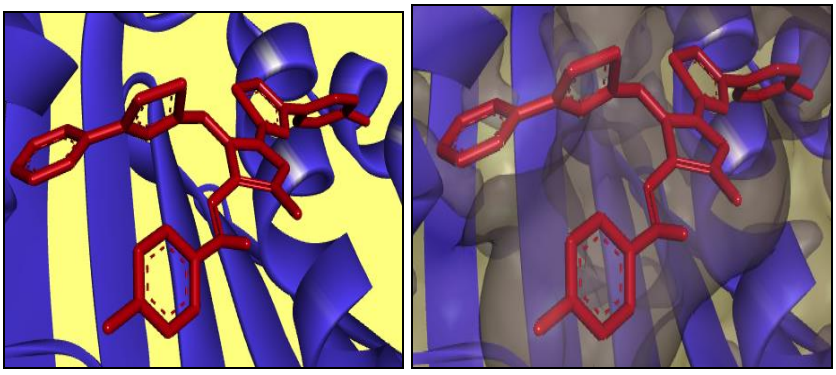


Fig. 6: 3D interaction of protein 1KZN with molecule 1d.

All the molecules 1(a-e) showed low GI absorption, no blood brain barrier permeation and were not recognized by the P-glycoprotein (P-gp).

A bioavailability score of ≥ 0.55 suggest that the compound exhibits excellent absorption by the body.[17] All the molecules showed poor absorption by the body. 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 except 1a and 1e have TPSA less than 140 $Å^2$.

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

Molecule	**1a**	**1b**	**1c**	**1d**	**1e**
GI absorption	Low	Low	Low	Low	Low
BBB permeant	No	No	No	No	No
CYP1A2 inhibitor	No	No	No	No	No
CYP2C19 inhibitor	No	No	No	No	No
CYP2C9 inhibitor	No	No	No	No	No
CYP2D6 inhibitor	No	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	No
P-gp Substrate	No	No	No	No	No
Lipinski # violations	2	2	2	2	2
WLOGP	7.05	7.90	7.79	7.45	7.15
TPSA	180.43	134.61	134.61	134.61	143.84
Bioavailability Score	0.17	0.17	0.17	0.17	0.17

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), none of the molecule showed blood brain barrier permeation.

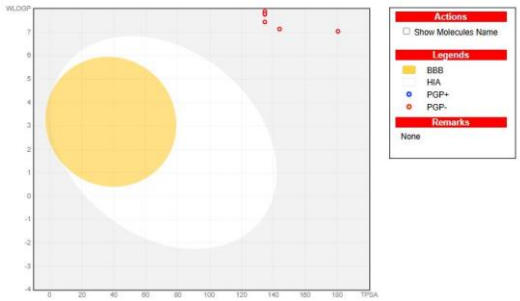


Fig. 7: Brain permeation and passive gastrointestinal absorption, (BOILED-Egg) of synthesized molecules.

CONCLUSION

The computational study analysis of five different derivatives having -NO_2, -Br, -Cl, -CH_3, -OCH_3 group at position 4 in the arylhydrazono group showed that all the synthesized molecules could bind with the receptor proteins. There is no remarkable influence of the nature of substituent on the activities of the molecules. 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 that all the derivatives have poor score of bioavailability.

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