Docking Studies on Anticancer Drugs for Breast Cancer Using Hex

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***Abstract*—Cancer can be described as the uncontrolled growth of abnormal cells. Breast cancer is the second most common type of cancer after lung cancer. Normal breast cells and most breast cancer cells have receptors that attach to circulating estrogen and progesterone. Estrogen and progesterone bind to the receptors and may work with growth factors (e.g., oncogenes and mutated tumor suppressor genes) to cause cancer cell growth and proliferation. Some of the most commonly used breast cancer drugs are Tamoxifen, Raloxifene, Toremifene etc, breast cancer cells need estrogen to grow. These drugs mainly work against the effects of estrogen on these cells. The Protein- Ligand interaction plays a significant role in structural based drug designing. In our research work we have taken the Human estrogen receptor and the commercially available drugs against breast cancer. The receptor was docked to the above said drugs and the energy value obtained as follows Tamoxifen (-49.0), Raloxifene (-158.0), Toremifene (-108.0) using the HEX docking software. Depending on the energy values we have chosen the best two drugs they are Raloxifene and Toremifene. We tried to improve the binding efficiency and steric compatibility of the two drugs namely Raloxifene and Toremifene. Several modifications were made to the probable functional groups which were interacting with the receptor molecule. Analogs of this drug molecule were prepared using ACD ChemSketch and docked using HeX docking software. Raloxifene Analog 7 and Toremifene analog 6 were detected with significant energy values and probable lead molecules. The Modified drugs was sketched using Chemsketch were found to be better than the conventional drugs available. Further from this work we can improve the steric compatibility and then ADME/T properties of the Analogs can be analyzed using Inslico ADME/T tools available.**

Keywords –Breast cancer, Chemsketch, Docking, Hex, Rasmol

I. Introduction

Breast cancer is a cancer that starts in the cells of the breast in women and men. Worldwide, breast cancer is the second most common type of cancer after lung cancer (10.4% of all cancer incidence, both sexes counted) and the fifth most common cause of cancer death. In 2005, breast cancer caused 502,000 deaths worldwide (7% of cancer deaths; almost 1% of all deaths) [1].

Because the breast is composed of identical tissues in males and females, breast cancer also occurs in males. Incidences of breast cancer in men are approximately 100 times less common than in women, but men with breast cancer are considered to have the same statistical survival rates as women [2].

Normal breast cells and most breast cancer cells have receptors that attach to circulating estrogen and progesterone. Estrogen and progesterone bind to the receptors and may work with growth factors (e.g., oncogenes and mutated tumor suppressor genes) to cause cancer cell growth and proliferation Breast cancers that are estrogen and progesterone receptor positive (i.e., ER+ and PR+) are more likely to respond to hormonal therapy (e.g., tamoxifen, Raloxifene, Toremifene) and have a better prognosis than cancers that are hormone receptor negative [9]. Tamoxifen (Nolvadex®) is a drug, taken orally as a tablet, which interferes with the activity of estrogen. Some of the most common side effects of tamoxifen are serious side effects of tamoxifen are blood clots, strokes, uterine cancer, and cataracts. Raloxifene may infrequently cause serious blood clots to form in the legs, lungs, or eyes. Other reactions experienced include leg swelling/pain, trouble breathing, chest pain, vision changes. The side effects of these drugs make the need for the necessity of new improved drugs hence in our research study we try to find the suitable analogues with high binding affinity, which could be a possible lead molecule [10].

Computational Biology and bioinformatics have the potential not only of speeding up the drug discovery process thus reducing the costs, but also of changing the way drugs are designed. Rational Drug Design (RDD) helps to facilitate and speedup the drug designing process, which involves variety of methods to identify novel compounds. One such method is the docking of the drug molecule with the receptor (target). The site of drug action, which is ultimately responsible for the pharmaceutical effect, is a receptor [4]. Docking is the process by which two molecules fit together in 3D space.

