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# Docking and molecular dynamic simulations: Study of 1, 3, 4-oxadiazole-chalcone hybrid derivatives to search new active anticancer agents

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## ABSTRACT

Chalcone hybrid derivatives are one of the anti cancer promising agents. **Objective:** To search chalcone hybrids derivatives as new active agents against cancer using molecular docking and molecular dynamic (MD). **Methods:** Blind docking of 81 chalcone derivatives in ortho, meta and para position with functional group OH, OCH<sub>3</sub> and F has been done using Genetic algorithm method in Autodock 4.0 software. **Results:** From the docking and MD indicated that compound 1, compound 7, compound 8, compound 11, compound 31, compound 34 and compound 41 were assumed to have good activity against cancer. **Conclusion:** These seven compounds were then chosen as the reference for the next stage in the drug design.

## INTRODUCTION

Cancer is one of the most dreaded diseases of the 20<sup>th</sup> century and spreading further with continuance and increasing incidence in the 21<sup>st</sup> century. It is a group of disease characterized by uncontrolled cell division leading to abnormal growth of the tissue. Each year 6.7 million people worldwide die from cancer. Globally, around 270,000 new cases occur annually and 145,000 deaths, of which two-third occur in developing countries [1]. Currently, the promising compound for anticancer is from chalcone derivatives [2].

Chalcones are polyphenolic organic compounds belonging to a class of natural products called flavonoids. They are found in many different plant tissues such as Lauraceae [3], Compositae, and Leguminosae [4] families. They are also known as pigments of the yellow to orange colored flowers of many plant species such as coreopsis and other Asteraceae taxa [5]. This group of natural products is abundant in vegetables and fruits. For example, significant amounts of

chalcones such as butein, phloretin, chalconargenin, arbutin, and phloridzin occur in tomatoes, apples, pears, bearberries and strawberries [6,7]. Chalcones are found to be one of the suitable intermediates for the synthesis of various heterocyclic derivative, viz., pyrimidine, imidazole, thiazine, thiazole, quinolone, oxazole, benzopyran, indole, and imidazolone derivatives [8]. These chalcone hybrids (i.e., having heterocyclic nuclei) are considered valuable pharmaceutical targets since they have been reported to possess a wide range of biological activity such as antioxidant [9], anti-inflammatory [10], and antimicrobial activities [11]. The hybrids of chalcones are also exhibiting intensified anticancer properties such as triazole, pyrrolobenzodiazepine, imidazolones, methyl piperidine, amidobenzothiazole through alkyl linkage or the fusion of heterocyclic groups such as coumarin, furan, indole, oxathialone, and thiazolein the chalcone structure enhances its anticancer activity over various cancer cells [8].

In the last decade, a number of investigations have been conducted on chalcone hybrids for their potential as anticancer agents such as human breast adenocarcinoma cell

line MCF-7, human prostate cancer cell line PC3, human lung adenocarcinoma cell line A549, and human adenocarcinoma cell line HT-29 (colorectal cancer) [8]. Thus far there are no so much reports on discovering an anticancer using molecular docking and molecular dynamic (MD). This study was conducted to investigate and to search new active agents against cancer using molecular docking and MD using an oncogene protein as the target. The oncogene protein has the possible for cause of cancer. In tumor cells, they were often mutated or expressed at very high levels. Mostly normal cells experience a programmed form of death (apoptosis). It is an important and striking target for anticancer drug development and discovery [12].

## RESEARCH METHODOLOGY

### Preparation of Ligand

Eighty one compounds with R and R' are modified in ortho, meta, and para position as presented in Table 1 were constructed and used as ligand. In this study, we selected only these three substituents, i.e., OH, F and OCH<sub>3</sub>, because OH represent as good electron donor, F represent as good electron acceptor and OCH<sub>3</sub> represent as normal functional group. The energies of all the ligand were minimized for then the minimized structures were subsequently prepared with detected root of torsion and number of torsions for flexible-ligand docking using Autodocktools 1.5.4 software [13]. The structures of these ligands are shown in Figure 1.

