ISO 9001 - 2015

ISSN 2349 - 4891

Monthly

IJRRAS

IF
4.665

Volume 4, Issue 2, February 2017

International Journal of

Recent Research and Applied Studies

SURRAGH PUBLICATIONS

ISSN: 2349 - 4891

International
Journal of Recent Research and Applied Studies
(Multidisciplinary Open Access Refereed e-Journal)

Prediction of Binding Affinity and Molecular Interactions of HER2 Receptor with Drug Targets

K.Ramanathan

Asst.Professor, Department of Bioinformatics, Thanthai Hans Roever College, Perambalur, Tamilnadu, India.

Received 10th January 2017, Accepted 5th February 2017

Abstract

This goal of this work is to predict the binding affinity and identify the molecular interactions of HER2 receptor with potential drug targets. Docking is performed to predict the binding affinity based on the molecular interactions of drug targets benzene propanoic acid and 1-phenathrenemethanol with the HER2 target receptor. The ligands were identified from the phytochemical studies and the target receptor HER2 interacted with the potential lead molecules shows high binding affinity. The hydrogen atoms of Thr 854 and the oxygen atom of the Leu 788 in the HER2 target receptor were strongly interacted with oxygen and hydrogen atom of the benzene propanoic acid respectively. The residue Ala 743 and other hydrophobic residues are strongly involved in the molecular interactions in which glide score and glide energy were calculated. The HER2 target receptor shows a good binding affinity based on the molecular interactions with hydrogen atom and hydrophobic residues of the ligand molecules. The drug likeliness such as molecular weight, H bond donor, H bond acceptor, Log P and Log S values were predicted by Qikprop.

Keywords: HER2 target receptor, docking, binding affinity, ligands, hydrophobic interactions.

Introduction

The receptor HER2 plays a vital role in the development of many human adenocarcinomas and it is an ideal target for therapeutic approaches. The epidermal growth factor family of ligands and receptors are readily interacting with cell division and differentiation. It is involved in the cell transformation in tumours and it is a modern target in chemotherapy. It has the potential to develop the drug resistance against breast cancer. [1] The progression of certain types of breast cancer occurs due to the over expression of this receptor. The HER2 target receptor has become an important biomarker and target of therapy for breast cancer. [2] To produce immunologic responses against cancer cells, the peptide vaccines can be delivered to the patients. Specifically designed peptides can associate with major histocompatibility complex molecules on the cell surface activating anti tumor effector mechanisms. [3] Binding site plays a significant role in the process of drug designing and it will be the strength of binding between the target receptor and the potential lead molecules. [4] The ligand binding sites in the target receptor is essential for molecular docking, de novo drug design and structural identification. Q Site Finder helps us to identify the ligand binding pockets in the target receptor. The interaction energy can be utilized by the binding sites

Correspondence
K.Ramanathan
E-mail: ramanathanbio@gmail.com

There are two important phases in the process of drug discovery such as hit identification and lead identification. Structure based drug design approaches depends on the three dimensional structure of the target receptor which is associated with the disease. Structure based drug design strategies are most important in the prediction of binding affinity, calculation of glide energy, glide scores and the identification of molecular interactions. [7] The potential lead molecules are identified based on glide scores and glide energy and these molecules are involved in the molecular interactions. Potential lead molecules have pharmaceutical properties for the stability of complex formation and molecular dynamics simulation. [8]

Methodology

The structure of the target protein HER2 was retrieved from the protein data bank. The Chemdraw assistance has been taken to sketch the structure of the ligands benzene propanoic acid and 1-phenthrene methanol. The structure of the ligands was docked with the active sites of the HER2 target receptor and the binding affinity was calculated. Glide is employed for the rapid docking of two molecules and the positions, orientations, conformations of the ligand were predicted using the Glide algorithm. Glide score and glide energy was analyzed using XP visualizer. The qikprop is employed for the assessment of drug like properties of the lead molecules.

