

In silico study of Inhibitory molecules on protein causing Breast Cancer using Molecular Docking

A

Thesis

**Submitted for the Partial Fulfilment of the Requirement for the Award of Degree of
Bachelor of Technology**

in

Biotechnology

by

Abhishek Tiwari (1613354002)

Anjali Shukla (1613354010)

Supervised by

Mr. Ankit Kumar

(Assistant Professor & Deputy Head)



Noida Institute of Engineering and Technology, Greater Noida

Affiliated to

**Dr. A.P.J. ABDUL KALAM TECHNICAL UNIVERSITY, LUCKNOW
(UTTAR PRADESH)
BATCH (2016-2020)**

Declaration

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the award of any other degree or diploma of the university or other institute of higher learning, except where due acknowledgement has been made in the text.

Name: Abhishek Tiwari

Roll no. 1613354002

Name: Anjali Shukla

Roll no. 1613354010

Certificate

This is to certify that the thesis titled "**Insilico study of Inhibitory molecules on protein causing Breast Cancer using Molecular Docking**" being submitted by **Abhishek Tiwari(1613354002) & Anjali Shukla (1613354010)** to the Noida Institute of Engineering and Technology, Greater Noida, for the award of the Bachelor of Technology, is an original research work carried out by them under my supervision. In my opinion, the thesis has reached the standards of fulfilling the requirements of the regulations relating to the degree.

The results contained in this thesis have not been submitted in part or full to any other university or institute for the award of any degree/diploma.

Supervisor

Mr. Ankit Kumar

Assistant Professor & Deputy Head

N.I.E.T, Greater Noida

Dr. Rashmi Mishra

Head of Department

N.I.E.T, Greater Noida

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Abhishek Tiwari

Anjali Shukla

Abstract

Background:

Approximately 5-10% of breast carcinomas have been related to hereditary conditions and are attributable to pathogenic variants in the BRCA1 and BRCA2 genes, which is referred to as hereditary breast cancer (BC) syndrome. The inclusion of additional genes that can be related to BC syndrome is under intense evaluation due to the high proportion of patients with HBOC criteria who do not present pathogenic mutations in BRCA genes, named BRCAx, despite having high clinical suspicion of hereditary cancer. The main aim is to identify new potentially pathogenic gene variants that may contribute to BC to improve the efficiency of routine diagnostic tests in this hereditary condition.

Method:

We would use molecular docking for the finding of the potential inhibitor which increases the diagnosis efficiency.

We use many docking technique, online as well as offline to see the best result.

Result:

Right now we have four potential inhibitors family mainly PARP, AROMATASE, MTOR, EGFR

Conclusion:

We identified that 8% of BRCAx patients were carriers of pathogenic variants in genes other than BRCA1 and BRCA2. Therefore, wide gene panels, including clinically actionable genes, should be routinely used in the screening of BC in our population. We observed differences from other studies in the prevalence of mutated genes, most likely due to differences in the selection criteria of the probands and in the population analyzed.

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Chapter : 1

Introduction

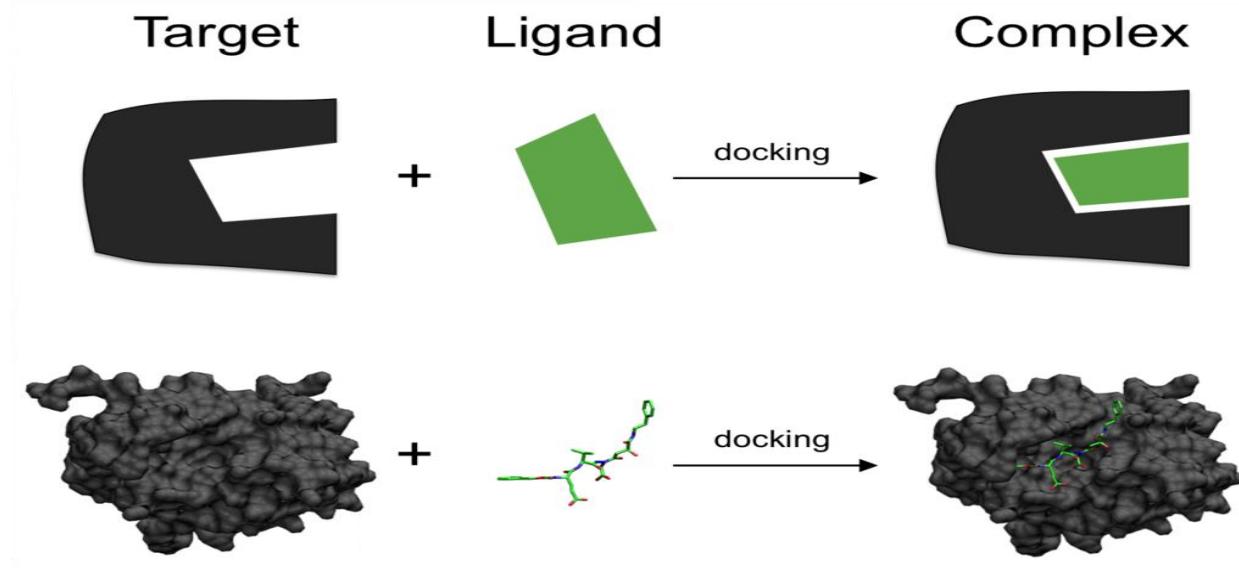
1. Molecular Docking

1.1 Definition

In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using, for example, scoring functions.

Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule ligands to the appropriate target binding site. Characterisation of the binding behaviour plays an important role in rational design of drugs as well as to elucidate fundamental biochemical processes.

protein can be thought of as the “lock” and the ligand can be thought of as a “key”. Molecular docking may be defined as an optimization problem, which would describe the “best-fit” orientation of a ligand that binds to a particular protein of interest. However, since both the ligand and the protein are flexible, a “hand-in-glove” analogy is more appropriate than “lock-and-key”. During the course of the docking process, the ligand and the protein adjust their conformation to achieve an overall "best-fit" and this kind of conformational adjustment resulting in the overall binding is referred to as "induced-fit"



1.2 Docking approaches :

Two approaches are particularly popular within the molecular docking community. One approach uses a matching technique that describes the protein and the ligand as complementary surfaces. The second approach simulates the actual docking process in which the ligand-protein pairwise interaction energies are calculated. Both approaches have significant advantages as well as some limitations.

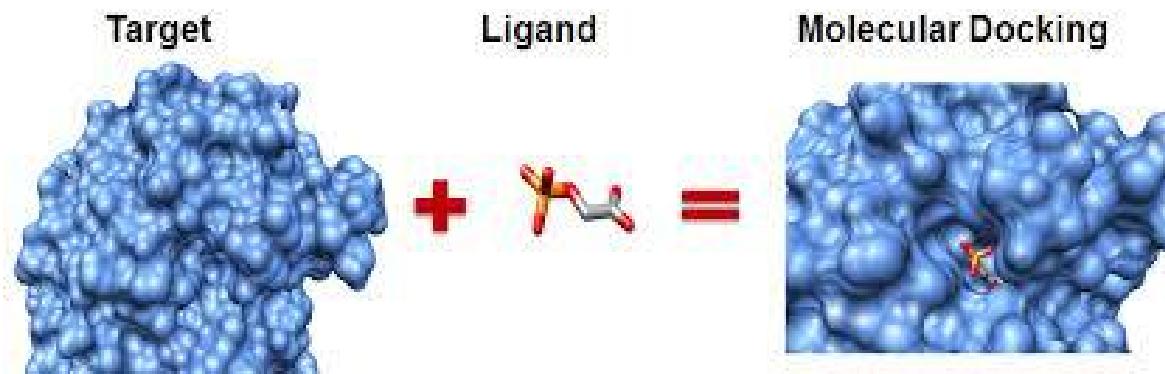
1.2.1 Shape Complementarity :

Geometric matching/ shape complementarity methods describe the protein and ligand as a set of features that make them dockable. These features may include molecular surface / complementary surface descriptors. In this case, the receptor's molecular surface is described in terms of its solvent-accessible surface area and the ligand's molecular surface is described in terms of its matching surface description. The complementarity between the two surfaces amounts to the shape matching description that may help finding the complementary pose of docking the target and the ligand molecules. Another approach is to describe the hydrophobic features of the protein using turns in the main-chain atoms. Yet another approach is to use a Fourier shape descriptor technique. Whereas the shape complementarity based approaches are typically fast and robust, they cannot usually model the movements or dynamic changes in the ligand/ protein conformations accurately, although recent developments allow these methods to investigate ligand flexibility. Shape complementarity methods can quickly scan through several thousand ligands in a matter of seconds and actually figure out whether they can bind at the protein's active site, and are usually scalable to even protein-protein interactions. They are also much more amenable to pharmacophore based approaches, since they use geometric descriptions of the ligands to find optimal binding.

1.2.2 Simulation :

Simulating the docking process is much more complicated. In this approach, the protein and the ligand are separated by some physical distance, and the ligand finds its position into the protein's active site after a certain number of "moves" in its conformational space. The moves incorporate rigid body transformations such as translations and rotations, as well as internal changes to the ligand's structure including torsion angle rotations. Each of these moves in the conformation space of the ligand induces a total energetic cost of the system. Hence, the system's total energy is calculated after every move.

