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Docking Study of Chrysin Derivatives "7-[2-Hydroxy-3(substitutedamino)propoxy]-5-hydroxy-2-phenyl-4*H*-chromen-4-one"

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ABSTRACT: Polyphenolic compounds have recently attracted considerable interest in the field of nutrition, health and medicine. This is the result of the growing body of evidence suggesting that these compounds may act as potent biological activities. Synthesized chrysin derivatives were docked with CYP1A2 PDB id 2HI4 and CYP2D6 PDB id 3QM4 using glide software and investigated the abilities of synthesized compounds (FC1 to FC8) to interact with cytochrom P450 CYP1A2 and CYP2D6 isoforms. The interactions between the derived flavonoid derivatives and amino acid residues of the protein were observed in 2HI4 [FC5 (-0.022731), FC6 (-0.016012)] and 3QM4 [FC6 (-0.1), FC7 (-0.074532)], such type of interactions are commonly not observed in FC1, FC2, FC3, FC4, FC8. Therefore the docking score of derivatives are comparatively higher in 2HI4 protein PDB.

Keywords: Flavonoid, CYP1A2, CYP2D6

Practical Application: Chrysin derivatives could serve as potential candidate for hypertension.

I. INTRODUCTION

Flavones are present in a wide variety of fruits and vegetables whereas flavones are mainly found in cereals and herbs [1-4]. In some countries flavonoids are commonly used as therapeutic agents and some flavonoids are administered orally or intravenously as drugs [5-6]. However, there was little awareness of the potential for flavonoid interactions with conventional drugs. Some clinical studies have demonstrated that flavonoids can affect the metabolism of other drugs [6-8].

In the field of molecular modeling, 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 [8-9]. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecule using scoring functions. Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding conformation of small molecule ligand to the appropriate target binding site. Characterization of the binding behaviour plays an important role in rational drug design as well as to elucidate fundamental biochemical processes [10]. Molecular docking research focuses on computationally simulating the molecular recognition process. It aims to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized. A binding interaction between a small molecule ligand and an enzyme protein may result in activation or inhibition of the enzyme. If the protein is a receptor, ligand binding may result in agonism or antagonism. Docking is most commonly used in the field of drug design. Molecular docking can accelerate and guide to the chemist or scientist for drug design and contribute to the understanding of the biochemical functions of gene products. These technique used for the study of organic, inorganic, biomolecules use theoretical and computationally based method to model or mimic the behavior of molecule and have been widely applied for understanding and predicting the behaviour of molecular systems [11].

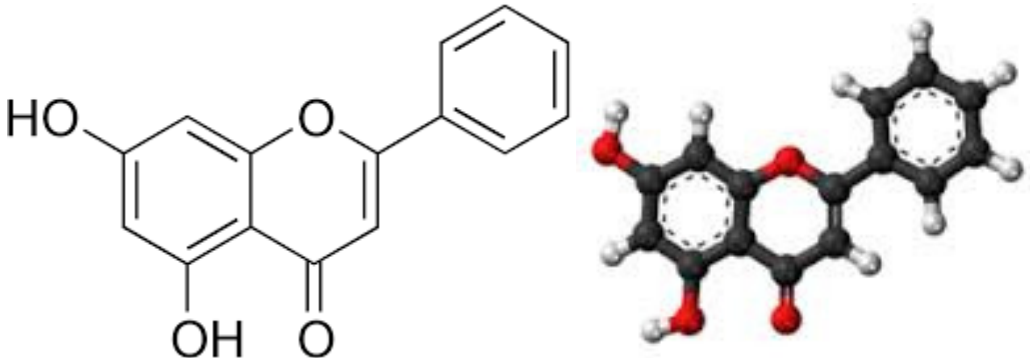


Fig. 1. Chrysin.

