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DOCKING ANALYSIS OF LIGAND 3-[1-HYDROXY-[METHYLETHYL] BENZONITRILE ON HUMAN GASTRIC CANCER PROTEIN (HGCP) IBJ7

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Abstract. Gastric cancer is the second leading cause of cancer-related deaths and the fifth most common malignancy worldwide. Docking studies yielded crucial information concerning the orientation of the inhibitors in the binding pocket of the target protein. In the present study the bioactive compound 3-[1-Hydroxy-[methylethyl] benzonitrile (ligand $C_{10}H_{11}NO$) was docked against the Human Gastric Cancer Protein (HGCP) IBJ7. The docking analysis was carried out by Auto dock tools (ADT) v1.5.4 and Autodock v4.2 programs. The probable binding sites of preferred target receptors were searched using Q-site Finder to predict the ligand binding site. All the visualization of the structure files were done using PyMol molecular graphics system. The results showed that the ligand 3-[1-Hydroxy-[methylethyl] benzonitrile (ligand -$C_{10}H_{11}NO$) showed minimum binding energy -5.41.kcal/mol. The binding profile of the 3-[1-Hydroxy-[methylethyl] benzonitrile (ligand $C_{10}H_{11}NO$) docked with cancer protein 1BJ7shows that ligand interacted with two basic polar amino acid HIS97/ARG341 and one non polar amino acid LEU342; one non polar amino acid LEU1676; one polar amino acids ASN86; one acidic polar amino acid ASP770 and one polar amino acid ASN51. This ligand interacted with several amino acid residues present in the target Human Gastric Cancer Protein (HGCP) IBJ7.

Keywords: Gastric Cancer Proteins, Autodock and Marine natural products.

1. INTRODUCTION

Gastric cancer is the second leading cause of cancer-related deaths and the fifth most common malignancy worldwide (Fitzmaurice et al ., 2015). Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The identification of oncogenes involved in the initiation and progression of tumors has generated targets for the development of new anti-cancer drugs (Rajamanikandan *et al.,*2011). The field of molecular docking has emerged during the last three decades and now is becoming an integral aspect in drug discovery and development area (Meshram and Jangle, 2009). Identifying the location of ligand binding sites on a protein is of fundamental importance for a range of applications including molecular docking, *de novo* drug design and structural identification and comparison of functional sites (Laurie and Jackson, 2006 and Sahu *et al.,* 2012).

Docking is a method which predicts the preferred orientation of one molecule to a second one when bound to each other to form a stable complex (Lengauer and Rarey, 1996). Several protein–ligand docking software's such as AutoDock or EADock have been used. There are also web services (Molecular Docking Server, Swiss Dock, *etc*.) That calculate the site, geometry and energy of small molecules interacting with proteins.

Docking studies have already proved the efficacy of mangrove derived compounds against oncoprotein of cervical cancer, sterol containing protein (AeSCP-2) and breast cancer protein BRCA1 (Senthilraja *et al.,* 2011; Senthilraja and Kathiresean, 2011ab; Senthilraja *et al.,* 2011), MCU1oncoprotein (Rajamanikandan *et al*., 2011). Mangrove-derived compounds such as triterpenoid and stigmasterol have been studied for computation selection against sterol carrying protein, AeSCP-2 (Senthil and Kathiresan, 2011) and cervical viral oncoprotein, HPV16 E6 (Senthil and Kathiresan, 2011).

2. MATERIALS AND METHODS

2.1. **Molecular-docking.** The chemical structures of the compound 3-[1-Hydroxy-[methylethyl] benzonitrile are drawn using the Chem sketch package 11.0 belonging to the ACD Chem laboratory (Baskaran and Ramachandran 2012 and Balamurugan *et al*., 2012). Three dimensional structures of Human Gastric Cancer Protein (HGCP) IBJ7 was retrieved from the Protein Data Bank (PDB) http://www.pdb.org. The probable binding sites of preferred target receptors were searched using Q-site Finder to predict the ligand binding site. The docking analysis was carried out by Auto dock tools (Wallace *et al.,* 1995) (ADT) v1.5.4 and Autodock v4.2 programs; (Autodock, Autogrid, Autotors, Copyright-1991-2000) from the Scripps Research Institute, http://www.scripps.edu/mb/olson/doc/ autodock.