The obvious advantage of docking simulation is that ligand flexibility is easily incorporated, whereas shape complementarity techniques must use ingenious methods to incorporate flexibility in ligands. Also, it more accurately models reality, whereas shape complementary techniques are more of an abstraction.



1.3 Docking Mechanism

To perform a docking screen, the first requirement is a structure of the protein of interest. Usually the structure has been determined using a biophysical technique such as x-ray crystallography or NMR spectroscopy, but can also derive from homology modeling construction. This protein structure and a database of potential ligands serve as inputs to a docking program. The success of a docking program depends on two components: the search algorithm and the scoring function.

1.3.1 Search Algorithm

The search space in theory consists of all possible orientations and conformations of the protein paired with the ligand. However, in practice with current computational resources, it is impossible to exhaustively explore the search space—this would involve enumerating all possible distortions of each molecule (molecules are dynamic and exist in an ensemble of conformational states) and all possible rotational and translational orientations of the ligand relative to the protein at a given level of granularity. Most docking programs in use account for the whole conformational space of the ligand (flexible ligand), and several attempt to model a flexible protein receptor. Each "snapshot" of the pair is referred to as a **pose**.

A variety of conformational search strategies have been applied to the ligand and to the receptor. These include:

- systematic or stochastic torsional searches about rotatable bonds
- molecular dynamics simulations
- genetic algorithms to "evolve" new low energy conformations and where the score of each pose acts as the fitness function used to select individuals for the next iteration.

1.3.2 Scoring Function

Docking programs generate a large number of potential ligand poses, of which some can be immediately rejected due to clashes with the protein. The remainder are evaluated using some scoring function, which takes a pose as input and returns a number indicating the likelihood that the pose represents a favorable binding interaction and ranks one ligand relative to another.

Most scoring functions are physics-based molecular mechanics force fields that estimate the energy of the pose within the binding site. The various contributions to binding can be written as an additive equation:

$$\Delta G_{bind} = \Delta G_{solvent} + \Delta G_{conf} + \Delta G_{int} + \Delta G_{rot} + \Delta G_{t/t} + \Delta G_{vib}$$

The components consist of solvent effects, conformational changes in the protein and ligand, free energy due to protein-ligand interactions, internal rotations, association energy of ligand and receptor to form a single complex and free energy due to changes in vibrational modes. A low (negative) energy indicates a stable system and thus a likely binding interaction.

1.3.3 Ligand Flexibility

Conformations of the ligand may be generated in the absence of the receptor and subsequently docked or conformations may be generated on-the-fly in the presence of the receptor binding cavity, or with full rotational flexibility of every dihedral angle using fragment based docking. Force field energy evaluation are most often used to select energetically reasonable conformations, but knowledge-based methods have also been used.

Peptides are both highly flexible and relatively large-sized molecules, which makes modeling their flexibility a challenging task. A number of methods were developed to allow for efficient modeling of flexibility of peptides during protein-peptide docking.

1.3.4 Receptor Flexibility

Computational capacity has increased dramatically over the last decade making possible the use of more sophisticated and computationally intensive methods in computer-assisted drug design. However, dealing with receptor flexibility in docking methodologies is still a thorny issue. The main reason behind this difficulty is the large number of degrees of freedom that have to be considered in this kind of calculations. Neglecting it, however, in some of the cases may lead to poor docking results in terms of binding pose prediction.

Multiple static structures experimentally determined for the same protein in different conformations are often used to emulate receptor flexibility.[21] Alternatively rotamer libraries of amino acid side chains that surround the binding cavity may be searched to generate alternate but energetically reasonable protein conformations.

1.4 Docking Assessment

The interdependence between sampling and scoring function affects the docking capability in predicting plausible poses or binding affinities for novel compounds. Thus, an assessment of a docking protocol is generally required (when experimental data is available) to determine its predictive capability. Docking assessment can be performed using different strategies, such as:

- docking accuracy (DA) calculation;
- the correlation between a docking score and the experimental response or determination of the enrichment factor (EF)
- the distance between an ion-binding moiety and the ion in the active site;
- the presence of induce-fit models.

2. Breast Cancer

2.1 Overview:

2.2 Cancer occurs when changes called mutations take place in genes that regulate cell growth. The mutations let the cells divide and multiply in an uncontrolled way.

Breast cancer is cancer that develops in breast cells. Typically, the cancer forms in either the lobules or the ducts of the breast. Lobules are the glands that produce milk, and ducts are the pathways that bring the milk from the glands to the nipple. Cancer can also occur in the fatty tissue or the fibrous connective tissue within your breast.

The uncontrolled cancer cells often invade other healthy breast tissue and can travel to the lymph nodes under the arms. The lymph nodes are a primary pathway that help the cancer cells move to other parts of the body.

2.3 Breast Cancer Symptoms :

In its early stages, breast cancer may not cause any symptoms. In many cases, a tumor may be too small to be felt, but an abnormality can still be seen on a mammogram. If a tumor can be felt, the first sign is usually a new lump in the breast that was not there before. However, not all lumps are cancer.

Each type of breast cancer can cause a variety of symptoms. Many of these symptoms are similar, but some can be different. Symptoms for the most common breast cancers include:

- a breast lump or tissue thickening that feels different than surrounding tissue and has developed recently
- breast pain
- red, pitted skin over your entire breast
- swelling in all or part of your breast
- a nipple discharge other than breast milk
- bloody discharge from your nipple
- peeling, scaling, or flaking of skin on your nipple or breast
- a sudden, unexplained change in the shape or size of your breast
- inverted nipple
- changes to the appearance of the skin on your breasts
- a lump or swelling under your arm

2.4 Types of Breast Cancer :

There are several types of breast cancer, and they are broken into two main categories: “invasive” and “noninvasive,” or *in situ*. While invasive cancer has spread from the breast ducts or glands to other parts of the breast, noninvasive cancer has not spread from the original tissue.

These two categories are used to describe the most common types of breast cancer, which include:

- **Ductal carcinoma *in situ*.** Ductal carcinoma *in situ* (DCIS) is a noninvasive condition. With DCIS, the cancer cells are confined to the ducts in your breast and haven’t invaded the surrounding breast tissue.
- **Lobular carcinoma *in situ*.** Lobular carcinoma *in situ* (LCIS) is cancer that grows in the milk-producing glands of your breast. Like DCIS, the cancer cells haven’t invaded the surrounding tissue.
- **Invasive ductal carcinoma.** Invasive ductal carcinoma (IDC) is the most common type of breast cancer. This type of breast cancer begins in your breast’s milk ducts and then invades nearby tissue in the breast. Once the breast cancer has spread to the tissue outside your milk ducts, it can begin to spread to other nearby organs and tissue.
- **Invasive lobular carcinoma.** Invasive lobular carcinoma (ILC) first develops in your breast’s lobules and has invaded nearby tissue.

Other, less common types of breast cancer include:

- **Paget disease of the nipple.** This type of breast cancer begins in the ducts of the nipple, but as it grows, it begins to affect the skin and areola of the nipple.
- **Phyllodes tumor.** This very rare type of breast cancer grows in the connective tissue of the breast. Most of these tumors are benign, but some are cancerous.
- **Angiosarcoma.** This is cancer that grows on the blood vessels or lymph vessels in the breast.

2.5 Inflammatory Breast Cancer

Inflammatory breast cancer (IBC) is a rare but aggressive type of breast cancer. IBC makes up only between (1-5) % of all breast cancer cases.

With this condition, cells block the lymph nodes near the breasts, so the lymph vessels in the breast can’t properly drain. Instead of creating a tumor, IBC causes your breast to swell, look red, and feel very warm. A cancerous breast may appear pitted and thick, like an orange peel.

IBC can be very aggressive and can progress quickly. For this reason, it’s important to call your doctor right away if you notice any symptoms.

2.6 Triple Negative Breast Cancer

Triple-negative breast cancer is another rare disease type, affecting only about 10 to 20 percent of people with breast cancer. To be diagnosed as triple-negative breast cancer, a tumor must have all three of the following characteristics:

- It lacks estrogen receptors. These are receptors on the cells that bind, or attach, to the hormone estrogen. If a tumor has estrogen receptors, estrogen can stimulate the cancer to grow.
- It lacks progesterone receptors. These receptors are cells that bind to the hormone progesterone. If a tumor has progesterone receptors, progesterone can stimulate the cancer to grow.
- It doesn't have additional HER2 proteins on its surface. HER2 is a protein that fuels breast cancer growth.

If a tumor meets these three criteria, it's labeled a triple-negative breast cancer. This type of breast cancer has a tendency to grow and spread more quickly than other types of breast cancer.

2.7 Metastatic Breast Cancer

Metastatic breast cancer is another name for stage 4 breast cancer. It's breast cancer that has spread from your breast to other parts of your body, such as your bones, lungs, or liver. This is an advanced stage of breast cancer.

2.8 Stages of breast cancer

Breast cancer can be divided into stages based on how large the tumor or tumors are and how much it has spread. Cancers that are large or have invaded nearby tissues or organs are at a higher stage than cancers that are small and still contained in the breast. In order to stage a breast cancer, we need to know:

- if the cancer is invasive or noninvasive
- how large the tumor is
- whether the lymph nodes are involved
- if the cancer has spread to nearby tissue or organs

Breast cancer has five main stages: stages 0 to 5.