Results

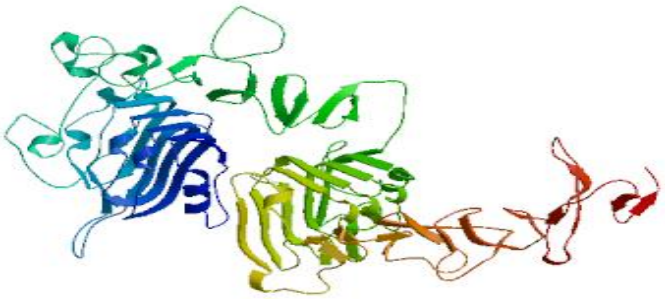

Figure I
Structural model for the target protein HER2

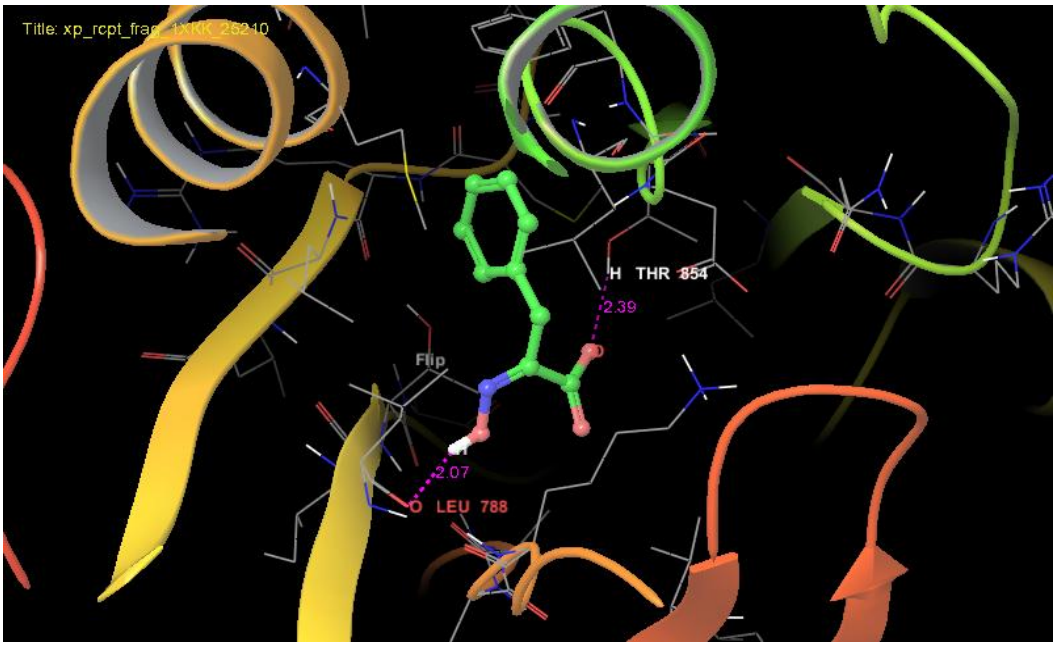

Figure II
Docked structure of target protein HER2 and the ligand Benzene propanoic acid

