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In Silico Molecular Docking Studies of Flavanoids as Anticoloncancer Agents

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ABSTRACT

In silico molecular docking studies were carried out to assess binding affinity on some newly synthesized flavanoid analogues on cyclin-dependent kinase (PDB ID 1D18) proteins mediating tumour growth. AutoDock Vina was used as a molecular-docking tool in order to carry out the docking simulations. Docking poses that matched correctly to the expected bioactive conformations was identified. It was observed from binding conformations that linear or nearly planar structure of flavones and chalcones plays an important role in their anticancer activity and the hydrogen bonding functional group on the aromatic ring have a significant role in binding affinity towards the standard ligand. In conclusion, this docking not only helped to understand in to structural features of the compounds responsible for its bioactivity but also further lead optimization of these types of anticancer compounds.

Key Words*: *Flavonoids, Docking, Anticancer, Cyclin-dependent kinase-9

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1. INTRODUCTION

Protein-ligand docking aims to predict the binding mode and the affinity of a ligand relative to a protein. In the present article, the Autodock Vina docking software was used in docking procedure.[1] It is released under a free software license (GNU GPL since 2007). The choice of Autodock Vina as docking software was directed by its ability to find bioactive conformations with a very good level of accuracy. From the literature survey, It was known that synthetic flavone and chalcones, are currently being investigated for anticancer activity and is in phase-I clinical trials,[2] This compound acts through the inhibition of CDK-2 to produce an anticancer effect. Hence, cyclin-dependent kinase (PDB ID 1DI8) was chosen as the preferred target for molecular docking studies.[3]

2. MATERIALS AND METHODS

2.1 Protein preparation

3D crystal structure of cyclin-dependent kinase (PDB ID 1DI8) was downloaded from Protein Data Bank (⟨http://www.rcsb.com). The protein for docking was prepared using the Dock Prep tool of Chimera. The missing side chains, back chains, and residues were updated. Water molecules present in the crystal structure was removed in the protein preparation process. Flexible torsions of peptide side chains at Lys33, Asp145 and Leu83 were assigned with AutoDock Tools.[4]

2.2 Ligand preparation

The ligands were prepared using Chemdraw. We have also performed our own energy minimizations of the ligands, with the methods implemented in Vina (--local_only option). With these optimized structures, the goal of decreasing the number of unsuccessful dockings is achieved.

2.3 Molecular modeling

Auto Dock Vina was used as the molecular-docking tool in order to carry out the docking simulations. The grid points in X, Y and Z axis were set at 20 × 20 × 20. The grid center was placed in the active site pocket centre at (-9 × 51 × 13). This grid box included the entire binding site

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of the enzyme and provided enough space for the ligand translational and rotational walk.

Table 1. 5-Amino-2-hydroxy chalcones a1-a14 and 6-aminoflavones b1-b14 with their Dock Scores (kcal/mol) and activity against cyclin-dependent kinase 2 (CDK2)

Ligand Code	R'	Dock score	pIC50 uM
5-Amino-2-hydroxy chalcones			
a1	H	-8.6	3.73
a2	4-Cl	-8.8	3.66
a3	4-F	-9.1	3.74
a4	4-NO2	-9.0	3.44
a5	4-OC2H5	-7.2	NA
a6	3-OCH3	-8.6	3.36
a7	4-OH, 3-OCH3	-8.1	3.11
a8	3-OH, 4-OCH3	-8.2	3.90
a9	3,4-dimethoxy	-9.8	3.47
a10	2-OH	-8.4	4.01
a11	4-OCH3	-8.2	3.03
a12	3, 4-diCl	-8.7	3.77
a13	3,4-methylenedioxy	-8.9	4.37
a14	3,4,5-trimethoxy	-8.6	4.20
6-aminoflavones			
b1	H	-9.1	3.01
b2	4-Cl	-9.4	3.16
b3	4-F	-9.6	3.67
b4	4-NO2	-9.8	3.06
b5	4-OC2H5	-8.4	3.06
b6	3-OCH3	-9.4	3.65
b7	4-OH, 3-OCH3	-9.9	3.99
b8	3-OH, 4-OCH3	-9.2	3.68
b9	3,4-dimethoxy	-9.8	4.63
b10	2-OH	-9.1	3.52
b11	4-OCH3	-9	3.71
b12	3, 4-diCl	-9.8	3.87
b13	3,4-methylenedioxy	-8.5	3.13
b14	3,4,5-trimethoxy	-9.7	4.52