Stage 0 breast cancer

Stage 0 is DCIS. Cancer cells in DCIS remain confined to the ducts in the breast and have not spread into nearby tissue.

Stage 1 breast cancer

- Stage 1A: The primary tumor is 2 centimeters wide or less and the lymph nodes are not affected.
- Stage 1B: Cancer is found in nearby lymph nodes, and either there is no tumor in the breast, or the tumor is smaller than 2 cm.

Stage 2 breast cancer

- Stage 2A: The tumor is smaller than 2 cm and has spread to 1–3 nearby lymph nodes, or it's between 2 and 5 cm and hasn't spread to any lymph nodes.
- Stage 2B: The tumor is between 2 and 5 cm and has spread to 1–3 axillary (armpit) lymph nodes, or it's larger than 5 cm and hasn't spread to any lymph nodes.

Stage 3 breast cancer

- Stage 3A:
 - The cancer has spread to 4–9 axillary lymph nodes or has enlarged the internal mammary lymph nodes, and the primary tumor can be any size.
 - Tumors are greater than 5 cm and the cancer has spread to 1–3 axillary lymph nodes or any breastbone nodes.
- Stage 3B: A tumor has invaded the chest wall or skin and may or may not have invaded up to 9 lymph nodes.
- Stage 3C: Cancer is found in 10 or more axillary lymph nodes, lymph nodes near the collarbone, or internal mammary nodes.

Stage 4 breast cancer

Stage 4 breast cancer can have a tumor of any size, and its cancer cells have spread to nearby and distant lymph nodes as well as distant organs.

2.9 Diagnosis of Breast Cancer

Tests that can help diagnose breast cancer include:

- **Mammogram.** The most common way to see below the surface of your breast is with an imaging test called a mammogram. Many women aged 40 and older get annual mammograms to check for breast cancer. If your doctor suspects you may have a tumor or suspicious spot, they will also request a mammogram. If an abnormal area is seen on your mammogram, your doctor may request additional tests.
- **Ultrasound.** A breast ultrasound uses sound waves to create a picture of the tissues deep in your breast. An ultrasound can help your doctor distinguish between a solid mass, such as a tumor, and a benign cyst.

2.10 Breast Cancer Treatment

Surgery is the most common treatment for breast cancer. Many women have additional treatments, such as chemotherapy, targeted therapy, radiation, or hormone therapy.

Surgery

Several types of surgery may be used to remove breast cancer, including:

- **Lumpectomy.** This procedure removes the tumor and some surrounding tissue, leaving the rest of the breast intact.
- **Mastectomy.** In this procedure, a surgeon removes an entire breast. IN a double mastectomy, both breasts are removed.
- **Sentinel node biopsy.** This surgery removes a few of the lymph nodes that receive drainage from the tumor. These lymph nodes will be tested. If they don't have cancer, you may not need additional surgery to remove more lymph nodes.
- **Axillary lymph node dissection.** If lymph nodes removed during a sentinel node biopsy contain cancer cells, your doctor may remove additional lymph nodes.
- **Contralateral prophylactic mastectomy.** Even though breast cancer may be present in only one breast, some women elect to have a contralateral prophylactic mastectomy. This surgery removes your healthy breast to reduce your risk of developing breast cancer again.

Radiation therapy

With radiation therapy, high-powered beams of radiation are used to target and kill cancer cells. Most radiation treatments use external beam radiation. This technique uses a large machine on the outside of the body.

Advances in cancer treatment have also enabled doctors to irradiate cancer from inside the body. This type of radiation treatment is called brachytherapy. To conduct brachytherapy, surgeons place radioactive seeds, or pellets, inside the body near the tumor site. The seeds stay there for a short period of time and work to destroy cancer cells.

Chemotherapy

Chemotherapy is a drug treatment used to destroy cancer cells. Some people may undergo chemotherapy on its own, but this type of treatment is often used along with other treatments, especially surgery.

In some cases, doctors prefer to give patients chemotherapy before surgery. The hope is that the treatment will shrink the tumor, and then the surgery will not need to be as invasive. Chemotherapy has many unwanted side effects, so discuss your concerns with your doctor before starting treatment.

Hormone therapy

If your type of breast cancer is sensitive to hormones, your doctor may start you on hormone therapy. Estrogen and progesterone, two female hormones, can stimulate the growth of breast cancer tumors. Hormone therapy works by blocking your body's production of these hormones, or by blocking the hormone receptors on the cancer cells. This action can help slow and possibly stop the growth of your cancer.

Medications

Certain treatments are designed to attack specific abnormalities or mutations within cancer cells. For example, Herceptin (trastuzumab) can block your body's production of the HER2 protein. HER2 helps breast cancer cells grow, so taking a medication to slow the production of this protein may help slow cancer growth.

3. Potential Inhibitors:

these are the family of inhibitor which would show the activity against the protein BRCA-1 and BRCA-2 gene

3.1 EGFR (Epidermal Growth Factor Receptor) Inhibitor

The epidermal growth factor receptor (EGFR; ErbB-1; HER1 in humans) is a transmembrane protein that is a receptor for members of the epidermal growth factor family (EGF family) of extracellular protein ligands.

The epidermal growth factor receptor is a member of the ErbB family of receptors, a subfamily of four closely related receptor tyrosine kinases: EGFR (ErbB-1), HER2/neu (ErbB-2), Her 3 (ErbB-3) and Her 4 (ErbB-4). In many cancer types, mutations affecting EGFR expression or activity could result in cancer.

Molecular targeting strategies for cancer therapy are distinct from conventional chemotherapy and radiotherapy in their potential to provide increased tumor specificity. One particular molecular target of high promise in oncology is the epidermal growth factor receptor (EGFR). The EGFR is overexpressed, dysregulated or mutated in many epithelial malignancies, and EGFR activation appears important in tumor growth and progression. Advances in signal transduction biology continue to sharpen our understanding regarding specific contributions of EGFR signaling networks to cancer behavior. Two predominant classes of EGFR inhibitors have been developed including monoclonal antibodies (mAbs) that target the extracellular domain of EGFR, such as cetuximab (Erbitux), and small molecule tyrosine kinase inhibitors (TKIs) that target the receptor catalytic domain of EGFR, such as gefitinib (Iressa) and erlotinib (Tarceva).

3.2 Poly (ADP-ribose) Polymerase Inhibitor

Poly (ADP-ribose) polymerase (PARP) is a family of proteins involved in a number of cellular processes such as DNA repair, genomic stability, and programmed cell death

The PARP family comprises 17 members (10 putative).[citation needed] They have all very different structures and functions in the cell.

- PARP1, PARP2, VPARP (PARP4), Tankyrase-1 and -2 (PARP-5a or TNKS, and PARP-5b or TNKS2) have a confirmed PARP activity.[citation needed]
- Others include PARP3, PARP6, TIPARP (or "PARP7"), PARP8, PARP9, PARP10, PARP11, PARP12, PARP14, PARP15, and PARP16.
- PARP1 and PARP2 show activity against breast cancer causing protein BRCA1 and BRCA2

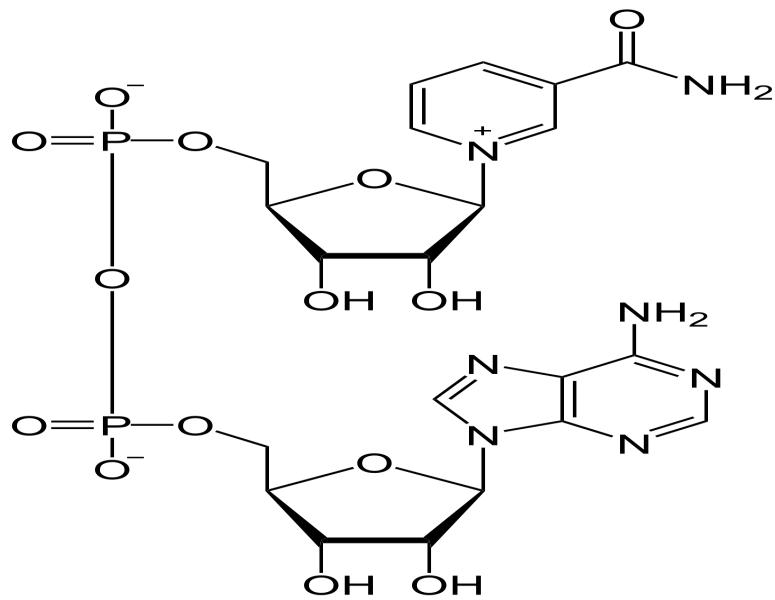


Figure : PARP1

3.3 Aromatase

Aromatase inhibitors are a class of medicines that work by blocking the enzyme aromatase, the enzyme that converts androgens into estrogen.

Aromatase inhibitors are used in the treatment of **breast cancer** to reduce levels of circulating estrogen.

This means that less estrogen is available to stimulate the growth of estrogen receptor (ER) positive breast cancer cells, slowing or inhibiting the progression of these cancers.
Approximately 80% of all breast cancers are ER positive.

Aromatase inhibitors are unable to prevent the ovaries from making estrogen, which means that they are only used to treat breast cancer in postmenopausal women.

There are three aromatase inhibitors: anastrozole, exemestane, and letrozole.

