Journal of Engineering Sciences

Vol 12, Issue 01, MAY /2021
ISSN NO:0377-9254

SYSTEMATIC COMPUTATIONAL AND EXPERIMENTAL INVESTIGATION OF THE OXADIAZOLE DERIVATIVE MONOMER

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Abstract

Cancer is usually named for the portion of the body it developed in; breast cancer thus refers to the erratic growth and proliferation of breast tissue-originated cells. In different areas of the breast there are several forms of tumours that may develop. The bulk of cancers are the product of benign alters within the breast (non cancer). In ordinary and diseased conditions, oestrogen receptors (ER) are essential for improving the relevant treatment strategies. Estrogen is the key factor of the prognosis of breast cancer and plays a large part in improving breast cancer. Molecular docking and linking, free energy experiments investigated potent oxadiazole derivatives binding mode, residue interaction patterns, and docking energy.

Keywords: Breast Cancer, Molecular Docking, oxadiazole

1. INTRODUCTION

Breast cancer is one of the leading causes of disease among female individuals in the world [1]. Around 25 percent of breast cancer patients were identified from developing countries. Breast cancer is one of the common forms of cancer contributing more than 27 percent in total cancer patients in Indian population [2]. In the year 2012 alone more than 144,937 breast cancer cases have been reported with 48.45 percent mortality. The number of cases of breast cancer in patients aged 50–64[3] has risen significantly. In towns, one in 22 women registered breast cancer and this concentration fell to one in 60 women in the rural sector. However, cases of breast cancer among men were also rarely registered. More than 1500 new cases are recorded annually in the United States [4]. This cancer is one of the world's second leading deaths in western countries. More than 60 percent of cases of breast cancer in Asian countries are diagnosed as Alpha-Positive (ERa) estrogen receptor cancers. However, ERa directly mediates the proliferation of estrogen-induced cells in autocrine mode of action in ERa breast cancer cell lines in vitro [5]. ERa plays a major role in breast cancer growth. Progesterone hormone receptor and mammaglobin are step-by-step approaches of diagnostic breast cancer with optimum positive benefit (88 percent) with estrogen [6].

A protein/drug database and molecular docking algorithm require at least two elements in silico approaches for docking experiments. However, while sometimes heterogeneous and incomplete, this information can be exploited by statistical methods to deepen these interactions [13]. Since experimental methods consume costs and resources, high-performance computational algorithms for processes for drug discovery are needed. The "docking" computer technologies will predict the binding of drug target complexes and the conformation of the ligand on the binding of a protein target. The free, binding energy of

goal–drug interactions determines the affinity and requirements for a dynamic relationship. Ranking free binding energies are not always accurate but can be used to pick new drugs, including small molecules, for virtual screening testing [14]. Small molecules are exciting new low-weight drugs that make it possible for cells to penetrate [15]. Molecular docking may also be used to forecast the results of a medicine; for example, to detect an unintended reaction between a compound and off target. To date, 57 000 summaries/papers have been published on molecular docking, which show the importance of this method for the development of medicines [16].

2. METHODOLOGY

2.1 Ligand Preparation

In this *in silico* studies, we have analysis our previously synthesized oxadiazole derivatives ((Z)-4-(4-amino-5-((4-hydroxybenzylidene)amino)-4H-1,2,4-triazol-3-yl)phenol (**M1**), (Z)-5-(4-amino-5-((4-hydroxybenzylidene)amino)-4H-1,2,4-triazol-3-yl)-2-hydroxybenzaldehyde (**M2**), The Anastrozole drug used as a standard for comparison study. The Anastrozole is used to treat breast cancer in women after menopause. Some breast cancers are made to grow faster by a natural hormone called estrogen. Anastrozole decreases the amount of estrogen the body makes and helps to slow or reverse the growth of these breast cancers. All the molecule structure were drawn in Chemdraw software and the energy of the all the molecules were minimized and saved in SDF file format for further docking studies.

