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MOLECULAR DOCKING STUDIES OF NOVEL COUMARINO PYRAZOLINONE DERIVATIVES AS POTENT ANTIBACTERIAL AGENTS

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ABSTRACT

The emerging resistance of some antimicrobial species to synthetic antimicrobial agents makes it necessary to continue the search for new antimicrobial agents. As vast number of reports are available pertaining to the antimicrobial activities of coumarins and pyrazolines, novel coumarino pyrazolin-5-one derivatives were designed. Molecular docking studies was carried out to identify the specificity of these derivatives using 'Glide' on two antibacterial targets; Dihydrofolate reductase (DHFR) of *Staphylococcus aureus* (PDB ID: 3SRW); Dihydrofolate reductase of *Escherichia Coli* (PDB ID: 1RX7). From the results obtained, it was found that compounds CP1c and CP1e were more potent against DHFR.

Key Words:- Coumarin, Pyrazoline, Antibacterial activity, Docking.

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INTRODUCTION

Coumarin derivatives exhibit a wide range of physiological activities such as antibacterial, antifungal, analgesic, anticoagulant and diuretic activities (Kontogiorgis *et al*., 2014). Pyrazolines exhibit broad spectrum of activity namely antibacterial, antifungal, analgesic, anti-inflammatory, anticonvulsant,antidiabetic, antioxidant and anticancer activities (Kini *et al*., 2008). Although a number of drugs are available in the market, the search for discovering a new drug with better pharmacokinetic profile, lesser toxicity has become important due to the fast development of microbial resistance towards existing molecules. Combination of coumarin and pyrazolinone moieties together may result in additive effect towards their biological activities. Dihydrofolate reductase, DHFR is one of the most intensely studied proteins and a target for many antibacterial agents. It is a critical enzyme involved in thymidine and purine nucleotide biosynthesis (Hawser *et al*., 2006). Although only a few DHFR inhibitors have progressed as antibiotics to the market, there is much renewed interest in the discovery and development of new generation DHFR inhibitors as antibacterial agents. Molecular docking is used to assess the potential of ligands to bind specific sites on target molecules such as proteins (Meng *et al*., 2011). Therefore the focus of the present study was to dock some coumarino pyrazolinone derivatives against DHFR to identify potent antimicrobial agents.

MATERIALS AND METHODS

Protein Structure Preparation

The X-ray crystal structures Dihydrofolate reductase (DHFR) of *Staphylococcus aureus* (PDB ID: 3SRW); Dihydrofolate reductase of *Escherichia coli* (PDB ID: 1RX7) retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank were used in this study. Water molecules of crystallization were removed and the

protein was optimized for docking using the protein preparation and refinement utility provided by Schrödinger L L C (Parasuraman P *et al*., 2014).

Ligand structure preparation

The structures of ten coumarino pyrazolinone derivatives, (Figure 1) were constructed using the splinter dictionary of Maestro 9.3 (Schrodinger, LLC) using the Optimized Potentials for Liquid Simulations-All Atom (OPLS-AA) force field with the steepest descent followed by curtailed Newton conjugate gradient protocol. Partial atomic charges were computed using the OPLS-AA force field (Kaminski *et al*., 2001).

Docking Protocol

All docking calculations were performed using the ‘‘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.

Table1: Docking Results of the Ligands against DHFR of *S aureus*

S.No	Compound	R	Gscore	E-model
1	CP1a	4-F	-5.6	-75.12
2	CP1b	2-CF_3	-6.25	-64.43
3	CP1c	2-Cl-5-CF_3	-6.97	-60.39
4	CP1d	4-NO_2	-5.30	-71.53
5	CP1e	4-CH_3	-5.33	-56.94
6	CP1f	4-F	-4.16	-64.74
7	CP1g	2-CF_3	-5.76	-56.29
8	CP1h	2-Cl-5-CF_3	-5.33	-64.94
9	CP1i	4-NO_2	-5.84	-54.10
10	CP1j	4-CH_3	-5.96	-70.87
Trimethoprim			-9.38	-57.67
Ciprofloxacin			-8.61	-67.23

Table2: Docking Results of the Ligands against DHFR of *E coli*

S.No	Compound	R	Gscore	E-model
1	CP1a	4-F	-3.83	-55.14
2	CP1b	2-CF_3	-3.68	-54.10
3	CP1c	2-Cl-5-CF_3	-4.99	-75.42
4	CP1d	4-NO_2	-5.49	-62.04
5	CP1e	4-CH_3	-5.50	-61.31
6	CP1f	4-F	-4	-64.20
7	CP1g	2-CF_3	-3.65	-64.76
8	CP1h	2-Cl-5-CF_3	-2.91	-54.07
9	CP1i	4-NO_2	-3.69	-64.15
10	CP1j	4-CH_3	-4.09	-54.68
Trimethoprim			-7.39	-47.19
Ciprofloxacin			-7.19	-49.36

