

Computer Aided Docking Studies on Anticancer Drugs for Breast Cancer

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Abstract

Cancer is the name for diseases in which the body's cells become abnormal and divide without control. 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 Raloxifene, Tamoxifen, 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 the present work, the human estrogen receptor and the commercially available drugs against breast cancer have been taken. 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 ChemSketch and docked using HeX docking software.

Keywords: Estrogen, progesterone, Docking, Breast cancer, Receptor.

Introduction

Computer aided drug design (CADD) and bioinformatics together are a powerful combination in drug research and development. As the information era dawns, computer aided drug design has become an indispensable component in current drug industries. And many computer aided drug design tools have been exploited, and been widely utilized in the modern drug design.

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 and the fifth most common cause of cancer death. In 2005, breast cancer caused 502,000 deaths worldwide. 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 [1].

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 [2]. Tamoxifen 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 [3].

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.

Materials and Methods

In the present study the bioinformatics tools, biological databases like Drug Bank, PDB (Protein Data Bank) and software's like Hex is used. It is the powerful all-purpose chemical drawing and graphics package from ACD/Labs developed to help chemists quickly and easily draw molecules, reactions, and schematic diagrams, calculation of chemical properties, and design professional reports and presentations.

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].

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 [5].

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 [6].

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 [7]. It contains Structural information of the macromolecules determined by X-ray crystallographic, NMR methods etc.

The structure of human estrogen receptor was retrieved from PDB (2I0K). 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.

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.

Results and Discussion

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. The structure of Raloxifene is shown in Figure.1

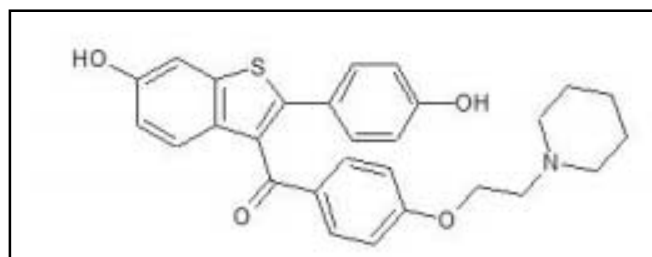


Figure 1: Structure of Raloxifene

Table 1: Docking results of estrogen receptor with Raloxifene analogs

Compound	Energy value
RALOXIFENE	-158
ANALOG 1	-95.0
ANALOG 2	-114.0
ANALOG 3	-128.0
ANALOG 4	-143.0
ANALOG 5	-163.0
ANALOG 6	-161.0
ANALOG 7	-175.0

Docking results tabulated between Human estrogen receptor and the conventional drug Toremifene (Table 2) as well as the modified drugs are shown below along with the changes or modifications within them.

Table 2: Docking Results of Estrogen Receptor with

Compound	Energy value
Toremifene	-108
ANALOG 1	-32.0
ANALOG 2	-47.0
ANALOG 3	-114.0
ANALOG 4	-120.0
ANALOG 5	-75.0
ANALOG 6	-181.0
ANALOG 7	-175.0

Based on the literature it has been shown clearly that the drugs Raloxifene and Toremifene [9] 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. The structure of Toremifene is shown in Figure.2

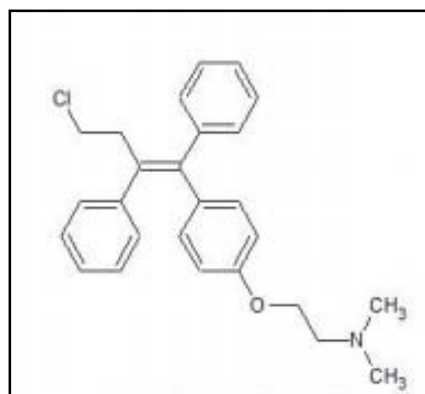


Figure 2: Structure of Toremifene

It is observed using RasMol that the carbonyl groups present in the drug was the site of binding to the receptor (210K) and methyl group present in the probable functional groups, which resulted in a decrease in the energy values. These 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. The structure of Raloxifene is shown in Figure.3

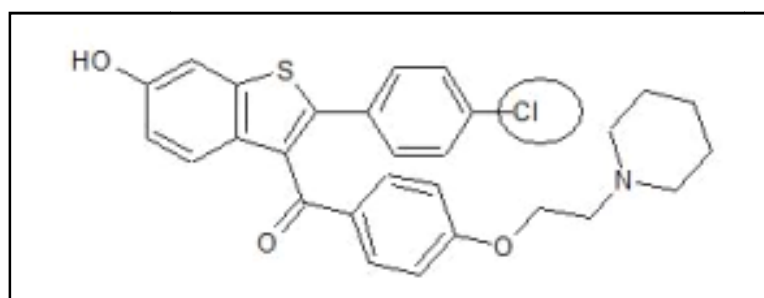


Figure 3: Structure of Analog 7

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. The structure of Raloxifene is shown in Figure.4.

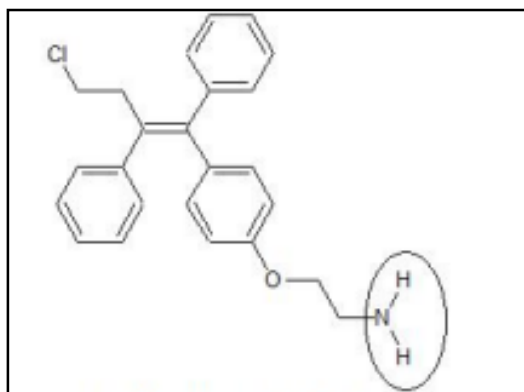


Figure 4: Structure of Analog 6

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.

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 (210 K) 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).
- On the whole, it can be concluded that some of the modified drugs are better than the commercial drugs available in the market.

References

- [1] World Health Organization International Agency for research on cancer. "World Cancer Report", (June 2005).

- [2] Cosman F, Clin, Geriatr Med. Selective estrogen-receptor Modulators”, 19 (2):371-379, May 2003.
- [3] Raloxifene a selective estrogen receptor modulator induces mitochondria-mediated apoptosis in human endometrial carcinoma cells”, 2008 Sep; 41(3):132-8, Springer Link
- [4] Computational Biology and Drug Discovery: From single - network Drugs”, Current Bioinformatics, 2006, 1, 3-13.
- [5] “Evaluation of Protein Docking Predictions using Hex 3.1 in CAPRI rounds 1-2, David. W. Ritchie, Proteins, Structure, Functioned Genetics, Wiley-liss Inc
- [6] “Drug Bank; a comprehensive resource for in silico drug discovery and exploration”, Nucleic Acids Research, 2006, Vol.34, Database Issue..
- [7] “The Protein Data Bank”, Nucleic Acids Research 2000, Vol. 28, Oxfords University Press.
- [8] “PubMed: Online Search Engine for science and biomedical articles, www.pubmedcentral.nih.gov.
- [9] Selective estrogen receptor modulators (SERMs): mechanisms of ant carcinogenesis and drug resistance”, 2005 Dec 11; 591(1-2):247-63, Elsevier Journal.