II. Tools & Materials Used

For our present study we used bioinformatics tools, biological databases like PubMed, Drug Bank, PDB (Protein Data Bank) and software's like Hex, ACD ChemSketch.
ACD/ChemSketch is the powerful all-purpose chemical drawing and graphics package from ACD/Labs developed to help chemists quickly and easily draw molecules, reactions,

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and schematic diagrams, calculate chemical properties, and design professional reports and presentations. ACD Chemsketch can convert SMILES notations to Structure and vice versa.

Hex is an Interactive Molecular Graphics Program for calculating and displaying feasible docking modes of pairs of protein and DNA molecules. Hex can also calculate Protein-Ligand Docking, assuming the ligand is rigid, and it can superpose pairs of molecules using only knowledge of their 3D shapes [8]. It uses Spherical Polar Fourier (SPF) correlations to accelerate the calculations and its one of the few docking programs which has built in graphics to view the result [13].

Drug Bank is a unique Bioinformatics/Cheminformatics resource that combines detailed drug (i.e. chemical) data with comprehensive drug target (i.e. protein). Each Drug Card entry contains greater than 80 data fields with half of the information being devoted to drug/chemical data and the other half devoted to drug target or protein data [7].

The PDB (Protein Data Bank) is the single world wide archive of Structural data of Biological macromolecules, established in Brookhaven National Laboratories (BNL) in 1971 [6].It contains Structural information of the macromolecules determined by X-ray crystallographic, NMR methods etc.

PubMed is a free digital archive of biomedical and life sciences journal literature at the U.S. National Institutes of Health (NIH), developed and managed by NIH's National Center for Biotechnology Information (NCBI) in the National Library of Medicine (NLM). PubMed is a free search engine for accessing the MEDLINE database of citations and abstracts of biomedical research articles [5].

RASMOL [Raster Display of Molecules] is a molecular graphics program intended for the structural visualization of proteins, nucleic acids and small biomolecules. The program reads in molecular coordinate files and interactively displays the molecule on the screen in variety of representations and color schemes.

III. METHODOLGY

Bioinformatics is seen as an emerging field with the potential to significantly improve how drugs are found, brought to the clinical trials and eventually released to the marketplace. Computer – Aided Drug Design (CADD) is a specialized discipline that uses computational methods to simulate drug – receptor interactions. CADD methods are heavily dependent on bioinformatics tools, applications and databases [4].

The structure of human estrogen receptor was retrieved from PDB (2IOK).Using Chemsketch the structures of the drugs were generated by their SMILES notation obtained from Drug Bank and the structural analogues of these drugs were sketched. The docking analysis of Raloxifene and Toremifene with Human estrogen receptor was carried by HEX docking software.

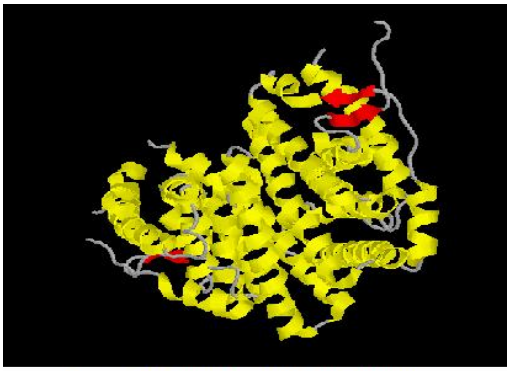

Fig.1 STRUCTURE OF HUMAN ESTROGEN RECEPTOR

Docking allows the scientist to virtually screen a database of compounds and predict the strongest binders based on various scoring functions. It explores ways in which two molecules, such as drugs and an enzyme Human estrogen receptor fit together and dock to each other well, like pieces of a three-dimensional jigsaw puzzle. The molecules binding to a receptor, inhibit its function, and thus act as drug. The collection of Raloxifene, Toremifene and receptor complexes was identified via docking and their relative stabilities were evaluated using molecular dynamics and their binding affinities, using free energy simulations.

The parameters used for the docking process were

- Correlation type – Shape only
- FFT Mode – 3D fast lite
- Grid Dimension – 0.6
- Receptor range – 180
- Ligand Range – 180
- Twist range – 360
- Distance Range – 40

The drug and its analogues were docked with the receptor using the above parameters.

