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MOLECULAR DOCKING STUDIES AND ADME PREDICTION OF NOVEL HYBRID MOLECULES OF BENZOXAZINYL PYRAZOLE ARYLIDENES

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ABSTRACT

Most of the nitrogen and oxygen containing heterocycles possess wide range of biological activities. Combination of heterocylic molecules proved to be a successful approach for augmenting biological activities. Novel hybrid Molecules of Benzoxazinyl Pyrazole Arylidenes were designed and synthesized by appropriate synthetic routes.Novel hybrid molecules were screened for their *in silico* antibacterial activity. This approach paved the way to explore the specificity of newly synthesized hydrid molecules. The novel hybrid molecules were docked with dihydrofolate reductase of *S.aureus* (PDB ID: 3SRW); dihydrofolate reductase of *E.coli* (PDB ID: 1RX7); The docked poses were ranked based on their docking scores and ligand –receptor binding free energy with the enzyme. The above studies revealed that docking of hybrid molecules (4-hydroxy.3-methoxybenzylidene substituted benzoxazinyl pyrazole) showed promising inhibitory activity. Thus molecular docking helped in exploring the selectivity of newly synthesized hybrid molecules in the active site of enzyme. ADME properties of hybrid molecules were predicted using QuikProp and all the molecules showed drug like properties.

Key Words:- pyrazole, benzoxazine, molecular docking.

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INTRODUCTION

Various alkyl benzoxazinyl derivatives and pyrazol are reported to possess antimicrobial activity (Sonia *et al.,* 2013). Dihydrofolate reductase enzyme plays a pivotal role in the biosynthesis of folate. Folate is essential for the synthesis of DNA and RNA in bacteria. Biosynthetic pathway of folic acid formation is a major target for the development of antibacterial agents.This enzyme has got high binding affinities and specificity towards the analogs than the natural substrates (Hawser *et al*., 2006). This paved the way to make DHFR as an ideal target for designing of antibacterial agents efficiently. The aim of present study is to screen a series of benzoxazinyl pyrazole arylidenes DHFR inhibitors. Docking studies reveals the binding mode of ligands on DHFR and structural requirements for its inhibition. ADME prediction of new hybrid molecules also carried out to ensure drug like properties of the compounds.

MATERIALS AND METHODS

Computational methods by Glide

Docking study was performed for all the benzoxazinyl pyrazole arylidenes by Glide integrated Maestro interface on the Linux operation system. The molecules were subjected to predict the pharmacokinetic or ADME properties using the QikProp (Parasuraman *et al*., 2014).

Protein structure preparation

The X-ray crystallographic structures of the proteins PDB ID: 3SRW and PDB ID: 1RX7 were obtained from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank was used in this study for dihydrofolate reductase in *S.aureus* and *E.coli*. Water molecules of crystallization were detached from the composite and the protein was optimized for docking using the protein preparation and refinement utility provided by Schrödinger LLC. Partial atomic charges were assigned according to the OPLS-AA force field.

Ligand Preparation

The ligand structures were prepared by LigPrep module of the software which produces single low energy 3D structures.

Ligand structures

Docking of molecule

Molecular docking calculations were performed using ‘‘Extra Precision’’ (XP) mode of GLIDE program.The binding site, for which the various energy grids were calculated and stored, is defined in terms of two concentric cubes: the bounding box, which must contain the center of any acceptable ligand pose, and the enclosing box, which must contain all ligand atoms of an acceptable pose, with a Root Mean Square Deviation (RMSD) of less than 0.5 Å and a maximum atomic displacement of less than 1.3 Å were eliminated as redundant in order to increase diversity in the retained ligand poses.

The scale factor for van der Waals radii was applied to those atoms with absolute partial charges less than or equal to 0.15 (scale factor of 0.8) and 0.25 (scale factor of 1.0) electrons for ligand and protein, respectively. The max keep variable which sets the maximum number of poses generated during the initial phase of the docking calculation were set to 5000 and the keep best variable which sets the number of poses per ligand that enters the energy minimization was set to 1000. Energy minimization protocol includes dielectric constant of 4.0 and 1000 steps of conjugate gradient. Upon completion of each docking calculation, at most 100 poses per ligand were generated.

The best docked structure was chosen using a GLIDE score (Gscore) function. Another scoring function used by GLIDE is E-model, which itself derived from a combination of the Gscore, Coulombic, van der Waals and the strain energy of the ligand.

ADME prediction

All the synthesized molecules were evaluated for the prediction of ADME properties using Quikprop. Quikprop predicts pharmaceutically and physically relevant properties. ADME prediction can be used as a tool for lead optimization to enhance the desired properties of a given compound (Pawar *et al*.,(2011),Lipinski *et al*.,(2001).