Molecular modeling has become an essential part of contemporary drug discovery processes of new molecules. A traditional approach for drug discovery of molecules relies on step-wise synthesis and screening of large numbers of compounds to optimize activity profiles of molecule which is to act as drug; this is extremely time consuming and costly method takes decades of years. The cost of these processes has increased significantly in recent years [12], and it takes over a decade for a very small fraction of compounds to pass the drug discovery pipeline from initial screening hits or leads, chemical optimization, and clinical trials before launching into the market as drug. The approaches and methodologies used in drug design have changed over time, exploiting and driving new technological advances to solve the varied bottlenecks found along the way. There are several programs used for docking, including DOCK-6, FlexX, GLIDE, GOLD, FRED, and SURFLEX has been assessed and these programs proved to generate reliable poses in numerous docking studies. Until 1990, the major issues were lead discovery and chemical synthesis of drug like molecules; the emergence of combinatorial chemistry, gene technology, and high-throughput tests [13-15] has shifted the focus, and poor absorption, distribution, metabolism and excretion (ADME) properties of new drugs captured more attention [16].

Predicting the fate of a drug in a particular patient and his or her subsequent response is still a vision and far away from application in routine clinical practice. Recognizing the sources and understanding the factors that contribute to the extraordinary pharmacokinetic and pharmacodynamic variability within and between individuals remains a challenge of particular importance for drugs with narrow therapeutic index [17]. The cytochrome p450 constitute the major enzyme family capable of catalyzing the oxidative biotransformation of most drugs and other lipophilic xenobiotics and are therefore of particular relevance for clinical pharmacology [18-19].

Cytochrome P450s, which are crucial phase I metabolizing enzymes, have been spotlighted for their effects on drug metabolism. Most drugs are detoxified via CYP-dependent pathways. Particularly, approximately 90% of drugs are metabolized by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 [20], which may be interrupted in case their activities are induced or inhibited [21]. A dozen enzymes belonging to the 1,2 and 3CYP-families responsible for the metabolism of the majority of drugs and other xenobiotics. Cytochrome p450s form a ubiquitous superflamily of monooxygenases characterized by the presence of a heme cofactor, that in humans plays a crucial role in phase I drug metabolism [22]. Besides being responsible for about 50% of drug clearance via metabolism, CYPs can also be responsible for prodrug activation or metabolism-dependent toxicity [23].

Aim of work. Protein docking is a computational problem to predict the binding of a protein with potential interacting partners. The interest for *in silico* methods has recently increased as a fast preliminary screening method in the drug discovery process [23]. However, these methods are still challenged by the substrate promiscutity and large catalytic site malleability of many CYP isoforms, including e.g. drug metabolizing CYP2D6 and 1A2 [24-25]. In our work we want to investigate the abilities of synthesized compounds (FC1 to FC8) to interact with cytochrom P450 CYP1A2 and CYP2D6 isoforms.

II. MATERIAL AND METHODS

A. Docking by Glide

The molecular docking tool, Glide (Schrodinger) software was used for ligand docking studies in to the protein tyrosine phosphatase 1-beta (PTP-1B) binding pocket. Glide is one of the most accurate docking tools available for ligand-protein, protein-protein binding studies.

Glide was found to produce least number of inaccurate poses and 85% of glides binding models had an RMSD of 1.4 Å or less from native co-crystallized structures [26].

B. Protein data bank

The PDB is the single, global archive for information about the 3D structure of biomacromolecules and their complexes, as determined by X-ray crystallography, NMR spectroscopy and cryoelectron microscopy, and includes more than a few Nobel Prize winning structure. CYP1A2 and CYP2D6 enzyme was downloaded from protein data bank with the specific resolution and the PDB id are 2HI4 and 3QM4 respectively.

