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In-Silico Interaction Studies of Quinazolinone Derivatives for Their Inhibitory Action on Breast Cancer

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Abstract: ***In present research, a series of 2{[2-(4-chlorophenyl)-4- oxoquinazolin-3(4H)-yl]amino}-N-(substitutedphenyl) acetamides were taken from literature survey. The molecular docking study was performed on the selected quinazolinone derivatives into four different cancer inhibitory proteins. All the compounds showed average binding towards 2W1C and 2WD3 proteins whereas very promising interaction towards 4CQ0 and 3HB5 proteins. The compound RS_1, 2 and 7 were found to be potent inhibitor as they showed good binding against carbonic anhydrase inhibitors (4CQ0) and hydroxysteroid dehydrogenase inhibitor (3HB5) and also interacting with the active site of amino acids present within the binding cavity.***

Keywords: Quinazolinone, Cancer, Molecular docking.

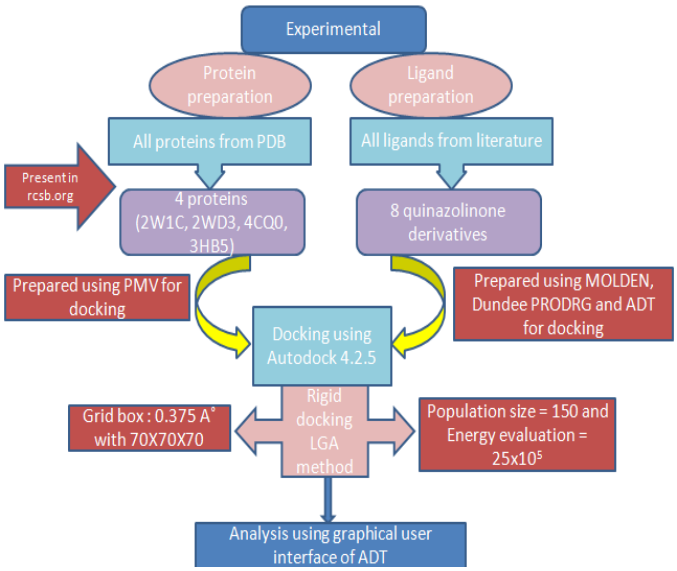
1. Introduction

In the field of molecular modeling, docking is a method which is used to predict the preferred orientation of one molecule to another when they are bound to each other to form a stable complex. The knowledge of the preferred orientation is used to predict the strength of association or binding affinity between two molecules using scoring functions. The relationship between biological molecules i.e. proteins, nucleic acids, carbohydrates, and lipids are very important signal transducer. The orientation or deviation of the two interacting molecules may affect the kind of signal produced. In structure-based drug design, molecular docking is one of the most frequently used methods because of its ability to predict the binding-conformation of small molecule into the target binding site. [1,2]

Cancer is rapid, uncontrolled growth, invasion and pathological proliferation of abnormal cells. It is one of the most leading causes of death in the world. One in ten of all new types of cancer diagnosed around the world each year is breast cancer and is the most common cancer in women in both developing and developed countries.[3] From past decades, designing of drugs for cancer chemotherapy has become very sophisticated and yet there is no treatment which is completely effective against cancer without or fewer side effects. Therefore, the search for potential anticancer drugs have led to the discovery of synthetic small molecules with anti-cancer activity and limited harmful side effects particularly modulating multiple targets either by the combination of multiple drugs with different mechanisms or by single chemical entity that could modulate several targets of a multi-factorial disease. As a result, there is increasing interest in the discovery of agents that concomitantly address more than one biological target for cancer treatment.[4]

The main focus of the present research is to investigate protein target responsible for cancer and to validate the selected chemical compound by performing molecular docking studies. Quinazolinone derivatives are an important category of compounds for designing anticancer drugs. They are found to possess potent and diverse biological activities. They have been used extensively in agriculture, medicine and pharmaceutical industry for their wide scope of biological activities. [5,6]

