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DOCKING STUDY OF CHRYSIN DERIVATIVES ON DIFFERENT TARGETS FOR ANTICANCER ACTIVITY

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ABSTRACT

Some anticancer molecules using natural flavonoid chrysin were designed and docking studies were performed using Molegro Virtual Docker (MVD) software. Of the available crystal structures of the non- mutated *Homo sapiens*, five were selected for the final docking studies. The docking results with selected crystal structures shown that designed legends forms hydrogen bonds with at least two out of three key active site residues (Asp, Val and Lys). It also form hydrogen bonds to other active site residues, in particular Glu. The average MolDock score and the MolDock Re-rank score were obtained as -156.704 Kcal/mol and-125.649 Kcal/mol respectively. The docking results shown that some molecules fit well in the active site and interact with the residues in the active site which are crucial for their biological activity.

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INTRODUCTION:

Cancer is a group of diseases characterized by uncontrolled growth and multiplication of abnormal cells that invade and metastases to other parts of the body[1]. Several techniques have been adopted for the treatment and eradication of cancerous cells. These techniques involved surgery, radiation, immunotherapy, chemotherapy and chemoprevention. Ideal anticancer drugs would eradicate cancer cells without harming normal tissues. Chrysin, also known as 5, 7-dihydroxyflavone with an IUPAC name of 5, 7-dihydroxy 2-phenyl-4H-chromen-4-one, belongs to the flavone sub-class of flavonoids. Its chemical structure is essentially based on a three ring nucleus with a phenyl ring attached to position 2 of the fused bicyclic and rings. Flavonoids including flavones, flavonols, and flavones possess various biological activities as antioxidant, anticancer etc. chrysin as a flavonoids shown activity for anticancer activity[2].

Binding of a small molecule (ligand) with a large molecule (protein) is called docking. Docking is the process by which two molecules fit together in 3D space. Docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex[3].

MATERIALS AND METHODS:

Designing of compounds

New molecules were designed by combining chrysin and cycloalkane derivatives. Four Molecules were designed on the basis of literature of their biological response towards cancer cells (Figure 1)

Target Selection

Three targets (Table 1) were selected for performing docking studies to check the binding affinity of designed molecules with the target and to predict the potential molecules to be synthesized with the aim to have anticancer activity[4].

Software

Ligand Preparation

The structures of Chrysin with cyclic compounds were converted into suitable chemical information using Chemdraw ultra v 10.0 (Cambridge software), copied to Chem3D ultra v 10.0 to create a 3D model and, finally subjected to energy minimization using molecular mechanics (MM2). The minimization was executed until the root mean square gradient value reached a value smaller than 0.001kcal/mol[5].

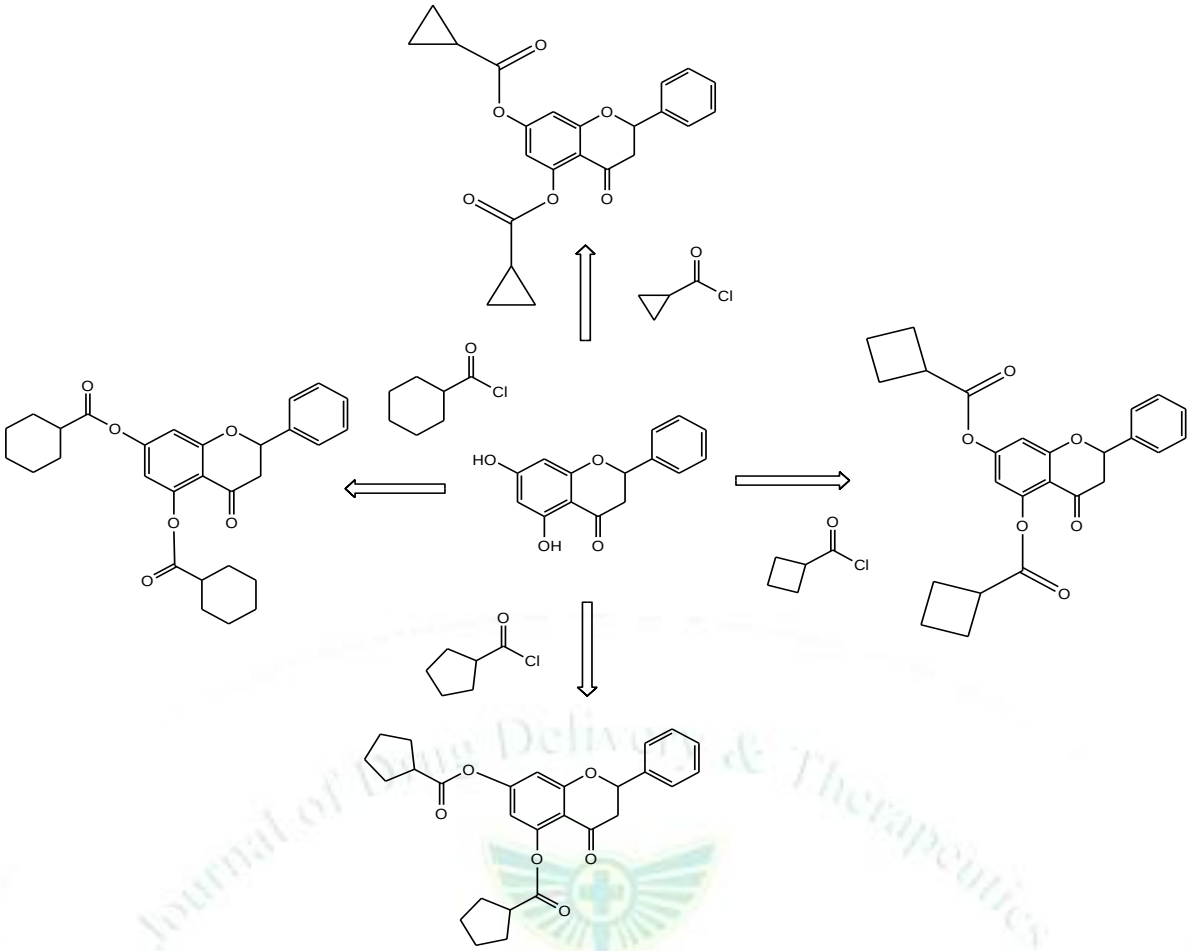
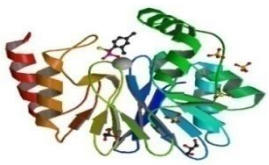
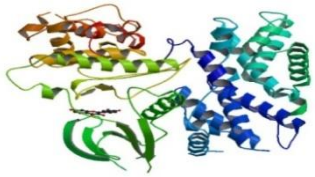
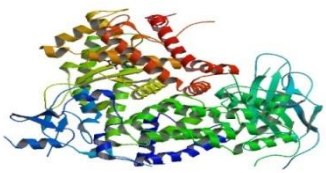