RESULTS

Grid generation

Glide (Grid-based ligand Docking with energetics) predicts favourable interactions of ligand and protein. Ligand poses have to go through a series of filters which evaluate the interaction between ligand and protein. G-score generated during docking process provides about the best fitting of ligand inside a binding pocket. The most negative value is the best G score which directly reveals most active ligand.

Table 1: Benzoxazinyl pyrazole arylidenes

Compound code	R
4a	3-NO_2
4b	4-F
4c	4-Cl
4d	2-Cl
4e	4-OCH_3
4f	4-CH_3
4g	4-OH,3-OCH_3
4h	4-$N(CH_3)_2$
4i	3-OCH_3
4j	4-OH

Table 2: Docking results of the ligands against dihydrofolate reductase of *S.aureus*

Ligands	G Score	G emodel
4g	-10.44	-71.23
4i	-9.038	-63.30
4f	-8.85	-63.85
4a	-8.73	-70.10

4h	-7.23	-75.72
4e	-6.89	-72.90
4j	-7.06	-71.89
4d	-5.64	-63.08
Trimethoprim	-9.38	-57.67
Ciprofloxacin	-8.61	-67.23

G score- Glide Score, G emodel -Glide emodel

Table 3: Docking results of the ligands against dihydrofolate reductase of *E.coli*

Ligands	G Score	G emodel
4h	-6.17	-63.50
4e	-5.20	-66.55
4b	-5.09	-60.28
4j	-4.75	-61.68
4g	-4.68	-66.17
4f	-4.45	-58.58
4i	-4.00	-60.78
4c	-3.90	-57.90
4a	-3.88	-62.73
4d	-3.03	-56.05
Trimethoprim	-7.39	-47.19
Ciprofloxacin	-7.19	-49.36

G score- Glide Score G emodel- Glide emodel

Table 4: Prediction of ADME properties of novel hybrid molecules of benzoxazinyl pyrazole arylidenes

Comp No.	Mol MW	QPlog Po/w	QPPCaco	Donor HB	Accpt HB	QPlogS	QPlog BB	QPPMDCK	% Human oral absorption	Rule of five
4a	420.38	2.07	34.78	1	8.25	-4.75	-2.34	13.11	66.68	0
4b	393.37	2.98	284.64	1	7.25	-4.99	-1.16	230.02	88.33	0
4c	409.83	3.23	284.64	1	7.25	-5.35	-1.12	313.83	89.81	0
4d	409.83	3.17	284.65	1	7.25	-5.21	-1.13	277.85	89.45	0
4e	405.41	2.78	284.64	1	8	-4.74	-1.35	127.21	87.16	0
4f	389.41	3.04	284.64	1	7.25	-5.17	-1.31	127.21	88.69	0
4g	421.41	2.15	91.48	2	8.75	-4.64	-1.96	37.30	74.63	0
4h	418.45	3.27	284.64	1	8.25	-5.57	-1.44	127.21	90.01	0
4i	405.41	2.78	284.64	1	8	-4.74	-1.35	127.21	87.16	0
4j	391.38	2.07	85.74	2	8	-4.51	-1.88	34.77	73.67	0

Fig. 1: Designed benzoxazinyl pyrazole arylidenes

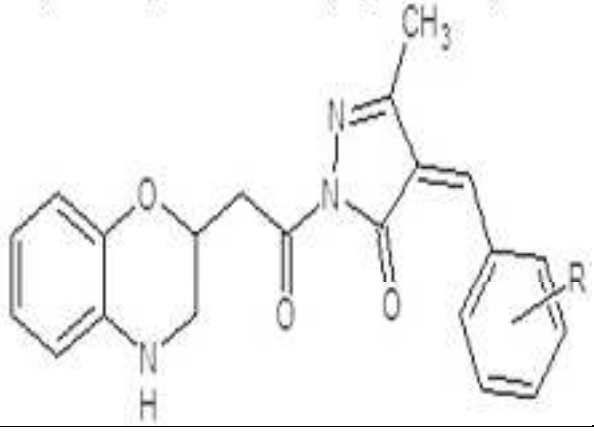


Fig. 2: 3-D docked view for binding of compound 4g in the active site of DHFR of *S.Aureus*

Fig. 3: 3-D docked view for binding of compound 4h in the active site of DHFR of *E.Coli*