2. Methodology



Protein preparation: The structure of the target receptor for breast cancer were obtained from the RCSB Protein Data Bank, http://www.rcsb.org/pdb. The existing three dimensional macromolecular structures of Aurora kinase inhibitor (2W1D[7]), dual aromatase-sulfatase inhibitor (2WD3[8]), carbonic anhydrase inhibitors (4CQ0[9]), hydroxysteroid dehydrogenase inhibitor (3HB5[10]) were extracted from the PDB file. The water molecules and hetero atoms along with the co-crystallized ligands in PDB crystal structures were removed. Polar hydrogen atoms and charges were assigned. The atom types defining hydrogen bond acceptor and donor and aromatic or

aliphatic carbon atoms were defined to all the proteins and the proteins were set as rigid with no flexible bonds.

Ligand preparation: All the ligands[11] were drawn in MOLDEN and the small molecule topology generator Dundee PRODRG server was used for ligand optimization. It is a tool for high-throughput screening which takes description of small molecule in various two-dimensional formats or co-ordinates and generates molecular topologies and energy minimized in variety of formats

Docking studies using AutoDock 4.2.5: Lamarckian genetic algorithm (LGA) method was adopted in this study. A grid box was generated using spacing of 0.375 A˚ with 70 x 70 x 70 points was set. The grid was placed around the catalytic clef of the protein for docking. For each docking simulation, 10 independent runs were carried out with a population size of 150 and $25x10^5$ energy evaluations and all other parameters were set to default values. The lowest binding energy with maximum cluster size was considered for all further interaction studies. Hence, the same protocol was used for all further docking studies.

3. Results And Discussion

The compounds RS_1-8 were docked on to the active site of 2W1C with resolution of 3.24Aº, 2WD3 with resolution of 1.8Aº, 4CQ0 with resolution of 1.45Aº and 3HB5 with resolution of 2.0Aº proteins. The results are given in Table-1.

The complex formed between protein and ligand after successful docking were analyzed based on the parameters such as binding energy, pose of the docked compound, hydrogen bond and π–π interactions between ligand and the amino acid within the binding cavity. The compound RS_2,4 and 8 have shown fair binding against aurora kinase inhibitor protein (2W1C) with interactions within active site of amino acid LYS143, LYS171. Against dual aromatase sulfatase inhibitor protein (2WD3), the compound RS_1,4,7 and 8 showed good binding energy with interactions within active site of amino acid LYS158. In the case of carbonic anhydrase inhibitors (4CQ0), 1,2,6,7 showed good binding with interactions within active site of amino acid ARG58, LYS171, SER173, GLY233. For binding against hydroxysteroid dehydrogenase inhibitor (3HB5), compounds RS_1,4,6 and 7 showed very good binding energy and interacting with the active site of amino acid - LEU18, ALA19, GLY141, SER142, LYS159, SER168, ARG266.