2.4 Molecular docking studies

5-Amino-2-hydroxy chalcones(A1-A14) and 6-aminoflavones (B1-B14) were docked against the cyclin-dependent kinase (PDB ID 1D18). AutoDock Vina, results were analysed using binding energy scoring function. The Vina scoring function is fully empirical calculates affinity between ligand and protein, including Gaussian steric interaction terms, hydrophobic and hydrogen-bond interaction terms.[5] For each calculation, nine posed ranked according to the scoring-function of Autodock Vina were obtained. Here we evaluate scoring functions with four criteria: ranking power, docking power, and screening power.

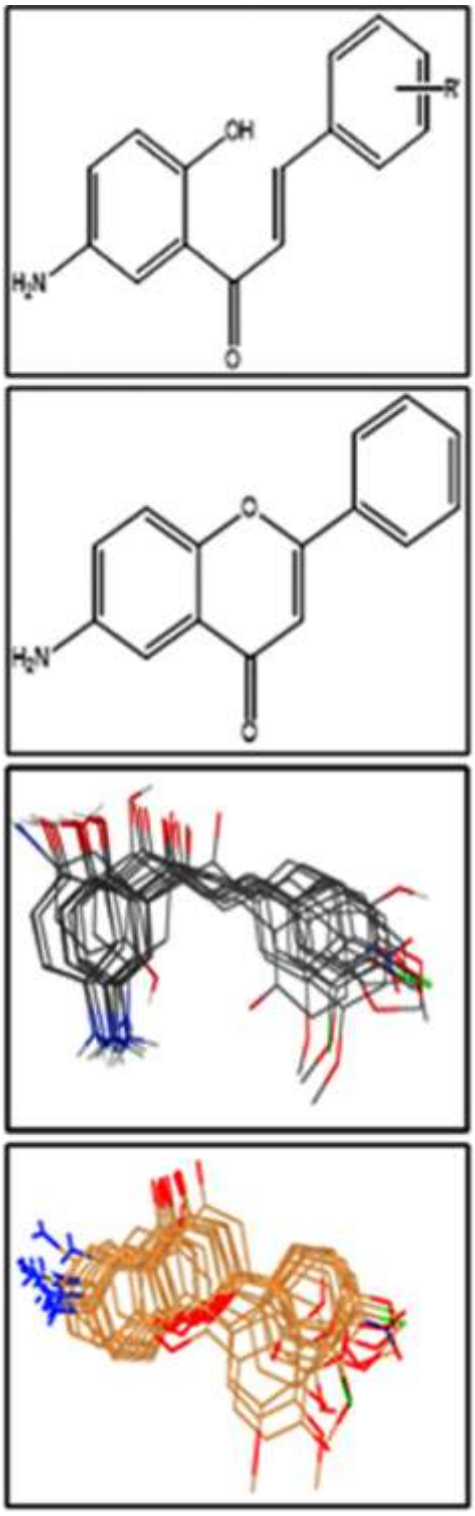

Figure 1. Superimposition of the most relevant docked structures of 5-Amino-2-hydroxy chalcones a1-a14 and 6-aminoflavones b1-b14.