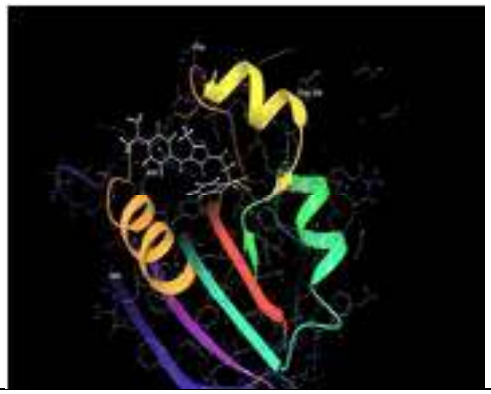


Fig. 4: Ligand interaction of 4g with protein 3SRW

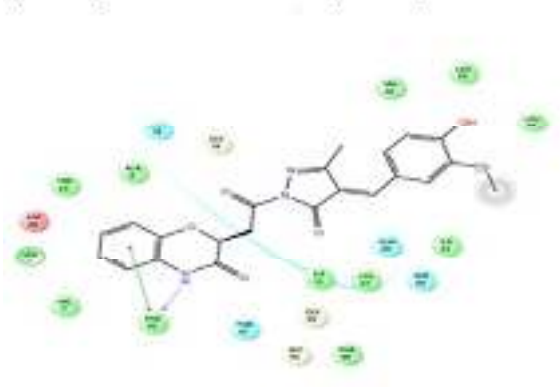
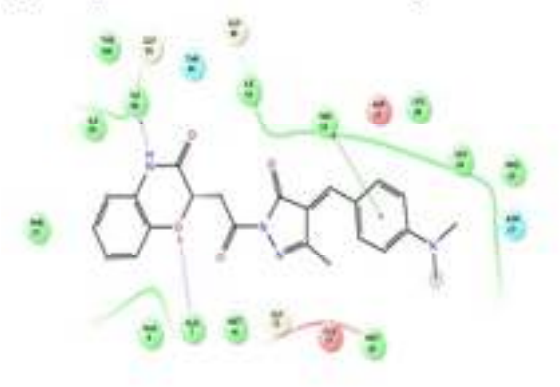


Fig. 5:Ligand interaction of 4h with protein 1RX7



DISCUSSION

The ligands and standards (trimethoprim and ciprofloxacin) were docked at the active site of targeted protein 3SRW in *S.Aureus* and 1RX7 in *E.coli* of dihydrofolate reductase . Test compounds showed different binding modes with amino acids located at the active site of protein. The G scores and G emodel values were shown in table (2) and (3). These values were compared with standards trimethoprim and ciprofloxacin. Docking results of 3SRW of *S.*aureus indicated that compound **4g** (4-hydroxy,3-methoxy phenyl substitution)showed good G score -10.44 and G emodel -71.23 kcal/mol when compared with the results obtained by trimethoprim and ciprofloxacin with a G score of 9.38,-8.61 and G emodel value as -57.6 , -67.23 respectively. From the docking study it was found that amino acid phenyl alanine formed hydrogen bond with ring N-H hydrogen of benzoxazine ring. Phenyl alanine also interacted with phenyl ring of benzoxazine ring through pi- pi stacking (Fig 4). Results obtained from docking of 1RX7 of *E.coli* revealed that compound **4h**(4-dimethylaminophenyl substitution) showed moderate G score -6.17 and G emodel -63.50 kcal/mol when compared with the results obtained by trimethoprim and ciprofloxacin with a G score of -7.39,-7.19 and G emodel value as -47.19, -49.36 respectively. Alanine and isoleucine form hydrogen bond with oxygen and NH of benzoxazine ring (Fig 5).ADME properties of analogs were predicted using Qikprop. Significant descriptors were considered which help in predicting drug-like properties of molecules. These properties were

1. Molecular weight (mol_MW) (150–650)
2. Octanol/water partition coefficient (Log Po/w) (-2–6.5)
3. Aqueous solubility (QPlogS) (-6.5–0.5)
4. Apparent MDCK cell permeability (QPPMDCK) (\25 poor, [500 great)
5. Brain/blood partition coefficient (QPlogBB) (-3.0–1.2)
6. Percent human oral absorption (C80% is high, B25% is poor)
7. Hydrogen bond donors (Donor HB)(less than 5)
8. Hydrogen bond acceptors (Accpt HB)(less than 10)

All the structures have significant values for the parameters analyzed .The ADME values of designed inhibitors are given in Table 5. All designed compounds had ADME properties in desirable range and showed drug-like characteristics based on Lipinski's rule of 5.

CONCLUSION

Molecular docking is an important tool in structural based drug design. The role of ligand-protein docking helps to predict the best binding pose(s) of a ligand with a protein whose three dimensional structure

is already known. The above studies revealed that docking of hybrid molecules (4-hydroxy.3-methoxybenzylidene substituted benzoxazinyl pyrazole) showed promising inhibitory activity against DHFR of *S. aureus*. Thus molecular docking helped in exploring the selectivity of newly synthesized hybrid molecules in the active site of enzyme. Some significant binding interactions were observed during docking study which would indicate that test compounds may act through bacterial DHFR inhibition. ADME properties of all the synthesized molecules showed drug like properties. Hence this study will be considered as a step for designing of new analogs which are more effective than clinically relevant bacterial strains.

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