Figure 1: Ligand structures

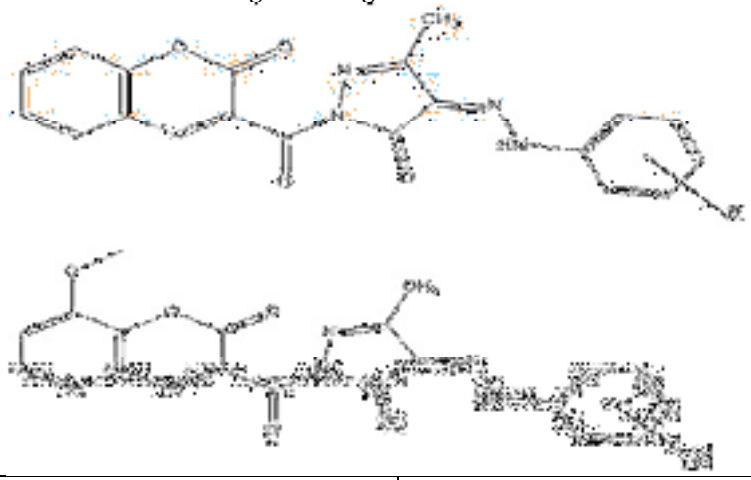

Figure 2: Ligand interaction of CP1c with DHFR of Staphylococcus aureus (PDB: 3SRW)

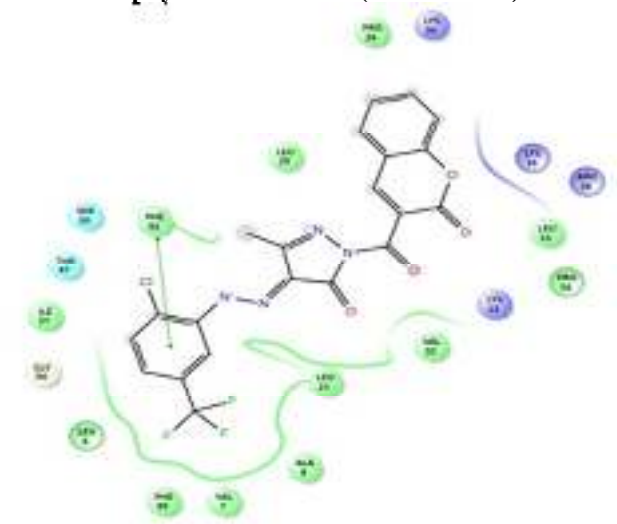

Figure 3: Ligand interaction of CP1e with DHFR of Escherichia coli (PDB: 1RX7)

RESULTS AND DISCUSSION

Receptor grid generation

GLIDE receptor grid was generated to determine the size of the active site. The most probable orientation of the ligands in the binding pocket was identified and a scoring function was used to quantify the strength of the interaction that a molecule can make in a particular orientation. In order to provide better correlation between good poses and good scores, the GLIDE XP precision was favoured over the standard mode.

Validation of the docking protocol

The docking analysis was done for the ligands such with the target proteins, Dihydrofolate reductase of *Staphylococcus aureus* and *Escherichia coli,* using the docking software GLIDE and the docked images were shown (figure 2&3). The structures docked by GLIDE were ranked according to the GLIDE scoring function (more negative). The scoring function of GLIDE docking program was presented in the G-score form.

All the ligands were docked into the active site of Dihydrofolate reductase of *Staphylococcus aureus* and *Escherichia coli.* The docking score varied from -4.16 to -6.97 for DHFR of *S aureus* and -2.91 to -5.50 for DHFR of *E coli* as given in Table 1&2. The G score for the standard trimethoprim and ciprofloxacin docked with DHFR of *S aureus* was found to be -9.38 and -8.61 and that for DHFR of *E coli* was found to be -7.39 and -7.19. The compound CP1c showed the finest inhibition for DHFR of *S aureus* with glide score of -6.97 and CP1e with glide score of -5.5 against DHFR of *E coli*. This result proves that these two compounds could be potential drugs for developing a new chemical entity against microbes. Conformational analysis of diverse docked complexes showed that the residues PHE 93 for DHFR of *S aureus* and TRP 22 & ASP 27 for DHFR of *E coli* play important role in this receptor activity. Docking

results showed that PHE 93 in DHFR of *S aureus* and TRP 22 in DHFR of *E coli* formed pi-pi stacking with substituted phenyl ring of the compounds CP1c and CP1e respectively. ASP 27 in DHFR of *E coli* formed intermolecular hydrogen bonding with –NH of coumarino pyrazolinone CP1e. Docking studies performed by GLIDE confirmed that above inhibitors fit into the binding pocket of DHFR of *S aureus* and *E coli.* From the results, it was observed that for successful docking, intermolecular hydrogen bonding and lipophilic interactions between the ligand and the receptor were very important.

CONCLUSION

The results of our present study will be useful for the design and development of novel coumarino pyrazolinone derivatives with potent antibacterial activity. Compounds CP1c and CP1e are considered as the potential drug candidates and will be analysed further in the wet lab.

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