The searching grid extended above the preferred target proteins; polar hydrogens were added to the ligand moieties. Kollman charges were assigned and atomic solvation parameters were added. Polar hydrogen charges of the Gasteiger-type were assigned and the nonpolar hydrogens were merged with the carbons and the internal degrees of freedom and torsions were set. The search was carried out with the Lamarckian Genetic Algorithm; populations of 150 individuals with a mutation rate of 0.02 were evolved for 10 generations. Evaluation of the results was done by sorting the different complexes with respect to the predicted binding energy. A cluster analysis based on root mean square deviation values, with reference to the starting geometry, was subsequently performed and the lowest energy conformation of the more populated cluster was considered as the most trustable solution. The hydrophobic effect of the ligand was retrieved by ALOGPS 2.1. All the visualization of the structure files were done using PyMol molecular graphics system (www.pymol.org).

2.2. **Results and Discussion.** The binding profile of the 3-[1-Hydroxy-[methylethyl] benzonitrile (ligand $C_{10}H_{11}NO$) (Figure1). docked with cancer protein 1BJ7shows that ligand interacted with two basic polar amino acid HIS97/ARG341 and one non polar amino acid LEU342; one non polar amino acid LEU1676; one polar amino acids ASN86; one acidic polar amino acid ASP770 and one polar amino acid ASN51 (Figure 2). This ligand interacted with several amino acid residues present in the target Human Gastric Cancer Protein (HGCP) IBJ7.

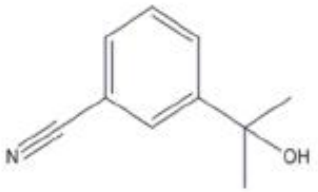

FIGURE 1. Molecular structure of ligand 3-[1-Hydroxy-[methylethyl] benzonitrile

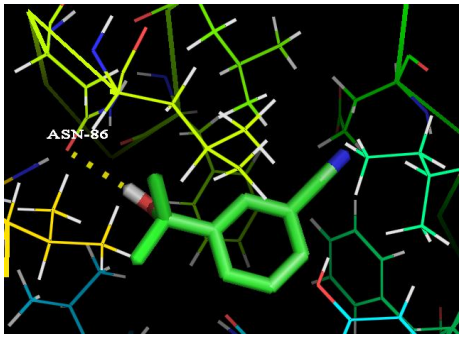

FIGURE 2. Ligand 3-[1-Hydroxy-[methylethyl] benzonitrile, binding with target protein of cancer 1BJ7.

Gaikwad, *et al*.(2011) docked the antitumor compounds against the cancer proteins. The ligand cabazitaxel showed least binding energy -709.75 kcal/mol with skin cancer protein (2VCJ) followed by -611.48 kcal/mol with brain cancer protein 1QH4, -587.21 kcal/mol with breast cancer protein, -513.08 kcal/mol with lung cancer protein 2ITO and -404.48 kcal/mol gastric cancer protein 1BJ7. The brown algae polysaccharide fucose forms hydrogen bonding interaction with the cancer associated p53 protein with the binding energy of 185.738 and G Score value -3.351469 (Preamnath, *et al*.,2012).

Rajamanikandan *et al*. (2011) reported that the docking between the ligand 14-hydroxyterezine and MUC1 oncoprotein, the docking score showed least energy -12.60 kcal/mol. Senthil *et al.* (2011a,b) studied the marine derived compounds (triterpenoid and stigmasterol) against the cervical cancer protein (HPV16E6) and breast cancer protein (BRCA1). The highest activation energy values (- 12.0691 Kcal/mol) and (- 13.386 Kcal/mol) respectively. The compounds derived from mangrove ecosystem (triterpenoid, stigmasterol and pyrethrin) could be novel chemical inhibitors for BRCA1 protein preventing the uncontrolled cell division (Senthil *et al*.,2011). The energy values reported in the above said study is in good agreement with the results of the present study.

3. Conclusion

The results obtained from this study would be useful in considerate the inhibitory mode as well as in quickly and precisely predicting the activities of new inhibitors on the basis of docking scores. The present study concluded that the compound 3-[1-Hydroxy-[methylethyl] benzonitrile are capable of blocking the target cancer protein 1BJ7 responsible for Human Gastric Cancer Protein.

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