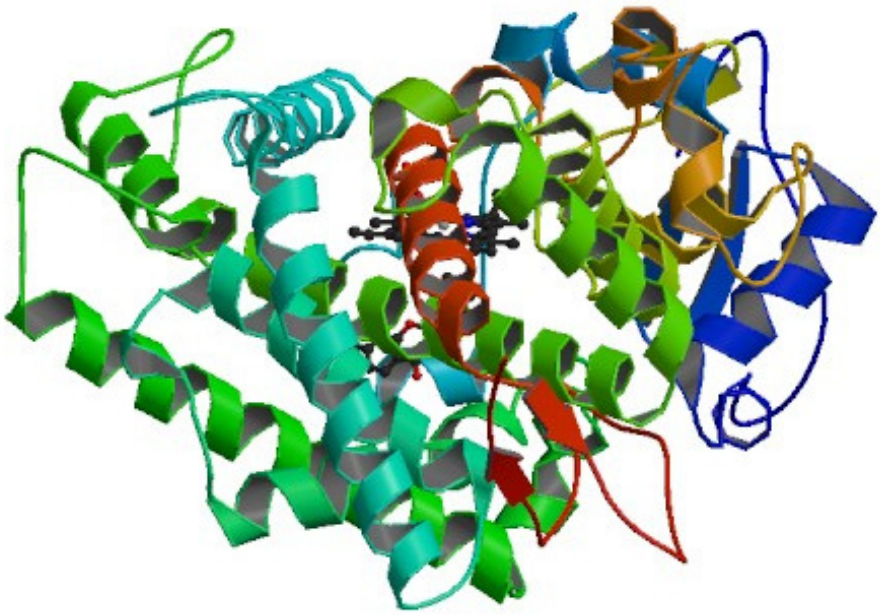


Fig. 2A. PDB structure of 2HI4.

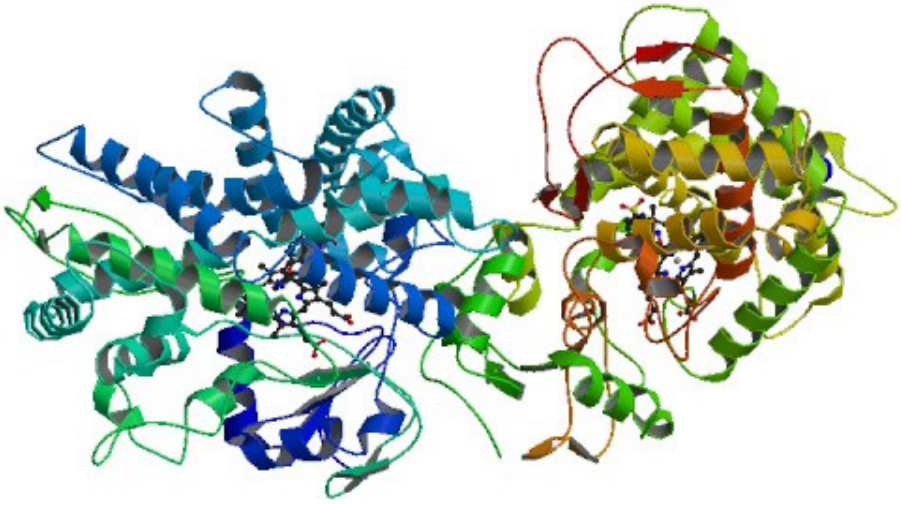


Fig. 2B. PDB structure of 3QM4.

Table 1: Protein structures selected for docking.

Protein	PDB	Worked as	Source
CYP 1A2	2HI4	Human Microsomal P450 1A2 in complex with alpha-naphthoflavone	Homosapience
CYP 2D6	3QM4	Human Cytochrome P450 (CYP) 2D6 - Prinomastat Complex	Homosapience

C. Protein preparation

A typical PDB structure file consists only of heavy atoms, can contain waters, cofactors, and metal ions, and can be multimeric. The structure generally has no information on bond orders, topologies, or formal atomic charges. Terminal amide groups can also be misaligned, because the X-ray structure analysis cannot usually distinguish between O and NH_2. Ionization and tautomeric states are also generally unassigned. Glide calculations use an all-atom force field for accurate energy evaluation. Thus, Glide requires bond orders and ionization states to be properly assigned and performs better when side chains are reoriented when necessary and steric clashes are relieved [27].