Table-1: Structure and docked compounds

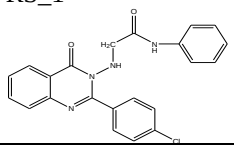
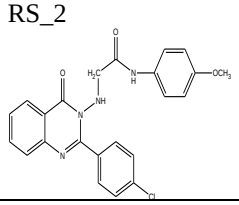
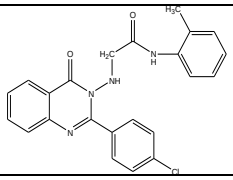
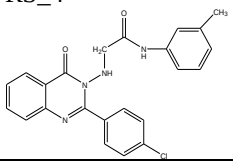
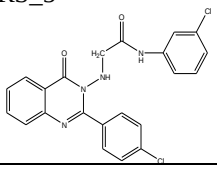
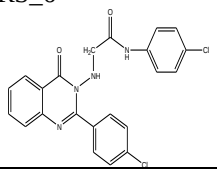
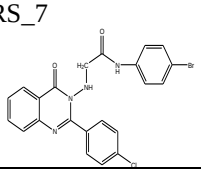
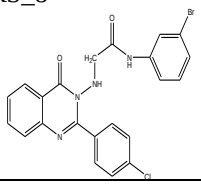
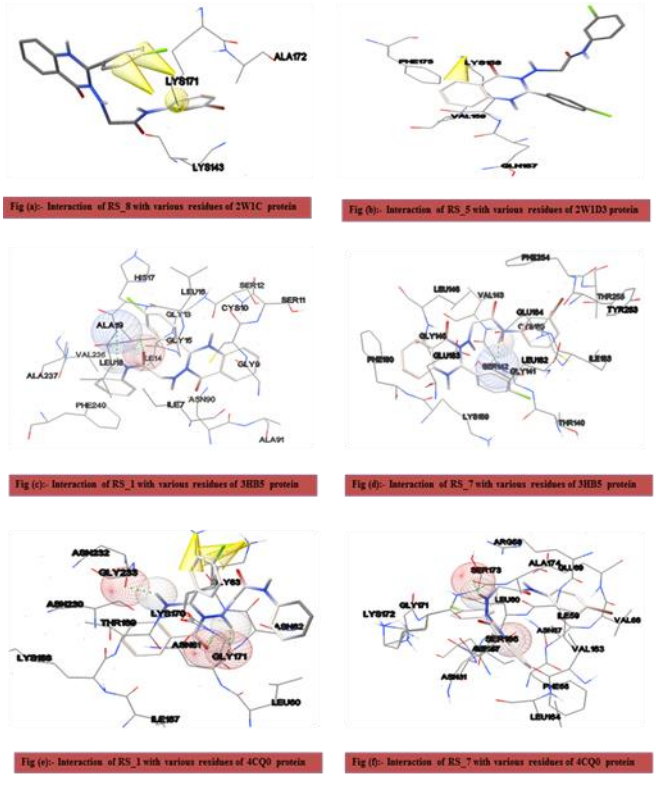
Sl. No	Compound code	2W1C	2WD3	4CQ0	3HB5
1.	RS_1 	-4.05	-5.63	-6.08	-9.67
2.	RS_2 	-5.92	-5.75	-8.40	-5.21
3.	RS_3				
		-5.69	-5.72	-4.70	-5.83
4.	RS_4 	-6.56	-7.07	-6.61	-7.10
5.	RS_5 	-5.63	-6.94	-5.71	-5.77
6.	RS_6 	-4.54	-5.62	-8.17	-8.74
7.	RS_7 	-4.29	-6.25	-7.06	-9.93
8.	RS_8 	-5.92	-6.33	-6.65	-5.64

Fig 1 : Molecular docking interaction



Thus, the evaluation showed that most of the quinazolinone derivative showed fair docking score with hydrogen bond interaction. But in particular, the compounds RS_1 and 7 have shown a promising binding against the carbonic anhydrase and hydroxysteroid dehydrogenase inhibitors with low binding energy with good number of interactions with the amino acids present in the active site - LEU18, ALA19, ARG58, GLY141, SER142, LYS159, SER168, LYS171, SER173, GLY233,ARG266.

4. Conclusion

The *in-silico* study revealed that the compound 2-[2-(4-chlorophenyl)-4- oxoquinazolin-3(4*H*)-yl]amino}-*N*-phenyl-acetamide (RS_1) , 2{[2-(4-chlorophenyl)-4- oxoquinazolin-3(4*H*)-yl]amino}-*N*-(-4-methoxyphenyl) acetamide (RS_2) and *N*-(4-bromophenyl)-2-{[2-(4-chlorophenyl)-4-oxoquinazolin-3(4*H*)-yl]amino}acetamides (RS_7) showed good binding energy against carbonic anhydrase inhibitors (4CQ0) and hydroxysteroid dehydrogenase inhibitor (3HB5) and also interacting with the active site of amino acids present within the binding cavity. Hence, further modification on these molecules may yield more potent compounds that shall be considered as pharmacophore against breast cancer targeting enzymes of both carbonic anhydrase and hydroxysteroid dehydrogenase .

Acknowledgement

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