2.2 PROTEIN STRUCTURE PREPARATION

In this analysis it was obtained from the protein Data Bank, RCSB, the structure of the estrogen receptor protein (PDB ID – 3ERT) and the structure of the PDB has different lack of detailed details on connectivity, along with structured shift and bond orders. The protein structure is imported by the protein preparation wizard from PDB into Maestro. The hydrogen polar display is only possible with the protein preparation wizard. These alternative reveals only polar atoms of hydrogen.

2.3 MOLECULAR DOCKING

CDOCKER was recruited with the DS, which was primarily focused on the CHARMm force field, to examine the binding affinities between protein and ligand. Consequently, a spontaneous rigid body rotation has been generalized to different conformations. The generation of 10 conformers was allowed for each ligand, holding all of the other parameters as default. The results of the docking were read through the -CDOCKER_energy interaction which means the energy of the non-connected interaction between ligand and protein. Higher energy exchange values also mean that the protein and ligand have a more desirable binding. 4 ligand molecules and 4 FDA licensed breast cancer medications (anastrozole) were performed to detect the ability of the latest medicines in Docking. For the introduction of the docking protocol, the prepared protein and ligands were imported on DS. The results based on the ---CDOCKER interaction energy, interaction between the hydrogen bonds and the binding mode patterns were evaluated.

In molecule M2, the -OH, -CHO and -NH_2 group forms three hydrogen bonds with Tyr383, His273 and Asp385 amino acids respectively (Figure 3). Further, Arg222 binding with aromatic benzene by Pi-Alkyl stacked interaction and Tyr383 binding with triazole in receptor active site. The Met414, Thr231, Met271, Gln254, His386 and His 274 shows van der Waals interaction with M2 molecule.Similarly, the molecule M3 (CDOCKER Energy is -19.3841 Kcal/mol^{-1}) forms two hydrogen bond, two Pi-Pi T- shaped, one Pi-Pi stacked, one Pi-Alkyl, one Pi-Anion and seven van der Waals interactions with respective active site amino acids of 3ERT receptor (Figure 4). Moreover, the molecule M1 (Figure 4) has strong hydrogen bond with Gly223, Asp385 and Gln254 amino acids (-18.9312 Kcal/mol^{-1}). Its shows more binding energy compared to standard Anastrozole drug (Figure 5). The CDOCKER energy of the Anastrozole is -11.2549 Kcal/mol^{-1}. The

Anastrozole forms hydrogen bond, Pi-Sigma, Pi-Pi Stacked, Pi-Pi T-Shaped, Alkyl, Pi-anion and van der Waals interaction with active site amino acids. It showed very lowest binding energy compared to synthesized oxadiazole derivatives. This research carried out molecular docking and analyzed the maximum values.Molecular docking is useful for deciding the right siteProtein recipient. The ligand-receptor interface energy wasget after docking the active site ligands (3ERT).

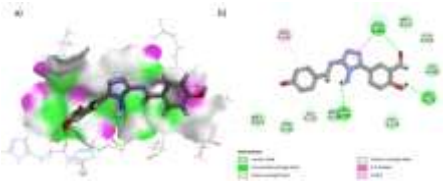

Figure 3. a) 3D and 2D) binding interaction of molecule M2 in Human Estrogen Receptor active site.

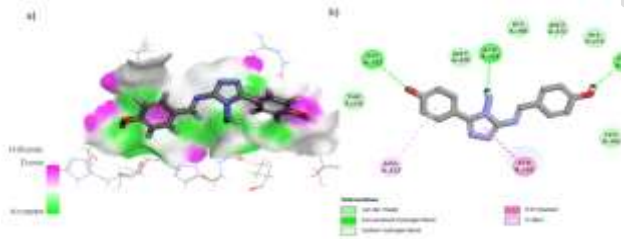

Figure 4. a) 3D and 2D) binding interaction of molecule M1 in Human Estrogen Receptor active site

CONCLUSION

In this study 3ERT was based on the logical approach to inhibit the growth of breast cancer cells in conjunction with its silicon predictive potential. In studying molecules with high binding affinity and biologically important interactions the research explored the ability of pharmacophores modelling. Following the recognition of the screened compounds over the reported compounds, the docking experiments have been completed.

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