D. Ligand preparation

The ligand preparation process consists of a series of steps that perform conversions, apply corrections to the structures, generate variations on the structures, eliminate unwanted structures, and optimize the structures. Many of the steps are optional and are controlled by selecting option in the ligand preparation panel. The process like convert the structure format, select the structures, add hydrogen atoms, remove unwanted molecules, neutralize charged groups, generate ionization states, generate tautomers, filter the structures, generate alternative chiralities, generate low-energy ring conformations, remove problematic structures, optimize the geometries and finally convert the output file are performed by during ligand preparation [28].

E. Docking

The active site of each protein were first identified. The ligand was docked into the active site separately using the 'Flexible fit' option. The ligand-receptor site complex was subjected to 'in situ' ligand minimization which was performed using the in-built CHARMm forcefield calculation. The nonbond cutoff and the distance dependence was set to 11Å and (e=1R) respectively. The determination of the ligand binding affinity was calculated using the shape-based interaction energies of the ligand with the protein. Consensus scoring with the top tier of s=10% using docking score used to estimate the ligand-binding energies.

F. Generation of Docking sites

The binding sites for the docking are generated by using glide software. The site of the protein having more site score is considered for the docking of ligand. The site which has maximum site protein, located on the site in different colours as hydrophobic and hydrophilic maps. The hydrophilic maps are further divided into donor, acceptor, and metal-binding regions. Other properties characterize the binding site in terms of the size of the site, degrees of enclosure by the protein and exposure to solvent, tightness with which the site points interact with the receptor, hydrophobic and hydrophilic character of the site and balance between them, and degree to which a ligand might donate or accept hydrogen bonds.

G. Molecular Docking

The estimation of binding affinity of the ligand-receptor complex is still a challenging task. Scoring functions in docking programs take the ligand-receptor poses as input and provides ranking or estimation of the binding affinity of the pose. These scoring functions require the availability of receptore complexes with known binding affinity and use the sum of several energy terms such as van der waals potential, electrostatic potential, hydrophobicity and hydrogen bonds in binding energy estimation. The second class consists of force field-based scoring functions, which use atomic force fields used to calculate free energies of binding of ligand-receptor complex.

The ligands were docked with the active site using the 'Extra precision' Glide algorithm. Glide uses a hierarchical series of filters to search for possible locations of the ligand in the active site region of the receptor. Final scoring of the docked ligand is carried out on the energy minimized poses glide score scoring function. Glide score is based on chemscore, but includes a stericclash term and adds buried polar terms devised by schrodinger to penalize electrostatic mismatches.

III. RESULT AND DISCUSSION

There are number of types of interactions observed between ligand and receptor such as hydrogen bonding, pi-pi interactions, ion—pi interactions, hydrophobic and hydrophilic interactions, ionic interactions, van der waal interactions, etc along with steric interactions determine the docking score. The docking structure of chrysin derivative shows in figure 3 and figure 4. Glide esite explain the polar interaction in the active site between ligand and amino acid residue at the docking site after recombination. The polar interactions between the derived flavonoid derivatives and amino acid residues of the protein were observed in 2HI4 [FC5 (-0.022731), FC6 (-0.016012)] and 3QM4 [FC6 (-0.1), FC7 (-0.074532), such type of interactions are commonly not observed in FC1, FC2, FC3, FC4, FC8.

All the values of docking with protein PDB id 2HI4 mentioned in table 2 and with protein PDB id 2QM4 in Table 3. Therefore the docking score of derivatives are comparatively higher in 2HI4 protein PDB.