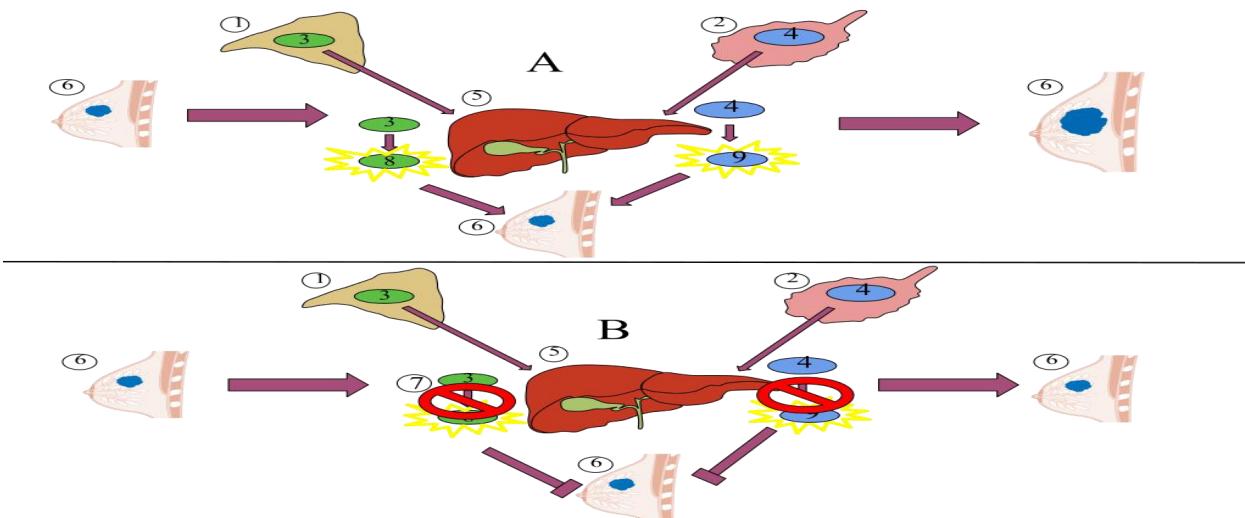


Fig: aromatase inhibition

Often used as a cancer treatment in postmenopausal women, AIs work by blocking the conversion of androstenedione and testosterone into estrone and estradiol, respectively, which are both crucial to the growth of developing breast cancers (AIs are also effective at treating ovarian cancer, but less commonly so). In the diagram, the adrenal gland (1) releases androstenedione (3) while the ovaries (2) secrete testosterone (4).

Both hormones travel to peripheral tissues or a breast cell (5), where they would be converted into estrone (8) or estradiol (9)

if not for AIs (7), which prevent the enzyme CYP19A1 (also known as aromatase or estrogen synthase)

(6) from catalyzing the reaction that turns androstenedione and testosterone into estrone and estradiol. In the diagram, Part A represents the successful conversion of androstenedione and testosterone into estrone and estradiol in the liver. Part B represents the blockage of this conversion by aromatase inhibitors both in peripheral tissues and in the breast tumor itself.

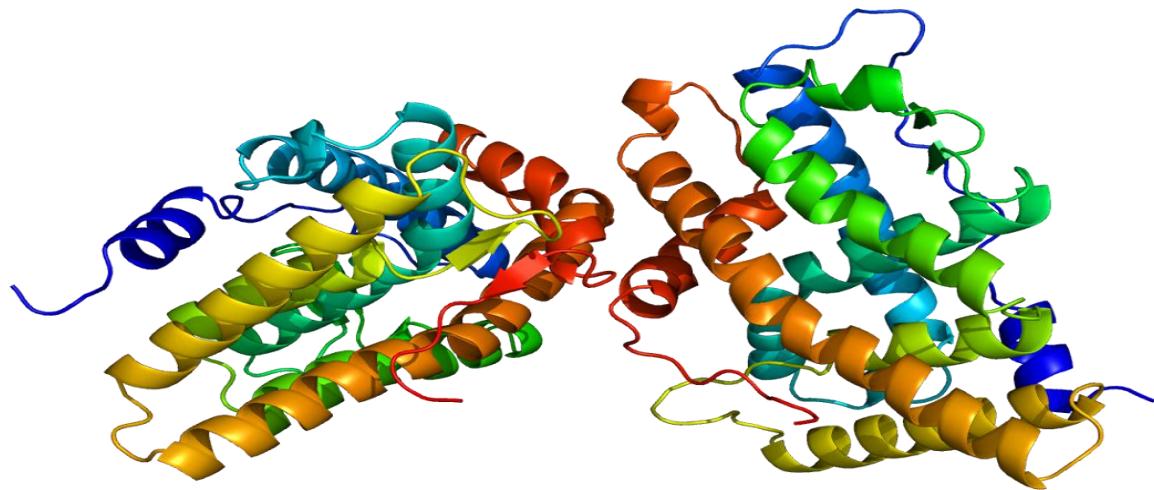


Fig: aromatase inhibitor

3.4 MTOR Inhibitor

mTOR inhibitors are a class of drugs that inhibit the mammalian target of rapamycin (mTOR), which is a serine/threonine-specific protein kinase that belongs to the family of phosphatidylinositol-3 kinase (PI3K) related kinases (PIKKs). mTOR regulates cellular metabolism, growth, and proliferation by forming and signaling through two protein complexes, mTORC1 and mTORC2. The most established mTOR inhibitors are so-called **rapalogs** (rapamycin and its analogs), which have shown tumor responses in clinical trials against various tumor types

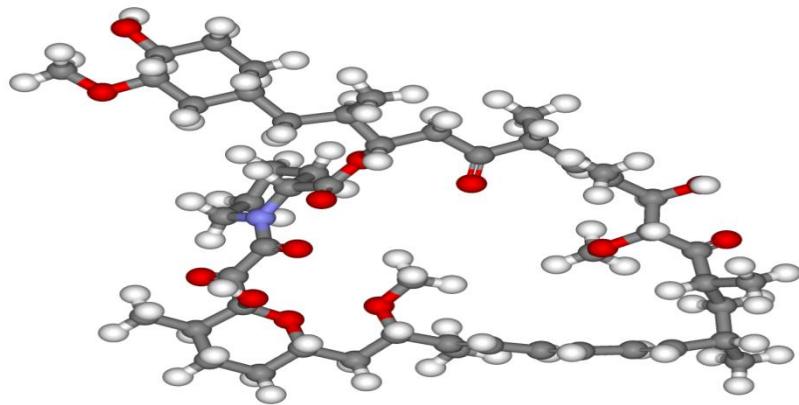


Fig: mtor inhibitor

Many human tumors occur because of dysregulation of mTOR signaling, and can confer higher susceptibility to inhibitors of mTOR. Deregulations of multiple elements of the mTOR pathway, like PI3K amplification/mutation, PTEN loss of function, AKT overexpression, and S6K1,

4EBP1, and eIF4E overexpression have been related to many types of cancers. Therefore, mTOR is an interesting therapeutic target for treating multiple cancers, both the mTOR inhibitors themselves or in combination with inhibitors of other pathways.

Upstream, PI3K/AKT signalling is deregulated through a variety of mechanisms, including overexpression or activation of growth factor receptors, such as HER-2 (human epidermal growth factor receptor 2) and IGFR (insulin-like growth factor receptor), mutations in PI3K and mutations/amplifications of AKT. Tumor suppressor phosphatase and tensin homologue deleted on chromosome 10 (PTEN) is a negative regulator of PI3K signaling. In many cancers the PTEN expression is decreased and may be downregulated through several mechanisms, including mutations, loss of heterozygosity, methylation, and protein instability.

Downstream, the mTOR effectors S6 kinase 1 (S6K1), eukaryotic initiation factor 4E-binding protein 1 (4EBP1) and eukaryotic initiation factor 4E (eIF4E) are related to cellular transformation.[1] S6K1 is a key regulator of cell growth and also phosphorylates other important targets. Both eIF4E and S6K1 are included in cellular transformation and their overexpression has been linked to poor cancer prognosis.

4. Targeted Protein:

the protein which is involved and under consideration in the growth of breast cancer is BRCA1 and BRCA2

4.1 BRCA1 and BRCA2:

The name “BRCA” is an abbreviation for “Breast Cancer gene.” BRCA1 and BRCA2 are two different genes that have been found to impact a person’s chances of developing breast cancer.

Every human has both the BRCA1 and BRCA2 genes. Despite what their names might suggest, BRCA genes do not cause breast cancer. In fact, these genes normally play a big role in preventing breast cancer. They help repair DNA breaks that can lead to cancer and the uncontrolled growth of tumors. Because of this, the BRCA genes are known as tumor suppressor genes.

However, in some people these tumor suppression genes do not work properly. When a gene becomes altered or broken, it doesn’t function correctly. This is called a gene mutation.

4.2 BRCA Mutations:

A small percentage of people (about one in 400, or 0.25% of the population) carry mutated BRCA1 or BRCA2 genes. A BRCA mutation occurs when the DNA that makes up the gene becomes damaged in some way.

When a BRCA gene is mutated, it may no longer be effective at repairing broken DNA and helping to prevent breast cancer. Because of this, people with a BRCA gene mutation are more likely to develop breast cancer, and more likely to develop cancer at a younger age. The carrier of the mutated gene can also pass a gene mutation down to his or her offspring.