IV. RESULTS

Docking results tabulated between Human estrogen receptor and the conventional drug Raloxifene (Table I) as well as with the modified drugs are shown below along with the changes or modification within them.

TABLE1
DOCKING RESULTS OF ESTROGEN RECEPTOR WITH RALOXIFENE ANALOGS

COMPOUND	E - VALUE
RALOXIFENE	-158.37
ANALOG 1	-97.0
ANALOG 2	-116.0
ANALOG 3	-132.0
ANALOG 4	-146.0
ANALOG 5	-166.0
ANALOG 6	-165.0
ANALOG 7	**-175.0**

Docking results tabulated between Human estrogen receptor and the conventional drug Toremifene (Table II) as well as the modified drugs are shown below along with the changes or modifications within them

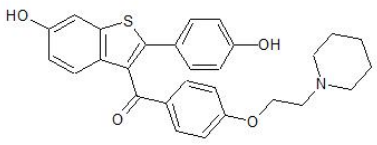

Fig.2 Structure of Raloxifene

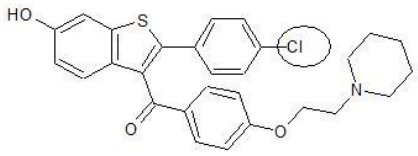

Fig.3 Structure of Analog 7

Based on the literature it has been shown clearly that the drugs Raloxifene and Toremifene [11] have been used to target the Human estrogen receptor. Raloxifene and Toremifene on docking with Human estrogen receptor produced an energy value of -158.37 and -108.0 respectively.

TABLE II
DOCKING RESULTS OF ESTROGEN RECEPTOR WITH TOREMIFENE

COMPOUND	E- VALUE
TOREMIFENE	- 108.0
ANALOG 1	- 34.0
ANALOG 2	- 49.0
ANALOG 3	- 116.0
ANALOG 4	- 126. 34
ANALOG 5	-78. 9
ANALOG 6	**-181.0**

It was observed using RasMol that the carbonyl groups present in the drug was the site of binding to the receptor (2IOK) and methyl group present in the probable functional groups, which resulted in a decrease in the energy values. These modifications were made using Chemsketch and the energy values were calculated using Hex. This way the pharmacophoric part of the drug was partially identified.

An analog with additional Cl atom (Raloxifene analog 7) was prepared virtually using ChemSketch. This particular analog showed an increase in the energy values (-175.0) and an analog in which methyl groups are removed (Toremifene Analog 6) was prepared virtually using ChemSketch.

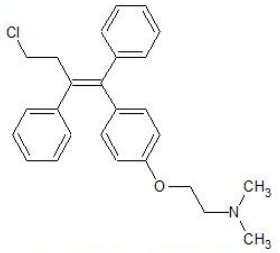

Fig.4 Structure of Toremifene

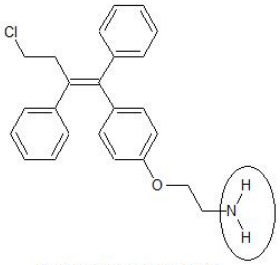

Fig.5 Structure of Analog 6

This particular analog showed an increase in the energy values (-181.0) which means the analog (Raloxifene analog 7) and (Toremifene Analog 6) was more compatible with the receptor than its predecessor. However, the binding site of the analog was similar to that of its predecessor, which means that functional groups involved were the same and by preparing the analog only the steric compatibility was increased.

V. CONCLUSION

The Protein-Ligand interaction plays a significant role in structural based drug designing. In the present work we have taken the receptor Human estrogen and identified the drugs that were used against Breast Cancer.

When the receptor (2IOK) was docked with the drugs the energy value obtained was; Raloxifene (-158.37), Toremifene(-108.0). When the modified drugs were docked against the same receptor the energy value obtained was Raloxifene Analog 7 (-175.0), Toremifene Analog 6(-181.0) from this we can conclude that some of the modified drugs are better than the commercial drugs available in the market. In future research work the ADME/T (Absorption, Distribution, Metabolism, Excretion / Toxicity) properties of these compounds can be calculated using the commercial ADME/T tools available thus reducing the time and cost in drug discovery process.

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