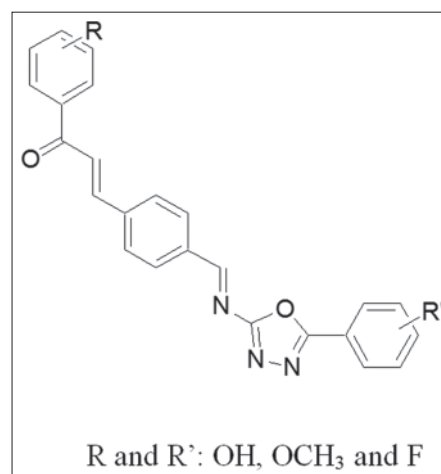
### Preparation of the Macromolecule

The three-dimensional crystal structure of the macromolecule was retrieved from the Protein Data Bank (pdb ID: 5P21), and chlorine, atoms, water, and glycerol were removed. In this study, we used a blind docking, thus the protonation state of ionizable amino acid will not determine. Autodocktools 1.5.4 software was then used to add all hydrogen atoms, merging non-polar hydrogen atoms, checking and repairing

missing atoms, adding Gasteiger charges, checking and fixing total charges on residues and assigning atom types to the protein structure. A grid box of the protein structure was then generated using Autogrid 4 software with default atom types (carbon, hydrogen, oxygen and nitrogen), grid spacing of 0.41 Å, dimensions of 126 × 126 × 126 points along the x, y and z axes and centered on the protein for the docking.

### Preparation of Autodock Parameter

The chalcone hybrid derivatives were docked into the protein using the Autodock 4.0 software. Docking into the active site of the macromolecule was executed using Lamarckian Genetic Algorithm using the following parameters population size 150 individuals and 10,000,000 number of energy evaluations for 100 runs to produce 100 distinct conformations using Lamarckian genetic algorithm search function [14]. All the docking parameter was verified before applying to these 81 compounds.



**Figure 1:** Structures of the ligand with modification of R and R' in ortho, meta and para position

**Table 1:** Various substituent of the 81 ligand

R	R'								
	Ortho			Meta			Para		
	2OH	2OCH <sub>3</sub>	2F	3OH	3OCH <sub>3</sub>	3F	4OH	4OCH <sub>3</sub>	4F
Ortho									
2OH	Cpd1	Cpd2	Cpd3	Cpd4	Cpd5	Cpd6	Cpd7	Cpd8	Cpd9
2OCH <sub>3</sub>	Cpd10	Cpd11	Cpd12	Cpd13	Cpd14	Cpd15	Cpd16	Cpd17	Cpd18
2F	Cpd19	Cpd20	Cpd21	Cpd22	Cpd23	Cpd24	Cpd25	Cpd26	Cpd27
Meta									
3OH	Cpd28	Cpd29	Cpd30	Cpd31	Cpd32	Cpd33	Cpd34	Cpd35	Cpd36
3OCH <sub>3</sub>	Cpd37	Cpd38	Cpd39	Cpd40	Cpd41	Cpd42	Cpd43	Cpd44	Cpd45
3F	Cpd46	Cpd47	Cpd48	Cpd49	Cpd50	Cpd51	Cpd52	Cpd53	Cpd54
Para									
4OH	Cpd55	Cpd56	Cpd57	Cpd58	Cpd59	Cpd60	Cpd61	Cpd62	Cpd63
4OCH <sub>3</sub>	Cpd64	Cpd65	Cpd66	Cpd67	Cpd68	Cpd69	Cpd70	Cpd71	Cpd72
4F	Cpd73	Cpd74	Cpd75	Cpd76	Cpd77	Cpd78	Cpd79	Cpd80	Cpd81

## MD Simulations

Preliminary MD simulations for the modeled protein were performed using the program NAMD (NANoscale Molecular Dynamics program; v 2.9) [15], and all files were generated using visual MDs (VMD) [16]. The protein was solvated with a TIP3P water box with a 2.5 Å layer of water for each direction of the coordinate structure, and a CHARMM (Chemistry at HARvard Macromolecular Mechanics) was used as a force field.