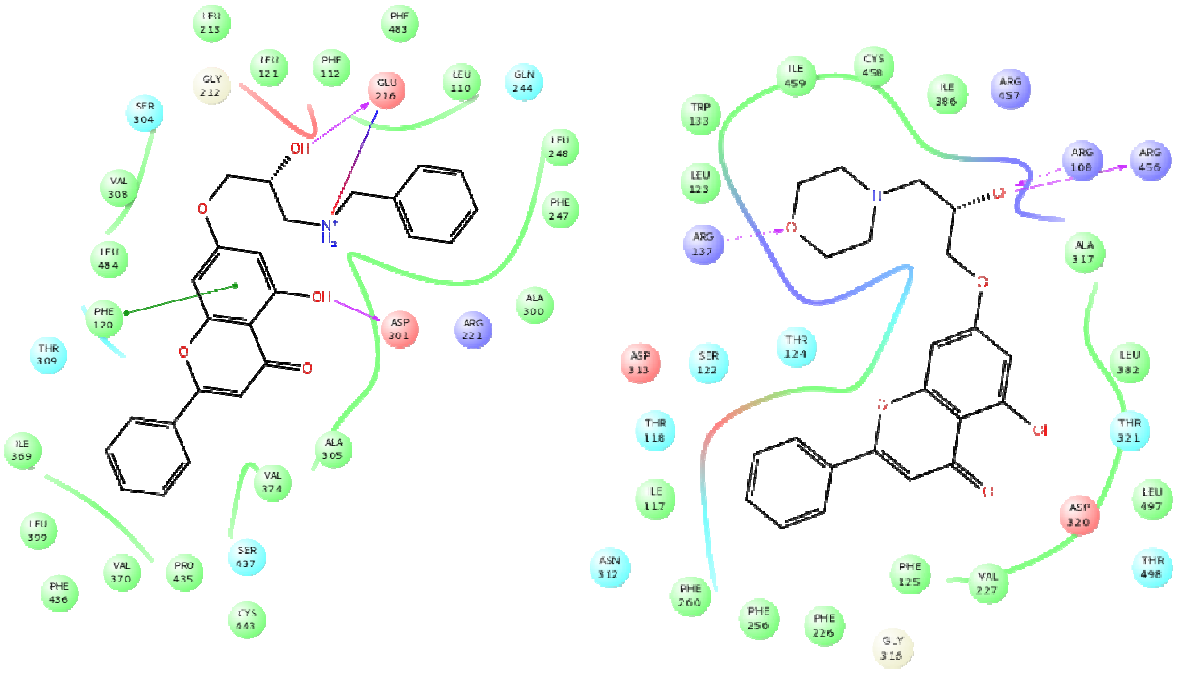


Fig. 3. 2D docking image of FC2.