Table: Potential inhibitor

EGFR Inhibitors (tyrosine kinase inhibitor)	osimertinib gefitinib erlotinib afatinib
Poly (ADP-ribose) polymerase inhibitor	PARP1 PARP2 VPARP PARP4
Aromatase	anastrozole, letrozole exemestane
MTOR	rapalogs

Chapter : 2

Literature Review

In the modern era, there are thousands of different kinds of disease because of various reasons that leads to death of living forms. Cancer is one of the most common occurring diseases that play a major role in mortality of the human life. Cancer cases have risen since last decade. Cancer is a disease that occurs due to uncontrolled growth of cells, in any part of the body that leads to increase in size of cells and lead to formation of tumor. Since every cells gets a sufficient amount of nutrition, but due to increase in size of these cancerous cells, cancerous start taking nutrition of another cells that lead to starvation of the neighboring cell and ultimately lead to death of the cell. Statistics have shown how cancer has become the leading cause of death worldwide. As per the NIH (National Institute of Health) in 2012, there were 14.1 million new cases and 8.2 million cancer-related deaths worldwide.

As per 2012 data , highest rate of cancer for both men and women was found in Denmark having 338 peoples for 1,000,000 being diagnose for cancer. According to WHO (world Health Organization) in 2012, 13% of the death of human life occur due to cancer. In 2017, India has ranked 3rd in world for highest number of cancer patient. There are many kinds of cancer 200 types. But the four most common cancers occurring worldwide are lung, female breast, bowel and prostate cancer.

The reason or we can say the cause behind such high rate of cancer cases over the world can be due to either internal factors like inherited genetic defects or hormonal imbalance or may be due to external factors like environmental factors (air pollution, infection, sun radiation), poor life style like smoking, obesity, drinking alcohol, chewing tobacco etc. All of these factors play a major role for occurring of cancer. Apart from these other factors can be chemical or toxic compound exposures, ionizing radiation, some pathogens, and human genetics. Among all the different kinds of cancer, we have done some study on the Breast cancer. Breast cancer is the most occurring non skin cancer in women all over the world. According to American Cancer Society approximately 230,480 new cases of invasive breast cancer and 39,520 breast cancer deaths are expected to occur among US women in 2011. In U.S. about 1 in 8 women in her lifetime over the course develops invasive breast cancer.

According to world cancer research fund international, in 2012 nearly 1.7 million new cases of breast cancer diagnosed. Breast cancer is more hazardous in compare to other cancers as entails about 85% survival rate for the five-year and the ten-year for 71%. Most of the time, diagnosis of cancer occur at the late or advance stage. There are various ways of screening of cancer methods like mammogram, breast self-examination, etc. that helps the patients for early detection.

Several studies have reported that EGFR gene amplification in breast cancer might be a predictor of response to TKIs. EGFR is a group of trans-protein glycomembrane that regulates signaling pathways to control cellular proliferation. EGFR belongs to the Human epidermal receptor (HER) family. It is a type I tyrosine kinase receptor which plays a vital role in signal transduction pathways, regulating key cellular functions such as cell proliferation, survival, adhesion, migration, and differentiation.

EGFR play an important role in cell growth and development. Its overexpression has been found linked to various types of cancer. EGFR, PARP, AROMATASE is the most common target for

treatment of cancer. EGFR family contains Erbb gene. Overexpression of EGFR leads to breast cancer and found to be associated with large tumor size, poor differentiation, and poor clinical outcomes. EGFR overexpression has been observed in triple-negative breast cancer (TNBC) and inflammatory breast cancer (IBC). EGFR are transmembrane glycoproteins containing an extracellular ligand binding domain and an intracellular receptor tyrosine kinase domain. Tyrosine kinases inhibitors (TKI) and anti-EGFR monoclonal antibodies (MAbs) are molecular anti-cancer agents. TYK has TKI which bind to the ATP binding site in tyrosine kinase domain of EGFR. Tyrosine kinase transforms the cells if they are mutated or having overexpression. EGFR inhibitors are of 3 types: pure EGFR TKIs and dual EGFR and HER2 TKIs. So EGFR is the main target for the breast cancer treatment. So scientists are trying to develop the inhibitors for it. Many medicines are available in the market based on this mechanism. Examples of medicine are Lapatinib, Afatinib and Neratinib specific Erbb kinase inhibitors. While EGFR specific kinase inhibiting drugs are Erlotinib, Gefitinib and Osimertinib. EGFR inhibitors are divided into 2 classes based on their use in cancer therapy:

Quinazoline derivatives

Pyrimidine derivatives

Both the classes consists of ATP- competitive small molecules. In wet lab conditions, usually investigators/ researchers need to synthesize many compounds and have to test their corresponding activities by different cell based assay method to discover new effective EGFR inhibitors. Discovering new effective EGFR, PARP inhibitors by wet lab is usually time consuming and manpower expensive. So, it is very important and effective method to develop reliable tools to predict biological activities before synthesis. So, using Cheminformatics is one of the methods.

Cheminformatics is a modern branch of science that considers acquisition, storage, retrieval, search, analysis and visualization of chemical information of any chemical compound. Cheminformatics make use of computational and informational techniques to understand the chemistry related problem like in silico mapping of chemical space (theoretical space occupied by all possible chemicals and molecules). This method is mainly use for drug discovery and for the large number of compounds to determine their specific properties.

There are two methods of drug designing

Ligand based

Structure based

Ligand based develop the drug using QSAR method which is based on principle of determining the activity on the basis of structure of molecule. QSAR method use both linear and nonlinear method. Such model allows understanding of properties of the selected molecule that influence biological activity. After validation of QSAR models, one can use them for predicting activities of a new set of molecules, which have not been synthesized yet.

There are different kinds of QSAR method use by researcher depending upon the requirement. Such as

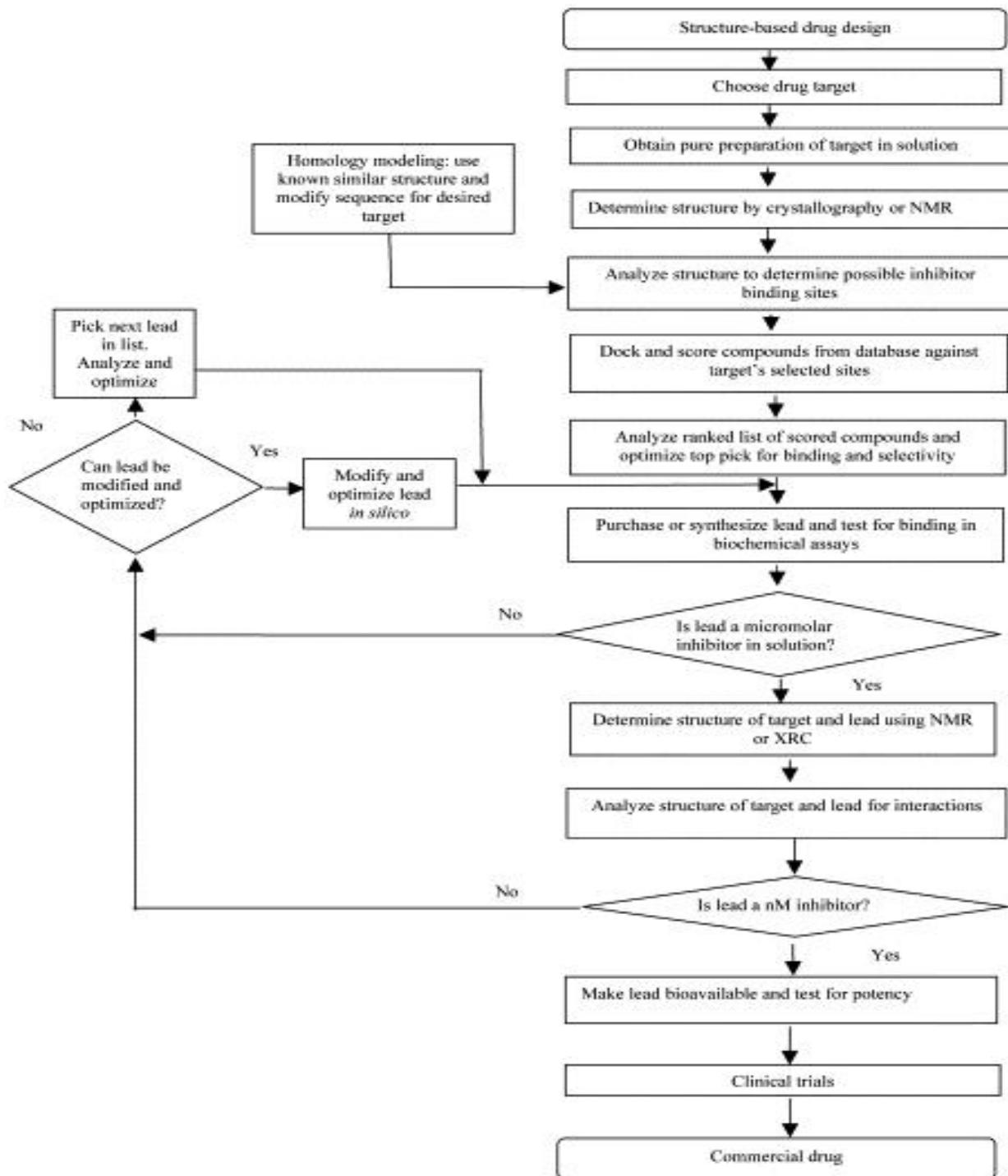
2D- QSAR

3D- QSAR

QSAR is a technique that is used to link chemical activities with molecular structure and composition. A QSAR is a mathematical relationship between biological activity of molecular system and its geometric and chemical characteristic[1]. QSAR find consistent relationship between biological activity and molecular properties, so that these “rules” can be used to evaluate the activity of new compound[1]. QSAR approach attempts to identify and quantify the physicochemical properties of a drug and to see whether any of these properties has an effect on drug’s biological activity using a mathematical equation. The use of QSAR techniques is based upon two underlying principles structurally similar compounds behave comparably under similar environmental conditions and behavioural differences among compounds are linked to structural and compositional variations[9]. The predictor variables are usually described as “descriptors” (or features, attributes, independent variables, structural/compositional components, etc.), and the resultant response variables (e.g., reactivity, toxicity or bioactivity) are termed as “activities” (or endpoints, dependent variables, etc.). As QSAR is a recent approach that is used for optimization of inhibitors against cancer.