## RESULTS AND DISCUSSION

### Molecular Docking

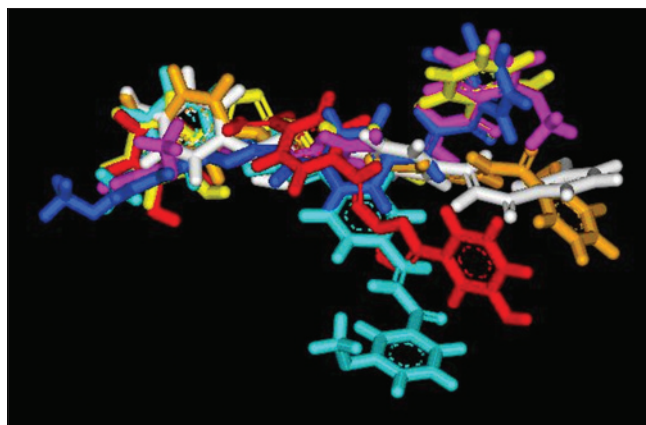
Docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge from of the preferred orientation, in turn, may be used to predict the strength of association or binding affinity between two molecules. The best poses from the docking results were selected based on the lowest docked energy values. Seven (highlighted in red - Table 1) of 81 compounds were observed to aligned in similar manner orientation around the active site of the protein. In addition, seven of these compounds also showed higher hydrogen bonding interaction. It may account for ligand to be more active [17], Table 2 is presented the docking output of the best binding conformation of these seven compounds. Superimposition of these compounds is depicted in Figure 2.

For compound 1 (R and R' is OH functional group in ortho position) showed to have one hydrogen bond between the carbonyl of the ligand and residue Lys147. This ligand also displayed  $\pi$  interaction with the residue Ser17. Tariq *et al.* reported that this protein with anticancer drugs formed a hydrogen bond with the residue Lys117 but no van der Waals interaction [12]. In our result, residue Lys117 shown interaction with ligand through van der Waals interaction (gray area) suggesting the importance of the residue in the formation of van der Waals pocket. It is indicating another possible mode of interaction between the ligand and this protein. This may be the reason for this ligand being active compounds. The binding interaction of this ligand with the protein is shown in Figure 3.

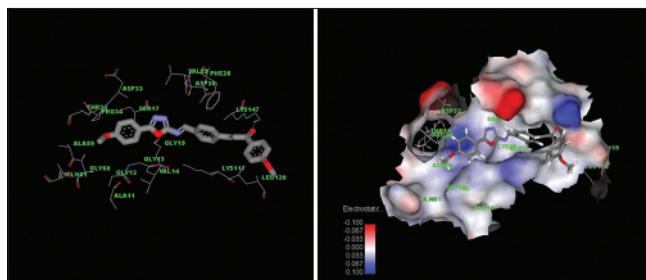
Another compound assumed as active compound is compound 7 with R and R' is OH functional group in ortho and para position, respectively. From the docking results, compound 7 showed to have two hydrogen bonding. One

hydrogen bonding is constructed between hydroxyl (R') of ligand with residue Asp33 and another hydrogen bond is between hydroxyl of ligand (R) with residue Asp119. The best docking poses of compound 8 found to interact with the residues via hydrogen bonding, i.e., between hydroxyl of ligand in R and the hydrogen of residue Asp30 and between the methoxy of ligand in R' with the hydrogen of residue Gly60. These binding interactions are shown in Figure 4.