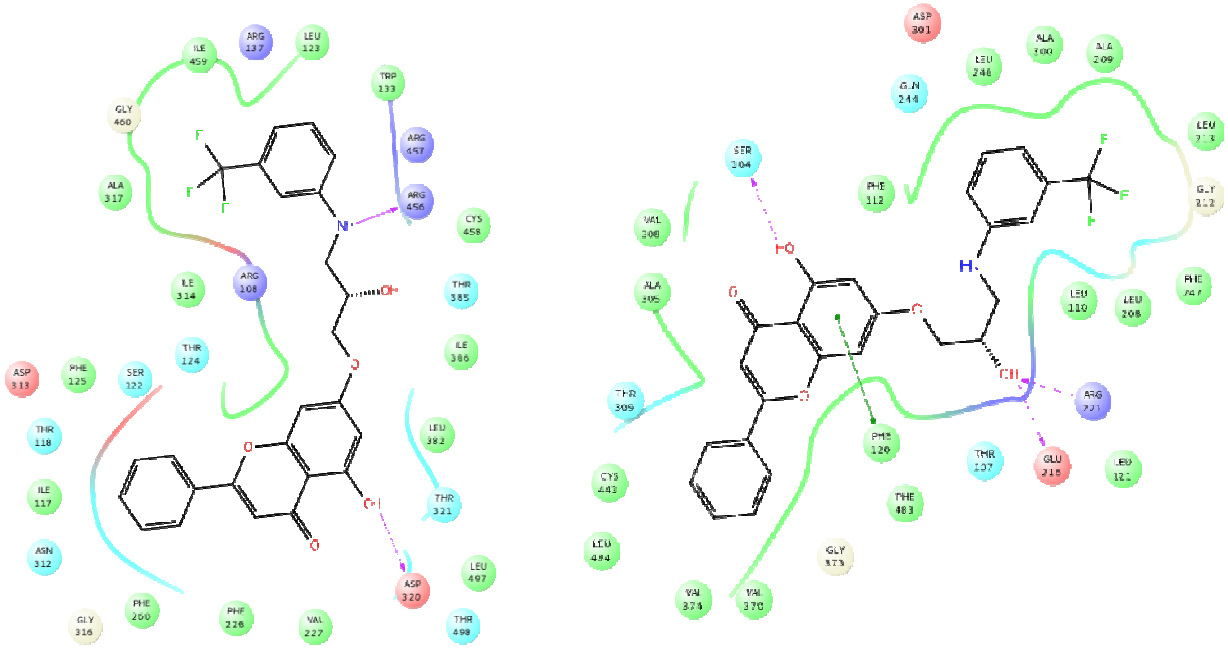


Fig. 4. 2D docking image of FC4.

Table 2 A: Docking properties of flavonoid derivatives with protein PDB 2HI4.

Properties Title	pot. Enrg	rms der	g. lignum	doc. Score	g. G score	g. lipo	g. h bond
FC1	168.343674	0.003362	28	-9.343099	-9.343099	-5.971229	0
FC2	95.924347	0.006792	3	-10.911133	-10.911133	-6.971314	0
FC3	---	---	---	---	---	---	---
FC4	120.901154	0.028745	21	-13.367924	-13.367924	-6.392996	0
FC5	117.567001	0.022674	15	-13.205443	-13.205443	-6.268827	0
FC6	114.667152	0.044917	2	-12.657705	-12.657705	-6.903045	-0.017482
FC7	116.531425	0.037908	3	-13.51441	-13.51441	-6.537107	0
FC8	155.814835	0.045647	33	-10.507547	-10.507547	-5.655258	-0.081681

Table 2 B: Docking properties of flavonoid derivatives with protein PDB 2HI4.

Properties Title	g. metal	g. rewards	g. evdw	g. ecoul	g. erotb	g. esite	g. emodel
FC1	0	-0.97341	-52.64248	-3.077655	0.695312	0	-82.3855
FC2	0	-1.335344	-55.43285	-4.155149	0.79044	0	-100.2199
FC3	---	---	---	---	---	---	---
FC4	0	-1.543034	-47.42932	-3.619826	0.636608	0	-98.85956
FC5	0	-1.805219	-52.35753	-2.37678	0.668956	-0.022731	-86.03762
FC6	0	-2.239453	-55.72128	-4.585138	0.668956	-0.016012	-87.45575
FC7	0	-2.611629	-48.75124	-3.583405	0.620171	0	-94.45331
FC8	0	-1.025577	-47.40433	-3.700292	0.616823	0	-76.79824

Table 2 C: Docking properties of flavonoid derivatives with protein PDB 2HI4.

Properties Title	g. energy	g. einternal	g.confnum	g. posenum	xp G score	XP H bond
FC1	-55.72013	10.181135	127	389	---	---
FC2	-59.588002	4.450532	8	151	---	---
FC3	---	---	---	---	---	---
FC4	-51.04915	9.929065	1	1	-13.367924	-1.66
FC5	-54.734313	11.126839	1	8	-13.205443	-1.352648
FC6	-60.306422	11.784204	1	4	-12.657705	-0.96
FC7	-52.334645	12.804959	1	2	-13.51441	-1.347412
FC8	-51.104624	5.519884	1	5	-10.507547	-1.148427

Table 3 A: Docking properties of flavonoid derivatives with protein PDB 3QM4.

