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MOLECULAR DOCKING STUDIES OF SOME SELECTIVE CANCER PROTEIN WITH 6-HYDROXYFLAVANONE: A THEORETICAL PREDICATION FOR PROTEIN-LIGAND BINDING SITE

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Abstract

Molecular docking is an optimization solution, which denote the ‘‘best-fit’’ for orientation of a ligand - protein interaction. Ligand is a small molecule can interacts with protein’s binding sites. There are different possible mutual conformations which having best binding modes. Molecular docking provides useful information about drug receptor interactions and used to predict the binding affinity. The Hydroxylated flavones and its derivatives are the natural derived products that exhibit anti-inflammatory, anticancer, anti-oxidant and antimicrobial activities. In this work we predict the best binding energy of 6-hydroxyflavanone with 1QH4, 2ITO and 2VCJ protein which may cause Brain, Lung and Skin cancer by using Auto Dock program package. Initially the 6-hydroxyflavanone is optimized by B3LYP/6-311G(d,p) method using Gaussian 09W as used as ligand. The docking results show that 6-hydroxyflavanone capable of interacting with 1QH4, 2ITO and 2VCJ proteins.

Keywords: Molecular docking; 6-hydroxyflavanone; cancer protein; Autodock.

INTRODUCTION

Cancer is the name known to a collection of related diseases. In normally the cancer refers to body’s cells can be divide without non stopping and also spread over the surrounding tissues. Cancer begin anywhere in the human body, which is made up of trillions of cells. Normally, human cells can grow and divide to appearance new cells as the body need. When cells grow older or damaged, they die, and new cells grow at their place. If a person have cancer this orderly process breaks down. The growth of cells becomes more and more abnormal, old or damaged cells survive, and new cells form, when they are not needed for human body.

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These extra cells can divide non stopping as the result called tumors. Many cancers are solid tumors, which are masses of tissue. In addition to these tumors grow, some cancer cells can separate and travel to places in our body through the blood or the lymph system to form new tumors like the original tumor. There are more than hundred types of cancer are found in human body these can be named for the organs or tissues where the cancers form. For example, lung cancer starts in cells of the lung, and brain cancer starts in cells of the brain. Cancers also may be described by the type of cell that formed [1].

MATERIAL AND METHODS

Computational Details

AutoDock software [2] is automated module virtual software is used for predicting the interaction of ligands with biomacromolecular targets. The motivation of our work is to find the binding site of bioactive compounds with protein which induce cancer. The recent version of AutoDock software [2], use Lamarckian Genetic Algorithm and empirical free energy scoring function, can give reproducible docking results for ligands with approximately 10 flexible bonds and other related software like Auto Dock Vina [3], offer scoring function and faster search method, and provides reproducible results for larger systems with upwards of 20 flexible bonds. Density functional theory (DFT) is proved to be effective tool for treating electronic structure of molecules. The basis set 6-311G(d,p) was used as an effective and economical tool to study fairly large organic molecules are employed in our study to minimization of the ligand by using Gaussian 09W [4] software.

Selection of Cancer Protein

Three types of cancer protein [5-7] are taken in our study from Protein Data Bank [8].

1) Crystal structure of brain-type creatine kinase [PDB ID: 1QH4] with resolution of 1.41Å determined by XRD method [5] as shown in Fig.13.1.

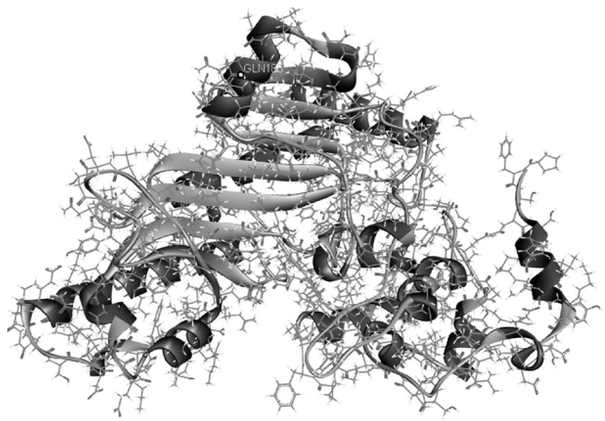

Fig.13.1: Structure of Brain-type Creatine Kinase Protein [PDB ID: 1QH4]

2) Structures of Lung Cancer-Derived Egfr Mutants [PDB ID: 2ITO] with resolution of 3.25 Å determined by XRD method [6] as shown in Fig.13.2.