For compound 11, there are two hydrogen bonds were observed between the residue Lys147 with carbonyl of the ligand and also with the methoxy group of ligand in R position. The best docking results of the compound 31 exhibited two hydrogen bonds between the carbonyl of the ligand with the residue Ala18, hydroxyl of the ligand in R position with the



**Figure 2:** Superimposition of compound 1 (red), compound 7 (pink), compound 8 (blue), compound 11 (dark blue), compound 31 (orange), compound 34 (yellow) and compound 41 (white)



**Figure 3:** The binding interaction of compound 1 (left) and surface area (right)

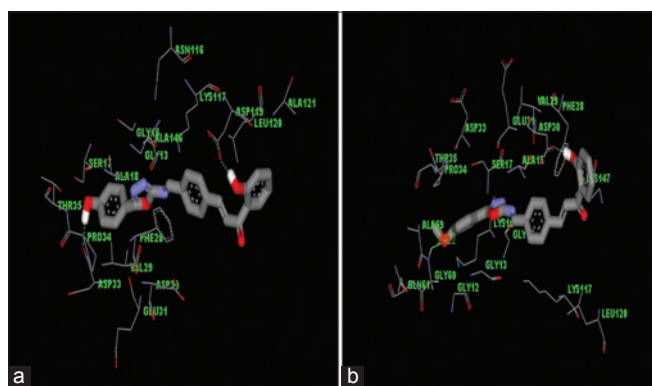
**Table 2:** Docking output of the best binding conformation

Molecule	Estimated free energy of binding (kcal/mol)	Estimated inhibition of constant ( $\mu\text{M}$ )	Number of interaction		
			H-bond	Van der Waals	$\pi$ -interaction
Cpd1	-5.85	16.83	1	1	1
Cpd7	-6.12	15.95	2	-	-
Cpd8	-5.34	14.78	2	-	-
Cpd11	-6.07	17.87	2	-	-
Cpd31	-7.65	17.99	2	1	-
Cpd34	-6.98	15.80	2	-	-
Cpd41	-6.43	16.98	1	-	-

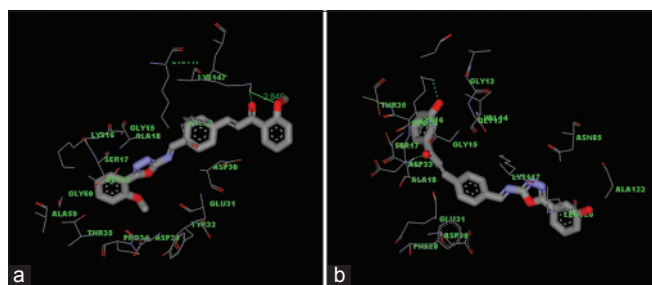
residue Lys16. In addition, van der Waals interaction was also observed with the residue Lys117. The spatial arrangement of the two ligands bound to the active site of the enzyme is presented in Figure 5.

As the other compound, compound 34 is seen to be active since this ligand observed many interactions with the residue in the active site. Compound 34 with OH functional group in the metha of R position and OH in the para of R' position. It was also seen to interact with the active site. From the best docking results, there are two hydrogen bonds were observed for compound 34. Hydrogen bond was constructed between the residues Asp33, Lys147 with the hydroxyl of the ligand in metha and para position, respectively. Likewise, in the case of compound 41, this ligand only has one hydrogen bond between the carbonyl of the ligand with the residue Asn85. The binding sites of these two ligands are shown in Figure 6.

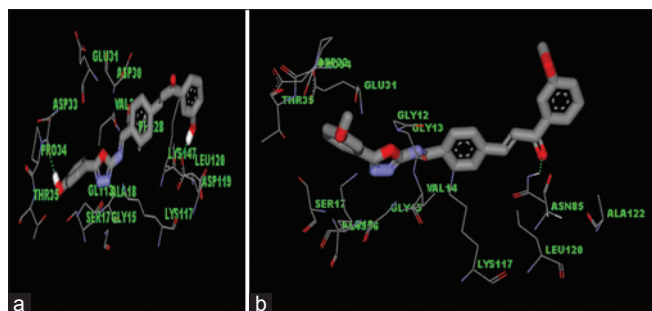
The binding energy was obtained with the docking of protein with the ligand complex; here only negative