Properties Table	pot. Energy	rms derv. Opls 2005	g. lig	dockin score	g. G score	glide lipo	glide h bond
FC1	158.4446	0.037722	29	-6.986713	-6.986713	-5.523423	0
FC2	95.92217	0.020512	31	-10.206862	-10.206862	-4.345689	0
FC3	120.7089	0.03262	22	-9.453116	-9.453116	-4.389898	0
FC4	120.8915	0.009622	28	-11.072221	-11.072221	-4.418587	0
FC5	117.567	0.022674	8	-12.069629	-12.069629	-3.938907	-0.32
FC6	114.6672	0.044917	23	-9.162203	-9.162203	-4.907478	0
FC7	116.5328	0.023927	5	-12.640064	-12.640064	-4.406126	-0.32
FC8	189.3671	0.047282	30	-8.835965	-8.835965	-4.588349	0

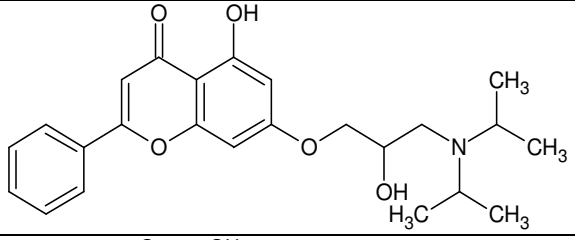
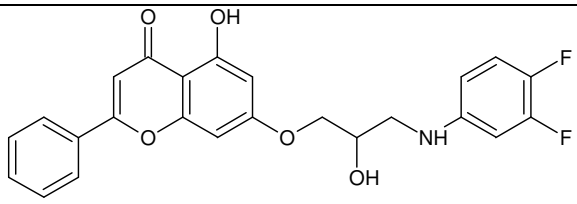
Table 3 B: Docking properties of flavonoid derivatives with protein PDB 3QM4.

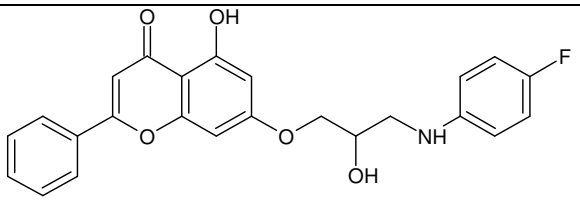
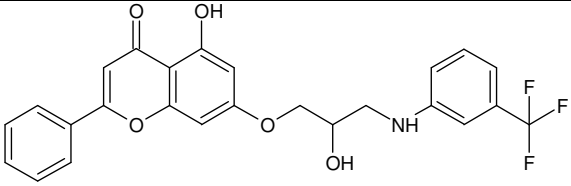
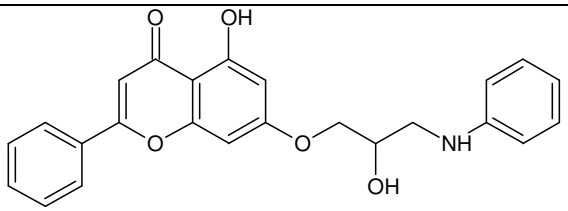
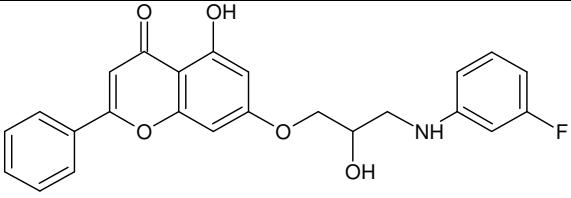
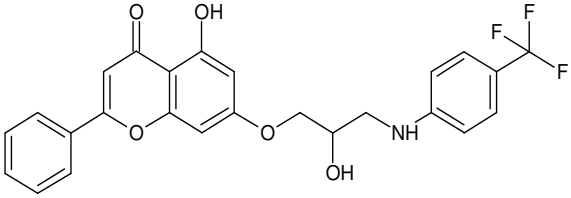
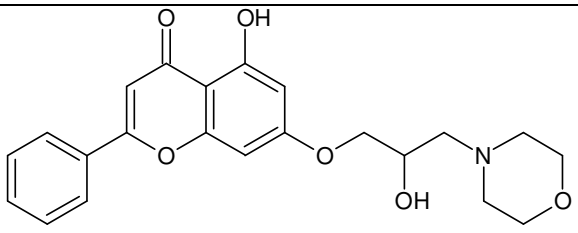
Properties Table	g.metal	glide rewards	glide evdw	glide ecoul	glide erotb	glide e site	glide e model
FC1	0	-0.59652	-9.84467	-7.132324	0.695312	0	-18.813381
FC2	0	-0.716274	-43.2088	-6.077048	0.79044	0	-64.933734
FC3	0	-1.017181	-46.9861	-4.439314	0.636608	0	-74.390265
FC4	0	-1.06604	-40.1379	-8.98544	0.636608	0	-65.130194
FC5	0	-2.317177	-49.5394	-5.345199	0.668956	0	-79.186025
FC6	0	-0.829812	-45.1804	-3.35356	0.668956	-0.1	-73.438624
FC7	0	-1.703627	-49.1467	-6.689647	0.620171	-0.074532	-85.829946
FC8	0	-1.038716	-36.564	-1.693351	0.619641	0	-63.719367