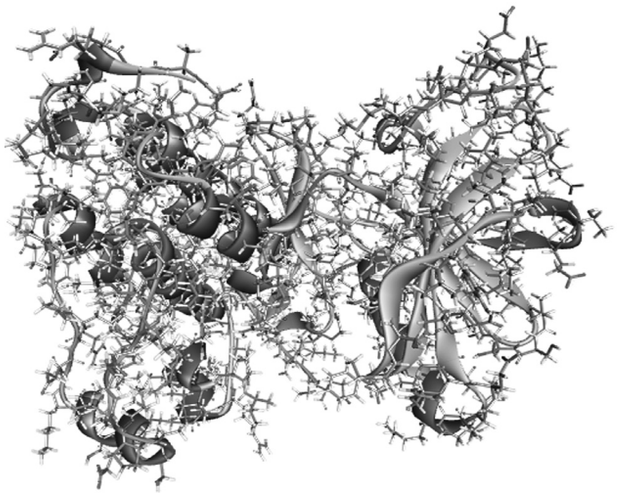

Fig. 13.2: Structure of Lung Cancer-Derived Egfr Mutants Protein [PDB ID: 2ITO]

3. 4,5 diaryl isoxazole hsp90 chaperone inhibitors it is a potential therapeutic agents for the treatment of cancer [PDB ID: 2VCJ] with resolution of 2.50 Å determined by XRD method [7] as shown in Fig. 13.2.

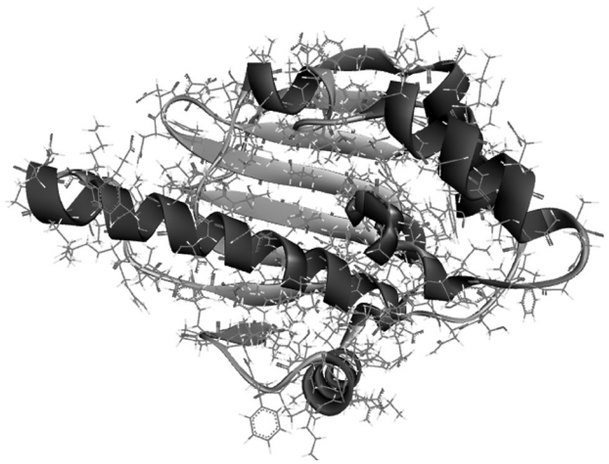

Fig. 13.3: Structure 4,5 Diaryl Isoxazole hsp90 Chaperone Inhibitors [PDB ID: 2VCJ]

Selection of Ligand

Flavonoids are polyphenolic compounds with diverse chemical structures, which are widely found in plants Flavanones have a unique structural feature known as chirality, which different from all other classes of flavonoids [9-11] Flavanones have been a potential foundation in the search biologically active components and make to spotlight for researches. Apart from plants, it has natural capability to obtain out biosynthesis of flavonoid compounds is a feature of some endophytic fungi [10]. The 6-hydroxyflavanone has exerted beneficial actions on the Central Nervous System (CNS) such as neuro protection, antianxiety, and cognitive enhancing effect. In addition to the beneficial health claims, various studies such as indications for possible adverse health effects of this compound. Computer aided methodology for the identification and optimization of organic molecules with desired biological activity have become a part of drug discovery process. Such techniques could lead to reduce the cost of drug design and development up to 50%.

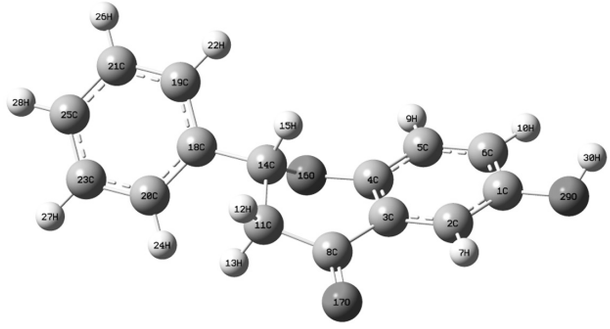

Fig. 13.4: Structure of 6-hydroxyflavanone (Ligand)