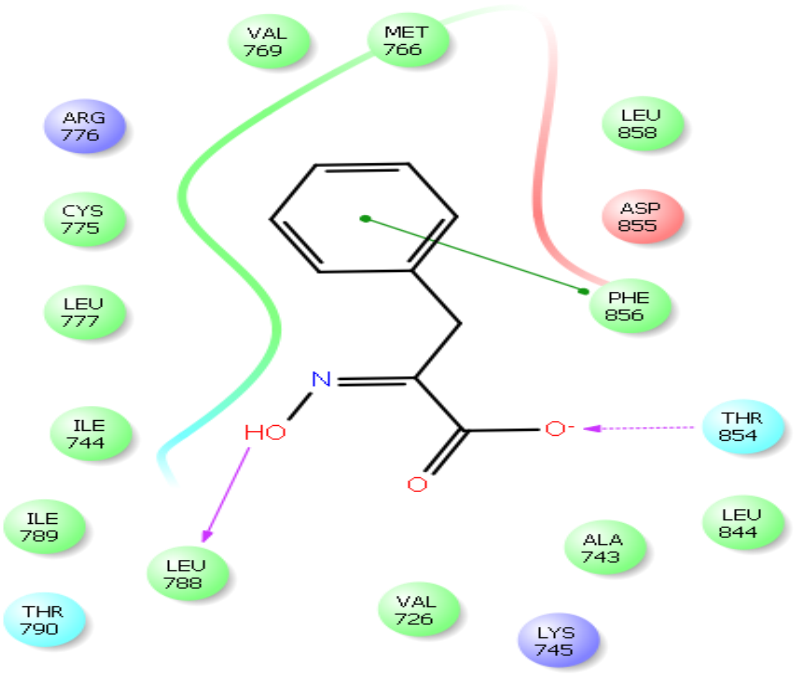

Figure III
2D view of docking simulation of Benzene propanoic acid into HER2

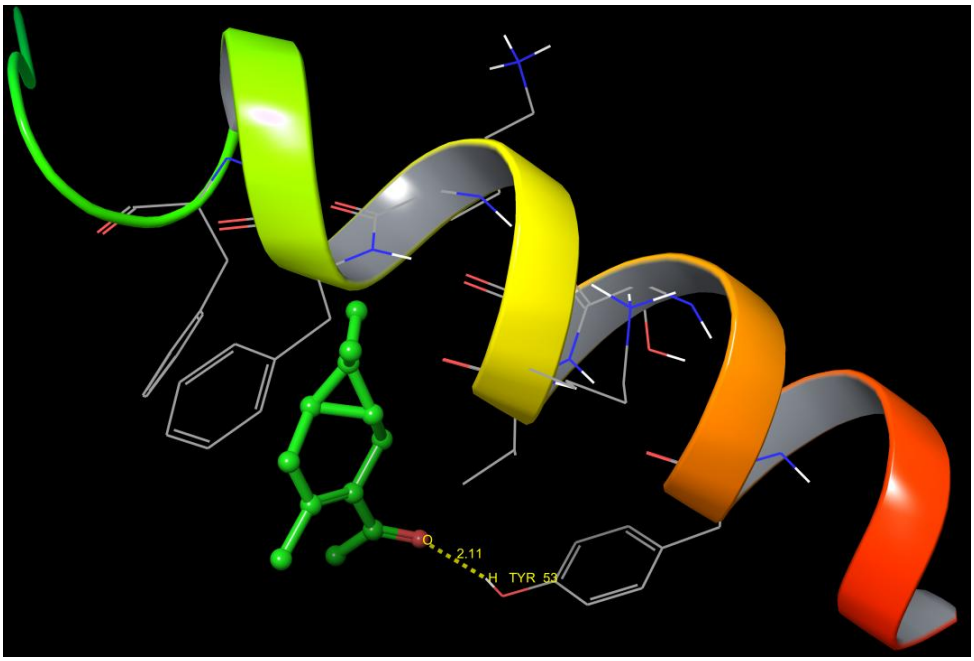

Figure IV
Docked structure of target protein HER2 and the ligand 1-phenathrenemethanol

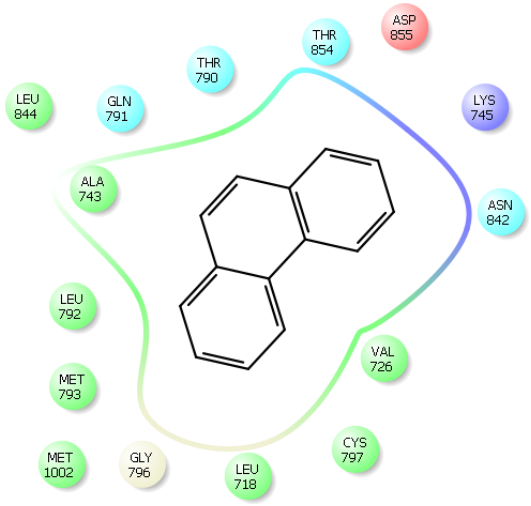

Figure V
2D view of docking simulation of 1-phenathrenemethanol into HER2

Table 1
Glide extra-precision (XP) results for the two molecules

Compound	Glide Score	Glide Energy	No. of hydrogen bond interaction	Interacting residue	Distance (Å)
Benzene propanoic acid	-6.8	-38.24	2	THR 854 LEU 788	2.39 2.07
1-phenathrenemethanol	-4.51	-45.37	1	ALA 743	1

Table 2
Assessment of drug like properties of the lead molecules by Qikprop

Compound Name	MW	HBD	HBA	QPLogPo/w	Caco-2	MDCK	QPLogHERG	QPLogS	QPLogB/B
Benzene propanoic acid	179.175	1.000	3.700	1.296	81	41	-2.127	-1.350	-1.009
1-phenathrenemethanol	178.233	0.000	0.000	4.460	9906	5899	-4.901	-5.263	0.192

Discussion

The structure for the target protein HER2 was predicted using Swiss model tool (Fig 1). The structure of the ligands Benzene propanoic acid and 1-phentharene methanol were predicted using chemsketch. Fig 2 shows that the docked structure of the ligand Benzene propanoic acid with the target protein HER2. The binding mode of this benzene propanic acid interacted with the target protein HER2 shows the hydrogen bonding and hydrophobic interactions in the active sites. The glide score (-6.8Kcal/mol) and glide energy (-38.24Kcal/mol) in the docked structure was calculated. Fig 3 represents that the side chain hydrogen atoms of Thr 854 in the HER2 target receptor were strongly interacted with oxygen atom of the benzene propanic acid with bond length (2.39Å), the hydrogen atom of the benzene propanic acid were strongly interacted with backbone oxygen atom of the hydrophobic residue of Leu 788 in the HER2 with bond length (2.07Å). The hydrophobic residues Phe 856 and Met 766 are effectively involved in the molecular interactions.