**Figure 4:** The binding site of (a) compound 7; (b) compound 8



**Figure 5:** Spatial arrangement of the binding site for the (a) Compound 11 and (b) compound 31



**Figure 6:** Binding site of the compound 34 (a) and compound 41 (b)

binding was considered which can interact by H-bond. The major interaction between oncogene protein with the active anticancer is the important hydrogen bond with these residues: Gly13, Gly15, Val20, Asp33, and Lys117 [12]. In our case, seven of these compounds interact well with these residues not only via hydrogen bonding but also via van der Waals or  $\pi$ -interaction. Its presumably these seven compounds can be used as new active agents against cancer. The interaction of the seven ligands with the amino acid is shown in Table 3.

## MD

Although docking analysis can provide an acceptable binding mode, the solvent effect and flexibility of protein were not fully taken into account. Therefore, MD simulation was carried out on these seven compounds to further explore the ligand-receptor interaction [18].

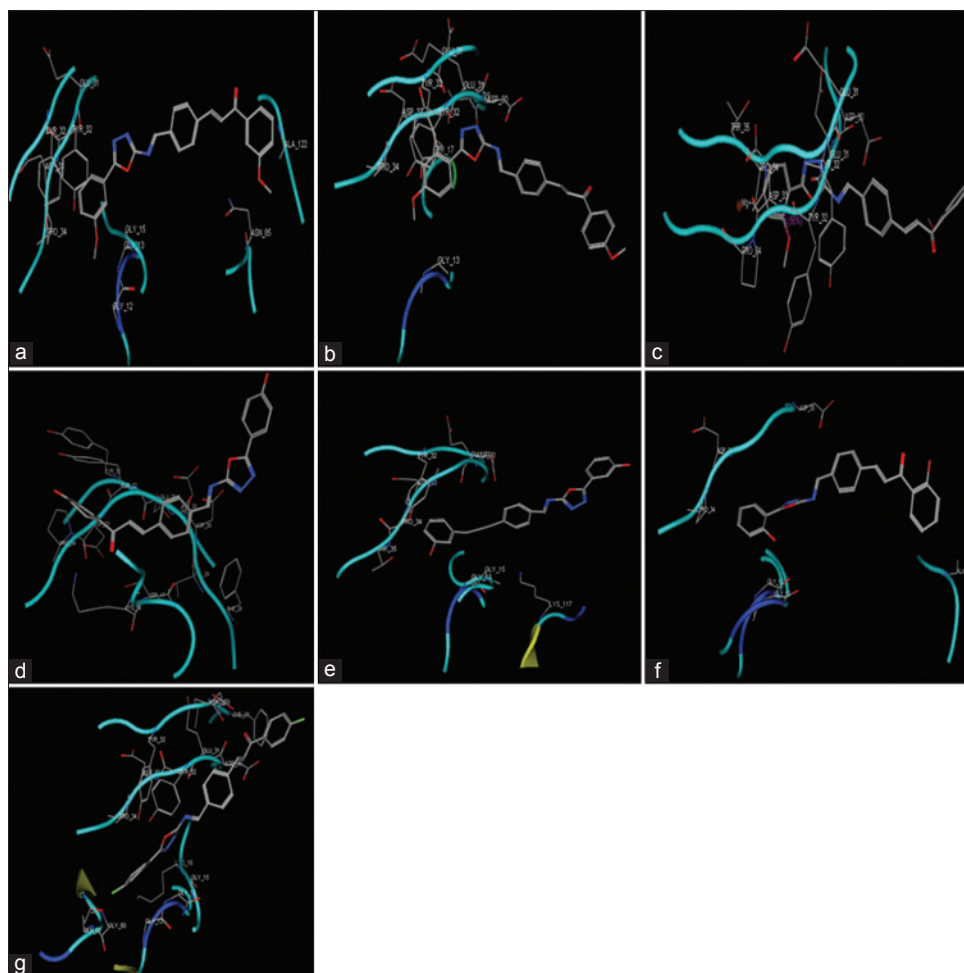
In order to evaluate the stability of the MD simulation, the properties (i.e., H-bond) of each complex was inspected. Hydrogen bonding interaction is quite important in the binding between ligand and receptor. In this study, the MD simulations were performed at temperature 300°K to see the affinity of the ligand to the binding site. In general, the conformations of these seven ligands are maintained to binding with the important residues as presented in Figure 7 and Table 3.