RESULTS AND DISCUSSION

Molecular Docking Study

The docking analysis is used to identify the possibility of pharmaceutical nature of PCA molecule. The structure of the target receptor is Gastric cancer (PDBID) Brain cancer (PDBID: 1QH4), Lung cancer (PDBID: 2ITO) and Skin Cancer (PDBID: 2VCJ) were obtained from RCSB protein data Bank [8]. Docking study can be done to find the best orientation of ligand with protein. Autodock.2 docking [12, 13] software tool is used for docking study. The protein structure were prepare with the help of Autodock Tools graphical user interface. Polar hydrogen was added to the protein and atomic charges were calculated by Kollman method. The water molecule and co-crystalline liquid were removed. The PCA molecule were prepared for docking by minimizing the energy by B3LYP/6-311G(d,p) method. The active site to the energies was defined to add residues of active side with the use of grid size 80Å×80Å×80Å using Autogrid [14, 15].

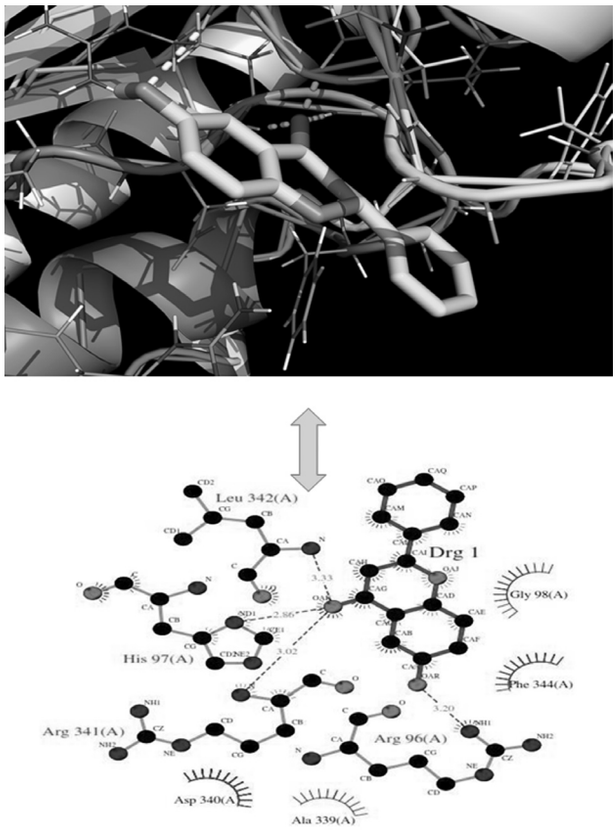

Fig. 13.5: The Hydrogen Bond Diagram of Target Protein 1QH4 with 6-hydroxyflavanone

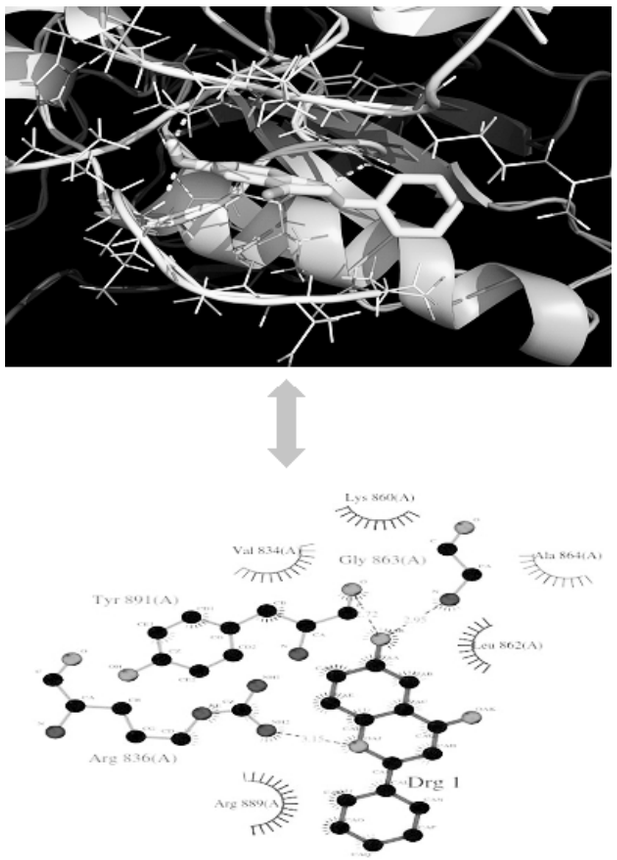

Fig. 13.6: The hydrogen bond diagram of Target Protein 2ITO with 6-hydroxyflavanone

