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Research Article

MOLECULAR DOCKING STUDIES ON EGF – 5 FLUOROURACIL

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ABSTRACT

Cancer can be described as the uncontrolled growth of abnormal cells. 5 Fluorouracil is an anticancer drug which has it effects on colon cancer, brain tumor, breast cancer, head & neck cancer. The aim of the present study was to find the targeting efficiency of the drug by molecular docking. The Protein- Ligand interaction plays a significant role in structural based drug designing. The drug, EGF and conjugation of drug and EGF were subjected to docking studies using the Argus Lab docking software to obtain the binding energy levels of each. The Drug with Epidermal Growth Factor (EGF) has higher binding energy of -107.649 with the responsible amino acids Cys6, gly12, Asp11, gly18, His13 when compared with the plain drug and plain EGF.

Keywords: EGF, Cancer, Brain Tumor, Binding energy.

INTRODUCTION

About 13 percent of all the death worldwide is due to cancer, surpassing cardiovascular disease and taking number one place [1, 2]. Chemotherapy of cancer is associated with various adverse effects viz.

bone marrow depression, alopecia, drug induced caner, etc. and is often associated with cytotoxicity, genotoxicity to normal cells together with the development of resistance [3]. Medicinal chemists have great perseverance in research and development (R & D) for the search of newer and safer anticancer agents. EGFR family of Tyrosine Kinases (TK) play a vital role in cancer proliferation and it is suggested that any agent which would inhibit the TK activity may have substantial role in the cancer treatment [4]. So we selected EGFR family of TK and explore the binding mode of the compounds to EGFR tyrosine kinase active site. Family proteins were retrieved from the Protein Data Bank [5] and the compound was subjected to docking for binding capacity confirmation studies Computational Biology and bioinformatics have the potential not only of speeding up the drug discovery process thus reducing the costs, but also of changing the way drugs are designed. Rational Drug Design (RDD) helps to facilitate and speedup the drug designing process, which involves variety of methods to identify novel compounds. One such method is the docking of the drug molecule with the receptor (target). The site of drug action, which is ultimately responsible for the pharmaceutical effect, is a receptor [6]. Docking is the process by which two molecules fit together in 3D space.

Methodology

Targeting Efficiency studies by Insilico Analysis

Bioinformatics is seen as an emerging field [7] with the potential to significantly improve how drugs are found, brought to the clinical trials and eventually released to the marketplace.

Sequence retrieval

Authentic structures for EGF and EGFR were retrieved from Protein data bank. Comparative availability of 3D structures was checked in NCBI Entrez, along with PDB and SWISSPROT databases.

Preparation of 5 fluorouracil

5 fluorouracil structure was retrieved from PUBCHEM project database (http://pubchem.ncbi.nlm.nih.gov/), and conversion of SMILES to PDB files was done for generation of 2D structure of 5 fluorouracil. The 2D model was optimized and energy minimized using clean geometry option in ArgusLab 4.0.1 (http: //www.ArgusLab. com) [8].

Ligand binding site prediction

Ligand binding sites were calculated using Q site finder http:// www.modelling.leeds.ac.uk/ qsitefinder/, surface topology and the pocket information were also analyzed by the castP server http://sts-fw.bioengr.uic.edu/castp/calculation.php. Pocket detection and occupancy of the protein was set up using Q-Site Finder. Clefts were tarnished in the protein-surface using Q-SiteFinder. The solvent available surface area (SASA) was found by the software server GETAREA http://curie.utmb.edu/getarea.html. The atomic Solvent Accessible Surface Area (SASA) enclosed by each cleft was calculated by utilizing radius of water probe 1.4 A^0 and the area/ energy per residue was also designed. Dielectric constant was set to a value of 80.0, and Poisson-Boltzmann method of computation for 20 cycles was used for calculating the electrostatic potential in SWISS-PDB viewer. All the ligand binding residues were amongst hotspots as predicted by Meta-PPISP. Furthermore, PIC was made to use to calculate the nature of interaction occurring in the ligand binding residues.

Docking studies

Molecular docking software ArgusLab 4.0.1 was used for ligand docking on to EGF, EGFR and 5 Fluorouracil. Grid calculations during Argusdock with scoring function as Ascore for flexible ligand docking was performed with grid calculations 15.00, 15.00, and 15.00, respectively, with grid resolution of 0.400 A°.

Assessment of protein-ligand interaction

Hydrogen bond interactions were calculated by using Discovery studio (http://accelrys.com/products/discovery-studio) and ligand map was generated using MOLEGRO.

(http://molegro-molecular-viewer.software.informer.com/2.5/).

Result & Discussion

Ligand binding interaction assessment formed between EGFR and 5-fluorouracil resulted in a sustainable complex when compared to EGF-5-Fluorouracil conjugate. Comparatively, the complex between EGFR and bound complex [9] showed better binding affinity patterns.5-FU docked in to the binding site (fig 3.1 and 3.2) of the EGF protein, EGFR protein individually and then the complex (EGF-5FU) docked with the protein EGFR protein with the help of protein-protein docking algorithm. The table 3.1 shows that active site amino acids responsible for forming complex.