Structure based drug discovery

The process of structure-based drug design is an iterative one (see figure) and often proceeds through multiple cycles before an optimized lead goes into phase I clinical trials. The first cycle includes the cloning, purification and structure determination of the target protein or nucleic acid by one of three principal methods: X-ray crystallography, NMR, or homology modeling. Using computer algorithms, compounds or fragments of compounds from a database are positioned into a selected region of the structure. These compounds are scored and ranked based on their steric and electrostatic interactions with the target site, and the best compounds are tested with biochemical assays. In the second cycle, structure determination of the target in complex with a promising lead from the first cycle, one with at least micromolar inhibition in vitro, reveals sites on the compound that can be optimized to increase potency. Additional cycles include synthesis of the optimized lead, structure determination of the new target:lead complex, and further optimization of the lead compound. After several cycles of the drug design process, the optimized compounds usually show marked improvement in binding and, often, specificity for the target. And this whole process is what we called molecular docking.



Chapter 3

Aims and Objective

- Data Selection
- Gene Evaluation and study
- Selection of potential inhibitors
- Pocket selection study of potent inhibitors
- Docking study of protein and inhibitors
- Model Evaluation
- Model Interpretation

Chapter 4

Data Retrieval Tool and Docking Software Used

DATA RETRIEVAL TOOL: Pubmed is the data retrieval tool used for literature review about the inhibitors and the gene responsible for Breast Cancer. It is a free resource supporting the search and retrieval of peer-reviewed biomedical and life sciences literature with the aim of improving health—both globally and personally.

The PubMed database contains more than 30 million citations and abstracts of peer-reviewed biomedical literature. It does not include full-text journal articles; however, links to the full text are often present when available from other sources, such as the publisher's website or PubMed Central (PMC). Available to the public online since 1996, PubMed was developed and is maintained by the National Center for Biotechnology Information (NCBI), at the U.S. National Library of Medicine (NLM), located at the National Institutes of Health (NIH).

DOCKING SOFTWARE USED:

- Autodock Vina
- Autodock Tools
- Openbabel : It is a file converter tool
- Mgl tools: It is used to create suitable environment so that Autodock can work
- Chimera studio

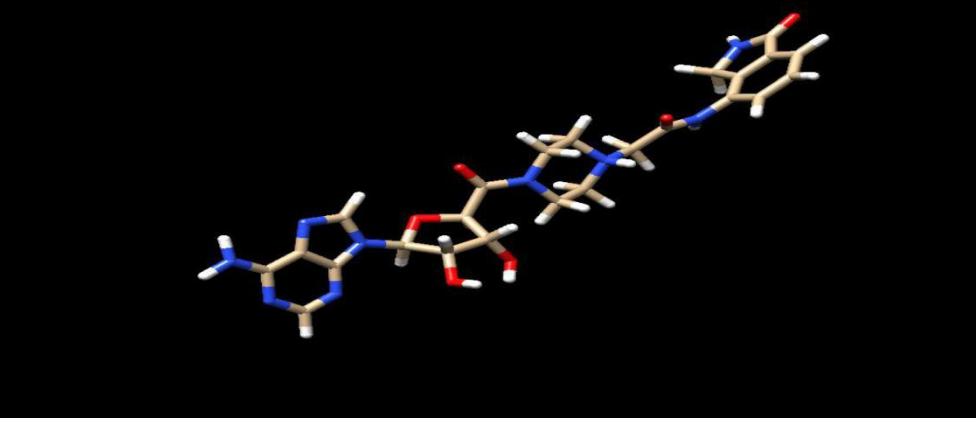
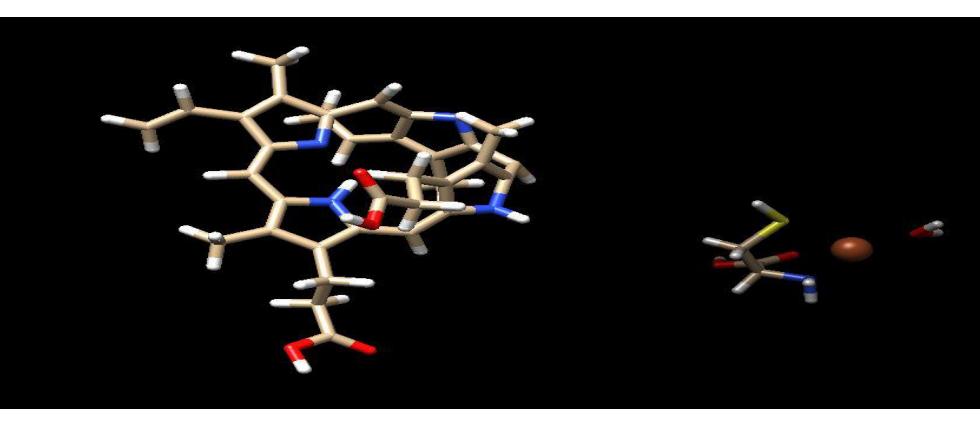
PROTEIN USED FOR DOCKING:

1JM7 (Solution structure of the BRCA1/BARD1 RING-domain heterodimer)