Table 3 C: Docking properties of flavonoid derivatives with protein PDB 3QM4.

Properties Table	glide einternal	glide confnum	g.posenum	xp G score	xp H bond
FC1	9.653969	2	6	---	---
FC2	10.255643	1	89	-10.20686	-1.86
FC3	7.768878	1	39	-9.453116	-1.55076
FC4	20.388039	1	1	-11.07222	-1.59858
FC5	11.45444	1	27	-12.06963	-1.18
FC6	11.970934	1	12	-9.162203	-1.18
FC7	8.331425	1	34	-12.64006	-1.66
FC8	2.571772	1	14	-8.835965	-0.48

Table 4: Table of docking score and glide energy of chrysin derivatives with different receptor or protein PDBs.

S. No.	Comp. Code	Structure	Dscore for 3QM4 & 2HI4	G. Energy for 3QM4 & 2HI4
1	FC1		-6.986713	-16.976998
			-9.343099	-55.72013
2	FC2		-10.206862	-49.285869
			-10.911133	-59.588002

S. No.	Comp. Code	Structure	Dscore for 3QM4 & 2HI4	G. Energy for 3QM4 & 2HI4
3	FC3		-9.453116	-51.425386
			–	–
4	FC4		-11.072221	-49.123363
			-13.367924	-51.04915
5	FC5		-12.069629	-54.884646
			-13.205443	-54.734313
6	FC6		-9.162203	-48.533974
			-12.657705	-60.306422
7	FC7		-12.640064	-55.83634
			-13.51441	-52.334645
8	FC8		-8.835965	-38.257316
			-10.507547	-51.104624

Glide evdw explains the van der waal energy of the complex of ligand and amino acid residue at the docking site after recombination. Glide energy is the some of coulomb energy and van der waal energy. The comparison between glide evdw and glide coulomb energy shows that vander waal energy shows major contribution in glide energy then coulomb energy. The van der waal interaction depends on surface area of the ligand and the contribution of glide evdw into the docking score is considerable. The glide evdw of the docking score is 2HI4>3QM4. Glide energy is summation of coulomb and van der waal energy of interaction. The glide energy indicates that, the comparatively coulombic force and van der waal interactions are higher for the flavones-2HI4 (FC6)>3QM4. This is due to higher surface area of 2HI4 available for interaction with FC6. Along with major interactions, there are some other interactions such polar interactions (faint blue colour), hydration sites (orange, interaction with water), electrostatic interactions (blue and pink) and hydrophobic interaction (major weak interaction with maximum number of amino acids) present between the ligand-protein complex.

CONCLUSION

CYP1A2 and CYP2D6 are significant members of cytochrome P450s family, and are considered as the main enzymes with responsibility of metabolizing various important exogenous and endogenous compounds in many species of microorganisms, plants and animals. The interaction between flavones derivatives and two CYPs were studied by molecular docking. The FC7, 7-(2-hydroxy-3-{[3-(trifluoromethyl)phenyl]amino}propoxy)-5-hydroxy-2-phenyl-4H-chromen-4-one shows strong interactions with CYP2D6 protein.

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