From Table 3, it can be observed that seven ligands during the docking process have hydrogen bond with the important residues such as Gly13, Gly15, Asp33, and Lys117. For MID simulation, at the temperature 300°K show that at the end of the simulation, these seven ligands seems lost their ability but

**Table 3:** Interaction of the ligand with amino acid through molecular docking and MD at temperature of 300°K

Ligand	Docking results	MD 300K
Cpd1	Gly13, Gly15, Ser17, Ala18, Asp33, Thr35, Asn85, Lys117, Leu120	Gly12, Gly13, Gly15, GLU31, Tyr32, Asp33, Pro34, Asn85, Ala122
Cpd7	Gly13, Gly15, Lys16, Ser17, Ala18, Phe28, Asp30, Asp33, Pro34, Thr35, Gly60, Asn85, Lys117, Leu120, Lys147	Lys16, Asp30, Glu31, Tyr32, Asp33, Pro34, Leu120
Cpd8	Gly13, Gly15, Lys16, Ser17, Ala18, Phe28, Asp30, Asp33, Pro34, Thr35, Lys117, Lys147	Asp30, Glu31, Tyr32, Asp33, Pro34, Thr35
Cpd11	Gly12, Gly13, Gly15, Ser17, Phe28, Val29, Asp30, Glu31, Pro34, Thr35, Lys117, Lys147	Lys16, Ser17, Asp30, Glu31, Tyr32, Asp33, Pro34
Cpd31	Gly12, Gly13, Gly15, Ser17, Ala18, Val29, Asp30, Asp33, Pro34, Thr35, Asn81, Lys117, Leu128	Gly13, Ser17, Tyr32, Asp33, Pro34, Thr35, Lys117
Cpd34	Gly13, Val14, Gly15, Lys16, Ser17, Ala18, Phe28, Val29, Asp30, Asp33, Pro34, Thr35, Lys117, Leu128	Gly13, Ser17, Ala18, Phe28, Lys117, Leu120
Cpd41	Gly13, Gly15, Ser17, Phe28, Val29, Asp30, Pro34, Thr35, Gly60, Lys117, Leu128	Gly12, Gly13, Gly15, Asp30, Tyr32, Asp33, Pro34, Gly80





**Figure 7:** Visualization of the binding mode of seven compounds (a) cpd 1 (b) cpd 7 (c) cpd 8 (d) cpd 11 (e) cpd 31 (f) cpd 34 and (g) cpd 41

still has interaction via hydrogen bonding with some of the important residues such as Asp33 and Lys117.

## CONCLUSION

The docking and MD simulation of 81 compounds of chalcone hybrids derivatives were carried out. In this work, seven compounds, i.e., compound 1, compound 7, compound 8, compound 11, compound 31, compound 34, and compound 41 are found to be good active agents against cancer. From the docking and MD studies suggested that in the presence of hydroxyl group or methoxy group or both of them in the R' position (ortho, meta and para) and hydroxyl or methoxy group or both in the R position (ortho, meta) may fill better into the adjunct pockets resulting more hydrogen bonding with the relative residues as Lys147, Asp33, Asp30, Lys117, Gly60, and Ala18, which presumably enhance the biological activity of these chalcone hybrid derivatives. This strategy reflects a logical progression for early stage drug discovery that can be used to successfully identify drug candidates.

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