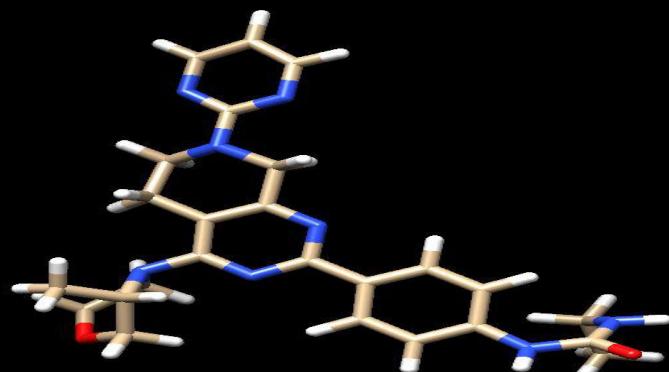
Chapter 5

Molecular Docking of protein BRCA1 with Aromatase Inhibitor

Table of inhibitors

1. Parp1	
2. Tyrosine kinase inhibitor (osimertinib)	
3. mtor (Rapalog)	

**4. Aromatase
(Anastrozole)**

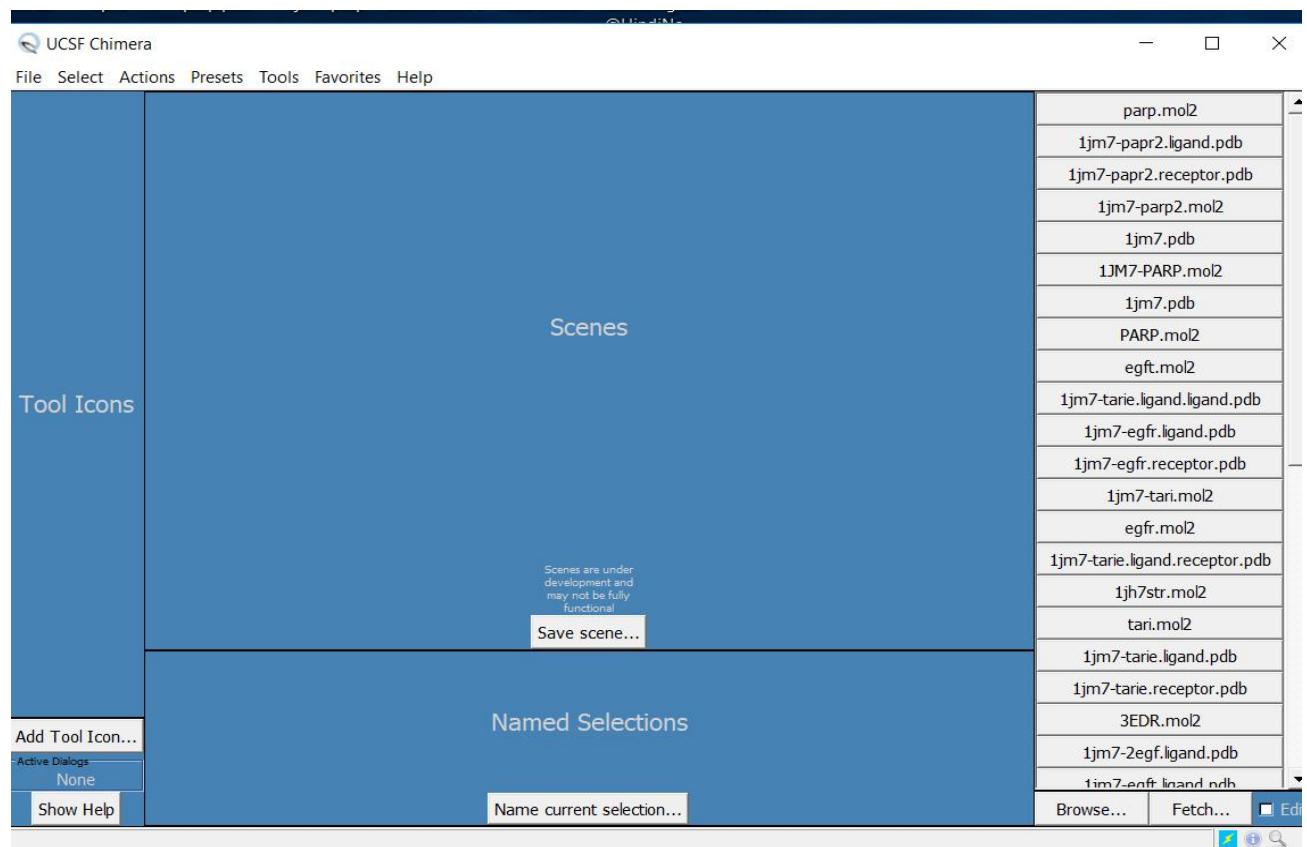


DOCKING:

Autodock Vina analysis

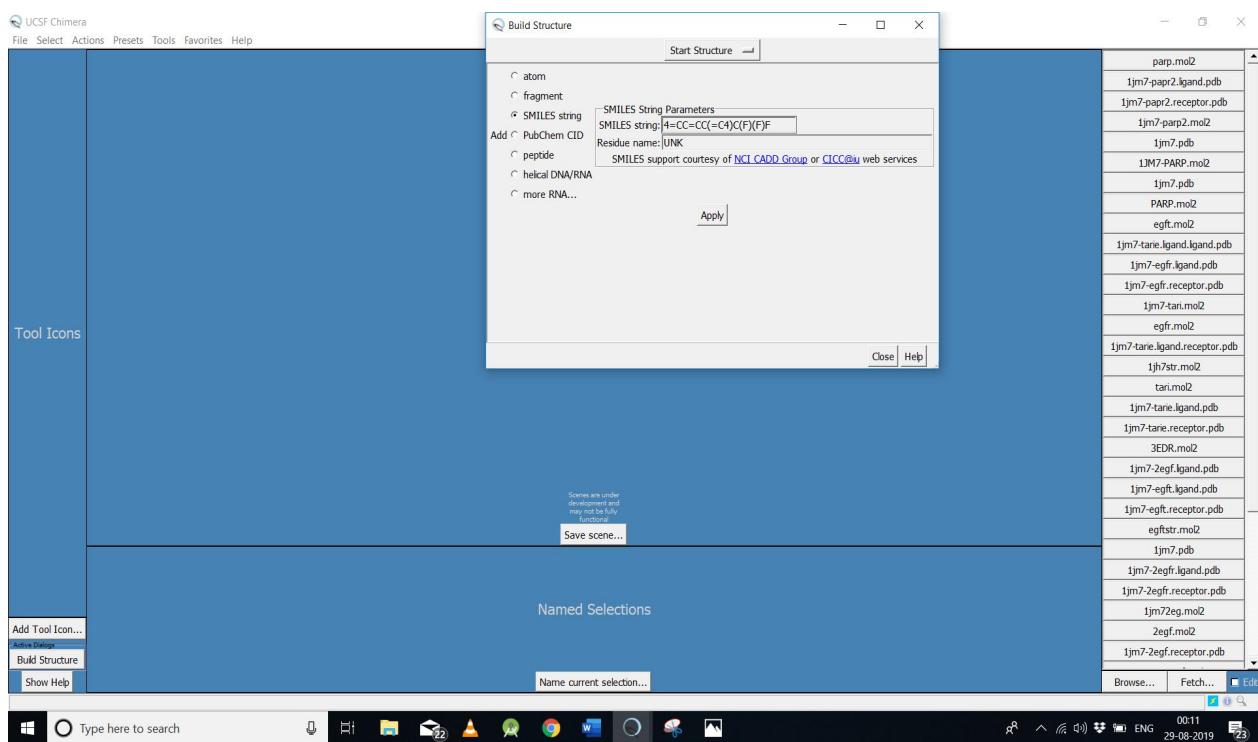
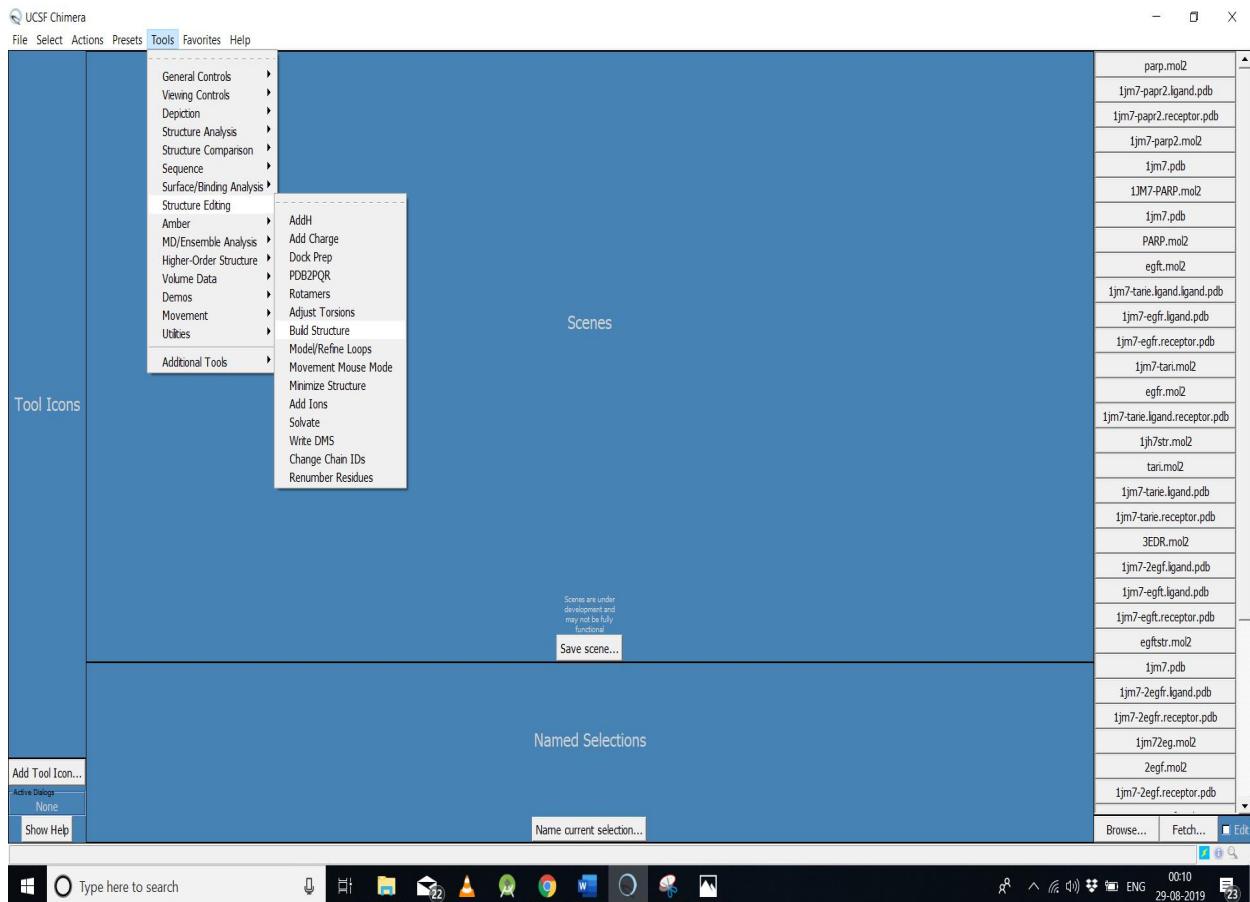
We have done the docking of listed inhibitor with the protein BRAC1(1jm7).