Table 3.1: Hydrophobic Interactions

Name of the complex	Docking energy	Responsible Amino acids
EGF-5FU	-59.175	Cys6,gly12,Asp11, gly18
EGFR-5FU	-20.855	Gly 18
COMPLEX(EGF-5FU)+EGFR	-107.649	Cys6,gly12,Asp11, gly18, His13

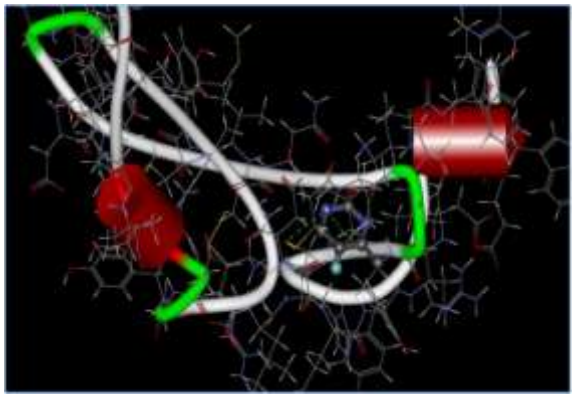

Fig 3.1 EGF 5-FU complex

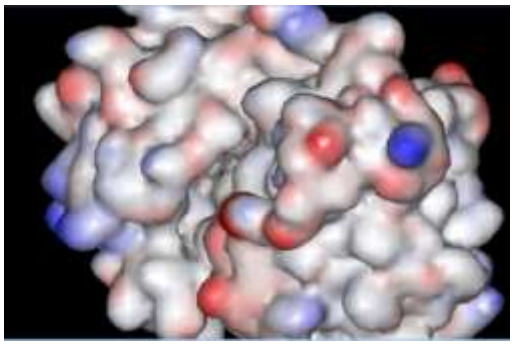

Fig 3.2: EGFR-5FU COMPLEX

Table 3.2:Protein –Protein dock

105	1.2									
0.000000	0.000000	0.000000								
RECEPTOR_FILE:	0	18.566	43.350	89.155						
LIGAND_FILE:	0	0.240	-0.818	0.806						
1.675516	1.640932	0.576808	14	84	8	13.84	6	-1	-1	-107.649
1.780236	1.622214	0.701509	15	95	7	13.38	8	-1	-1	-103.467
-1.570796	1.001920	0.848054	87	11	99	14.04	25	14	-1	-95.3697
1.047198	2.417386	-0.443697	15	87	94	13.62	2	-1	-1	-93.8505
1.675516	1.622214	0.701509	14	84	8	15.08	8	-1	-1	-90.5983

Table 3.2 shows the binding energy of the docked molecules. Hydrophobic Interactions within 5 Angstroms showed distinct donor and acceptor atoms in protein complexes. The complexes visualized in MOLEGRO shows unique binding patterns. Figure 3.4 shows the ligand map between various complexes.

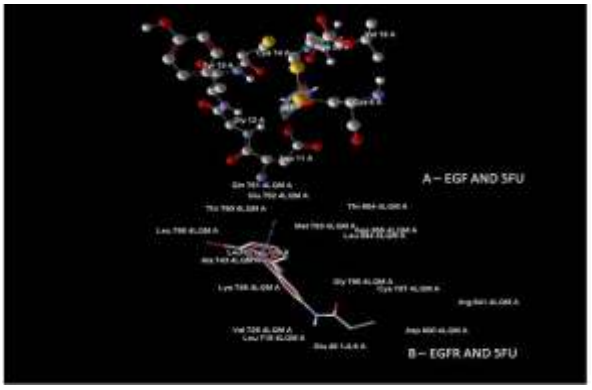

Fig 3.3 Interacting aminoacid residues between EGF, EGFR and 5FU

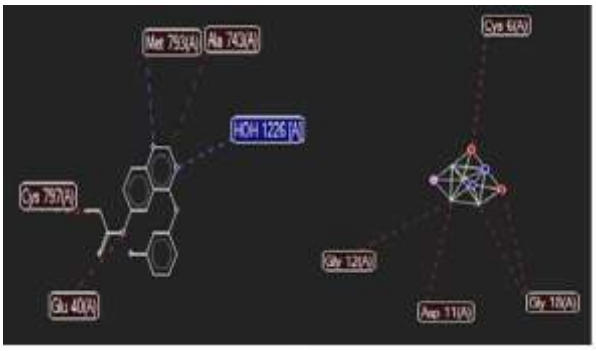

Fig 3.4 ligand map showing interactions of hydrogen bond

Incidently, there were no protein-protein aromatic-sulphur interactions and no protein-protein cation-pi interactions found [10]. Moreover, no protein-protein disulphide bridges are found. This docking studies shows that the complex (EGF-5FU) having the high dock score of -107.649 with the EGFR protein compare to other two docking complex. This docking study confirms that the EGF-5FU complex binds with EGFR tightly, and this improves the targeting efficiency, this study can be performed for Invivo studies for brain targeting.

CONCLUSION

The Protein-Ligand interaction plays a significant role in structural based drug designing. This docking study confirms that the EGF-5FU complex binds with EGFR tightly, and this improves the targeting efficiency, this study can be performed for Invivo studies for brain targeting.

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