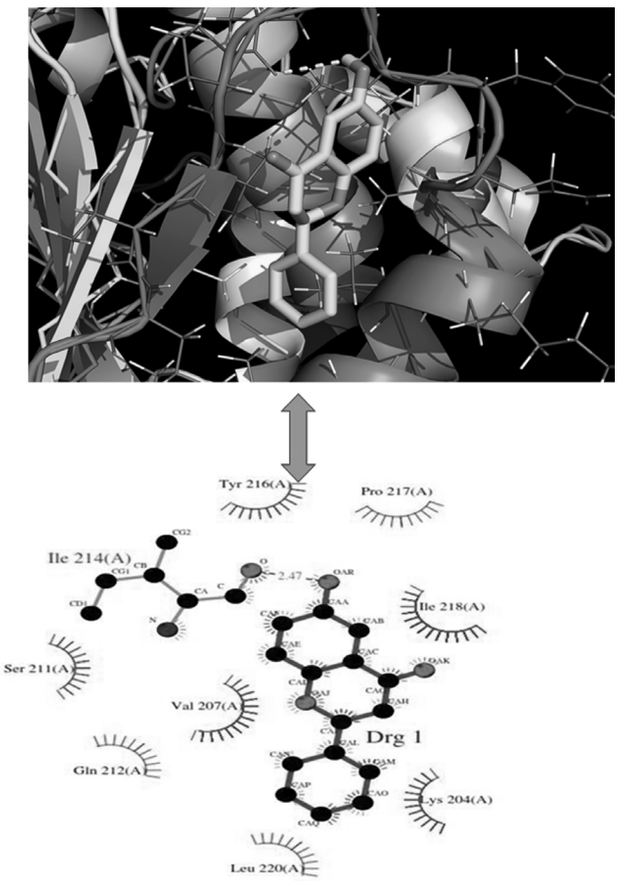

Fig. 13.7: The Hydrogen Bond Diagram of Target Protein 2VCJ with 6-Hydroxyflavanone

The Lamarckian Genetic Algorithm is implemented in Autodock were employed for docking [14]. AutoDock Binding Energy (kcal/mol) and inhibition constants (μM) were computed and Tabulated in Table 1. Among the three proteins the lowest free energy at -6.64 Kcal/mol and most docked inhibitor interaction with ligand within 2ITO binding site are GLY 863, ARG 836, TRY 891 through H- bond (C=O…H. C=O…H-N) are shown in Fig.13.6. and hydrogen bond residue are shown in Table 2. The computation suggests confirm the O-H moiety is engaged in hydrogen bond with amino acid residues with RMSD value of 13.6 shown in Table 1. The protein which induce brain cancer (PDB ID: 1QH4) binding with ligand are LEU 342, HIS97, ARG 341 and ARG 96 through H-bond (C=O…H-N) are shown in Fig.13.5. The binding site of protein which induce skin cancer (PDB ID: 2VCJ) bind on ILE 214 with ligand as shown in Fig. 13.7.

Table 1 Molecular Docking Results of 6-Hydroxyflavanone Molecule with Different Types of Cancer Protein Targets

Drug	Protein PDB ID	Type of Cancer	Binding Energy (Kcal/mol)	Estimated Inhibition Constant Ki (μM)	RMSD
6-hydroxy flavanone	1QH4	Brain cancer	-6.54	140.72	56.53
	2ITO	Lung Cancer	-6.64	68.88	13.64
	2VCJ	Skin Cancer	-6.53	16.24	18.77

Table.2: Summary of Hydrogen Bonding of 6-Hydroxyflavanone Molecule with Different types of Cancer Protein Targets

Protein (PDB ID)	No. of Hydrogen Bond	Bonded Residues	Bond Distance
1QH4	4	LEU 342	3.33
		HIS 97	2.86
		ARG 341	3.02
		ARG 96	3.20
2ITO	3	GLY 863	2.72
		ARG 836	3.15
		TRY 891	2.95
2VCJ	1	ILE 214	2.47

CONCLUSION

The molecular docking studies on 6-hydroxyflavanone with different cancer proteins target were carried out for the first time. By conclusion among the three proteins, ligand molecule exhibit inhibiting activity against lung cancer protein evident from formation of three hydrogen bond. The obtained hydrogen bond lengths suggest that all the bond lengths are capable for hydrogen bond formation. So we conclude that the ligand molecule have capable for inhinit lung cancer protein when compare to other proteins. Biological need to be carried to validate the computational assumptions.

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