Figure 1: Designed compounds

Protein Selection

The selection of protein for docking studies is based upon several factors i.e. structure should be determined by X-ray diffraction, and resolution should be between 2.0-2.5Ao, it should contain a co-crystallized ligand; the selected protein should not have any protein breaks in their 3D structure.

Table 1: Selected anticancer drug targets with PDB ID

S. No.	Name of anticancer target protein	PDB ID	3D structure of target
1	Crystal structure of CphA N220G mutant with inhibitor 18	3IOG	
2	Crystal structure of a human cyclin-dependent kinase 6 complex with a flavonol inhibitor, fisetin	1XO2	
3	Structure determinants of phosphoinositide 3-kinase inhibition	1E8W	

Protein Preparation

All the X-ray crystal structures of the selected target proteins were obtained from the RCSB Protein Data Bank (http://www.rcsb.org/pdb). Subsequent to screening for the above specific standards the resultant protein targets.

Software Method Validation

Software method validation was performed in MVD Molegro Virtual Docker 6.0 2013 and Marvin Sketch Product version 6.2.3 2013 were using Protein Data Bank (PDB) protein 3IOG, 1XO2, 1E8W.

RESULTS AND DISCUSSION

Dockings results reveals that compound no. 4 has shown best affinity towards all the targets selected for the study.

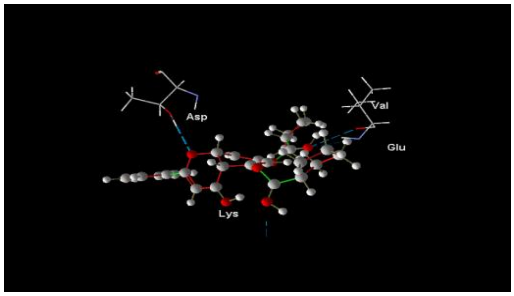


Figure 2: Biding affinity of Compound (a) with target (where carbon is grey, oxygen is red, nitrogen is blue and sulphur is yellow and hydrogen in white). Green lines represent the hydrogen bonds in between the ligand and the active site).

PDB code	Ligand name	MolDock Score	Rerank Score	HBond
3IOG	Compound (a)	-135.548(b)	-106.292	-5.66085

Figure 3: Biding affinity of Compound (b) with target (where carbon is grey, oxygen is red, nitrogen is blue and sulphur is yellow and hydrogen in white). Green lines represent the hydrogen bonds in between the ligand and the active site).

PDB code	Ligand name	MolDock Score	Rerank Score	HBond
1XO2	Compound (B)	-155.357	-124.456	-3.68857

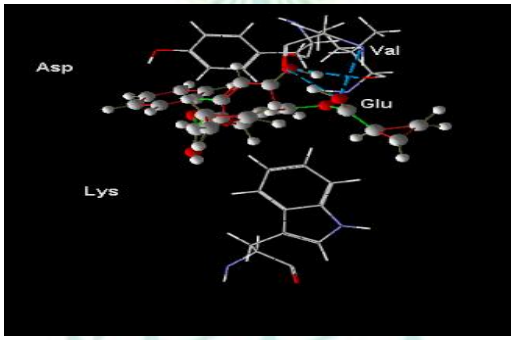


Figure 4: Biding affinity of Compound (b) with target (where carbon is grey, oxygen is red, nitrogen is blue and sulphur is yellow and hydrogen in white). Green lines represent the hydrogen bonds in between the ligand and the active site).

PDB code	Ligand name	MolDock Score	Rerank Score	HBond
1E8W	Compound (b)	-126.682	-105.89	-4.50612

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