The docked structure of the ligand 1-phenathrene methanol with the HER2 target protein was illustrated in the Fig 4. The binding affinity of the 1-phenathrenemethanol at the active site of HER2 shows hydrophobic interactions and the glide score (-4.51Kcal/mol) and glide energy (-45.37Kcal/mol) were calculated. Fig 5 shows that the docking simulations of 1-phenathrenemethanol with HER2 and only hydrophobic integrations were formed with structure of the HER2. The hydrophobic residue Ala 743 is strongly involved with other residues such as Met 793, Val 726, Leu 718, Met 1002 in the molecular interactions.

Table 1 represents that the comparison of glide score, glide energy, hydrogen bond interactions, interacting residues and distance for the Benzene

propanoic acid and 1-phenathrene methanol with HER2 target protein. QikProp predicts the significant descriptors and pharmaceutically relevant properties of organic molecules and it provides ranges for comparing particular molecular properties with those of 95% of known drugs [8]. Table 2 shows that the assessment of drug like properties such as molecular weight, hydrogen bond donor, hydrogen bond acceptor, Log P and Log S values for the benzene propanoic acid and 1-phenathrene methanol.

Conclusion

The structure for the HER2 target protein was predicted for docking with the potentially lead molecules. The structure of the ligands benzene propanoic acid and 1-phentharene methanol were predicted using chemsketch. The docking of the target receptor HER2 with the benzene propanoic acid shows high binding affinity and the hydrogen bonds with hydrophobic interactions were analyzed. The benzene propanoic acid docked with the HER2 target protein with the hydrogen bonding and hydrophobic interactions of glide score (-6.8Kcal/mol) and glide energy (-38.24Kcal/mol). The hydrogen atoms of Thr 854 and backbone oxygen atom of the Leu 788 were strongly interacted with oxygen atom and hydrogen atom of the benzene propanoic acid respectively. The ligand 1-phenathrenemethanol docked with the target protein HER2 shows hydrophobic interactions with glide score (-4.51Kcal/mol) and glide energy (-45.37Kcal/mol). The residue Ala 743 is strongly involved in the molecular interactions. From these results, I have observed that the HER2 target receptor shows a good binding affinity with molecular interaction of hydrogen atom and hydrophobic residues. It could be the potential lead molecule and act as an anti tumour agent against breast cancer and these observations will be useful for further drug discovery process.

Acknowledgement

I express my sincere thanks to University Grants Commission (UGC) for providing financial assistance to done this research (Minor Research Project for a period 2015-2017) and I also thank to Thanthai Hans Roever College, Perambalur for providing necessary facilities to done this research.

References

1. Gullick WJ. (2001). Update on HER-2 as a target for cancer therapy: alternative strategies for targeting the epidermal growth factor system in cancer. Breast Cancer Res. 3 (6):390-4.
2. Mitri Z, Constantine T, O'Regan R (2012). "The HER2 Receptor in Breast Cancer: Pathophysiology, Clinical Use, and New Advances in Therapy". Chemotherapy Research and Practice 2012: 743193.
3. Mahdavi M, Moreau V.(2016) In silico designing breast cancer peptide vaccine for binding to MHC class I and II: A molecular docking study. Computational Biology Chem. 65:110-116. doi: 10.1016/j.compbiolchem.2016.10.007. Epub 2016 Oct 19.
4. Zuercher M (2008). "Structure-Based Drug Design: Exploring the Proper Filling of Apolar Pockets at Enzyme Active Sites". Journal of Organic Chemistry 73: 4345–4361.
5. Laurie AT, Jackson RM. (2005) Q-Site Finder: an energy-based method for the prediction of protein-ligand binding sites. Bioinformatics .1; 21(9):1908-16. Epub 2005 Feb 8.
6. Parkinson EI, Bair JS, Cismesia M, Hergenrother PJ. (2013) Efficient NQO1 substrates are potent and selective anticancer agents.ACS Chem Biol. 18;8 (10):2173-83.
7. Kalyaanamoorthy, S.; Chen, Y.P. (2011) Structure-based drug design to augment hit discovery. *Drug Discov. Today 16*, 831–839.
8. John A, Sivashanmugam M, Umashankar V, Natarajan SK. (2016) Virtual screening, molecular dynamics, and binding free energy calculations on human carbonic anhydrase IX catalytic domain for deciphering potential leads. J Biomol Struct Dyn. 2:1-14.
9. Jorgensen WL (2006) QikProp, version 3.0; Schrodinger, LLC: New York, 2013.