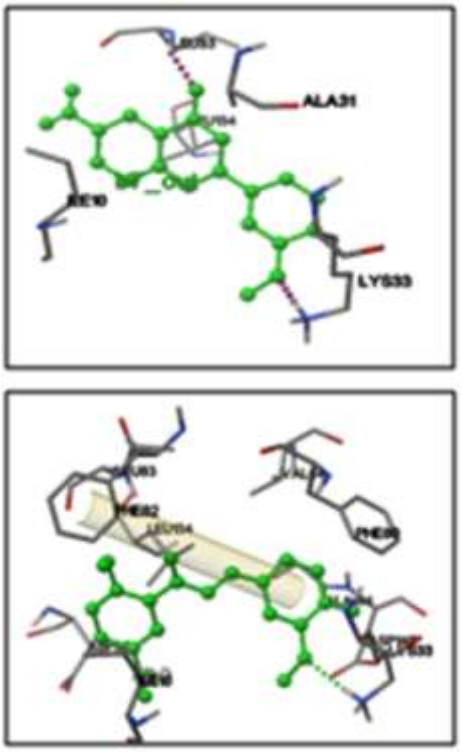

Figure 2. ligand protein interactions of top pose of flavone a6 and chalcones b6 to the active site of cyclin-dependent kinase (PDB ID 1D18)

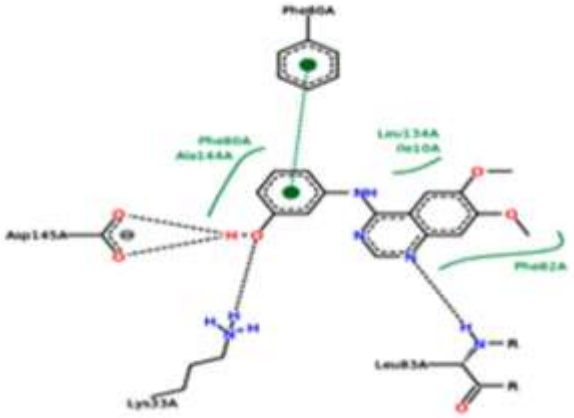

Figure 3 : Ligand protein interactions of standard ligand 4-[3-hydroxyanilino]-6,7-dimethoxyquinazoline (DQT) to the active site of cyclin-dependent kinase (PDB ID 1D18)

3. RESULTS AND DISCUSSION

Flexible docking of ligands selected in this study was carried out in the active site of kinase. Nine tops pose for each ligand were returned in the simulation, out of which one best pose for each ligand was selected on the basis of their binding energy calculation score. As seen from figure docking conformation of selected ligand matched correctly to the expected bioactive conformation of the standard ligand 4-[3-hydroxyanilino]-6,7-dimethoxyquinazoline (DQT) conforms that our Docking model had a very good level of accuracy. As seen from Table 3, aminoflavones displayed better binding affinity than their corresponding aminochalcones and hence could fit well in the receptor cavity forming energetically more stable drug receptor complex. It was observed from binding conformations that linear or nearly planar structure of flavones and chalcones is the essential feature for the receptor binding. The hydrogen bond interactions of the ligands were observed mainly with the residues Leu 83and Lys33 of protein. From the dock score, compounds b4, b7, a9, and b9, b14 were found to have highest dock score indicating that these compounds having an oxygen atoms from the methoxy group are an acceptor of proton for H-bond bind more effectively to the active site of than other compounds of the series. The all bioactive conformation was systematically top ranked by the Vina scoring function conforms with the good raking power of our docking study. However, No real correlations were established between the experimental and the calculated results with Vina scoring function. In order to optimize this docking study will require the consideration different knowledge-based scoring function based on hydrogen-bonding potential for improvement of predictive power of our docking model.

4. CONCLUSIONS

The present study represents systematic target identification and lead optimization for newly synthesized flavanoid compounds. Accurate binding of the ligand with Cyclin-dependent kinase-2 (CDK-2) was considered to validate it as one of the targets for anticancer activity of chalcones and flavones. In conclusion, this systematic computer-aided drug-designing approach not only helped to gain information on the possible putative targets of the compounds but also gave insights into structural attributes of the compounds responsible for anticancer activity.

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