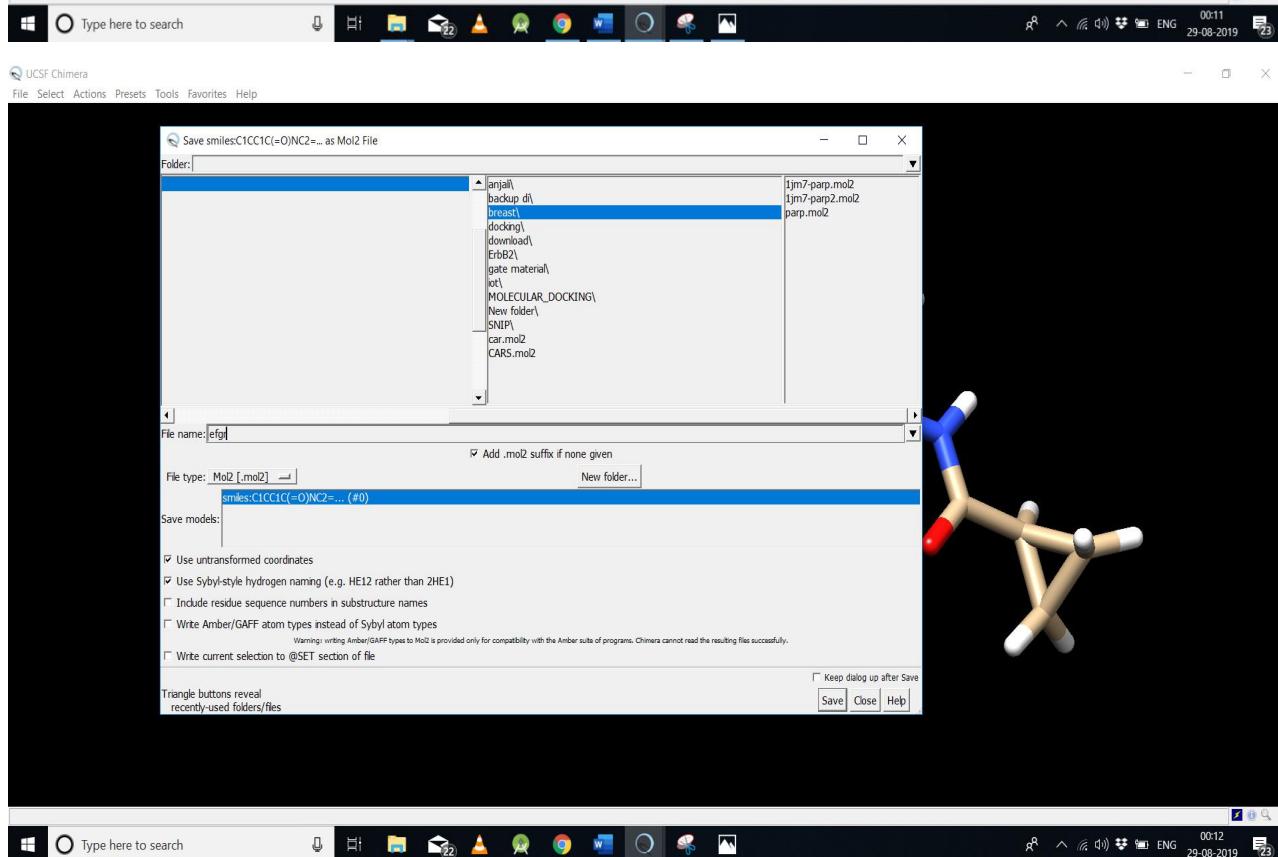
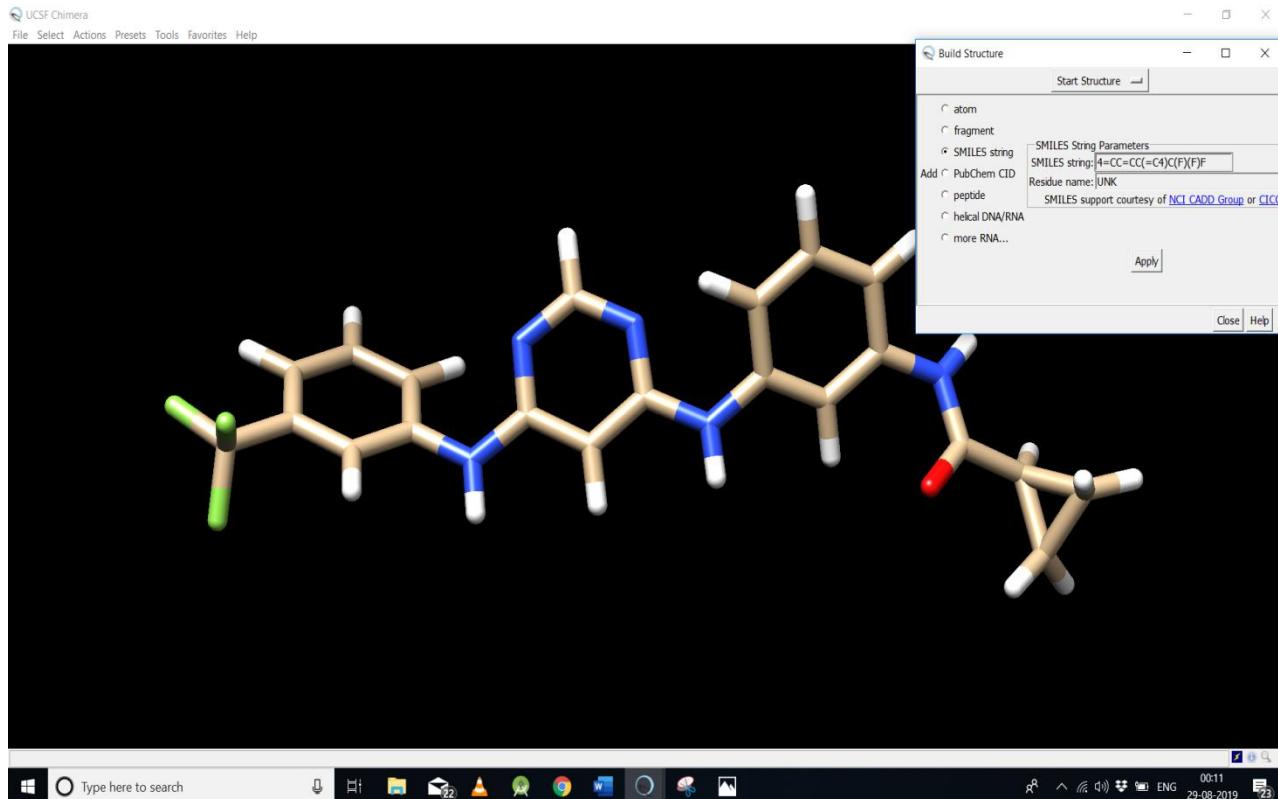
1. We would prepare the structure of the inhibitor which we have extracted from the pubchem data base. From here we only take the canonical form of the structure which is the computer form of the inhibitor. And the we prepare and save the structure.



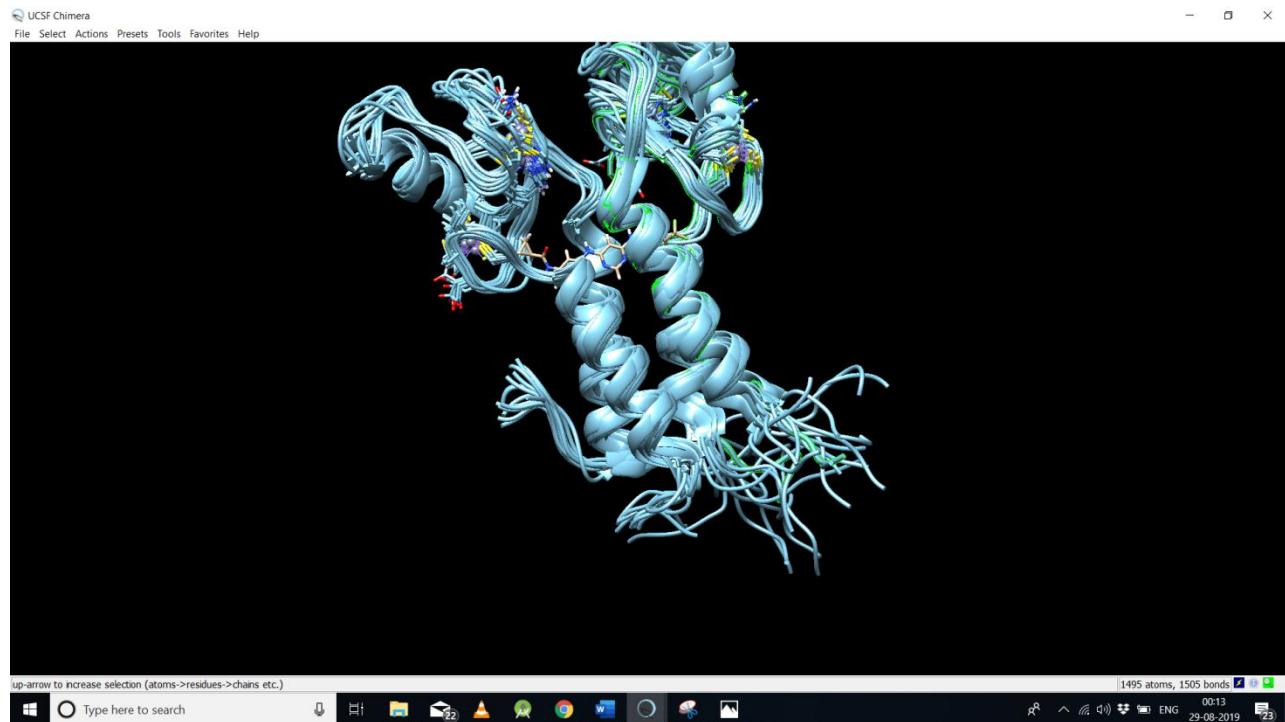
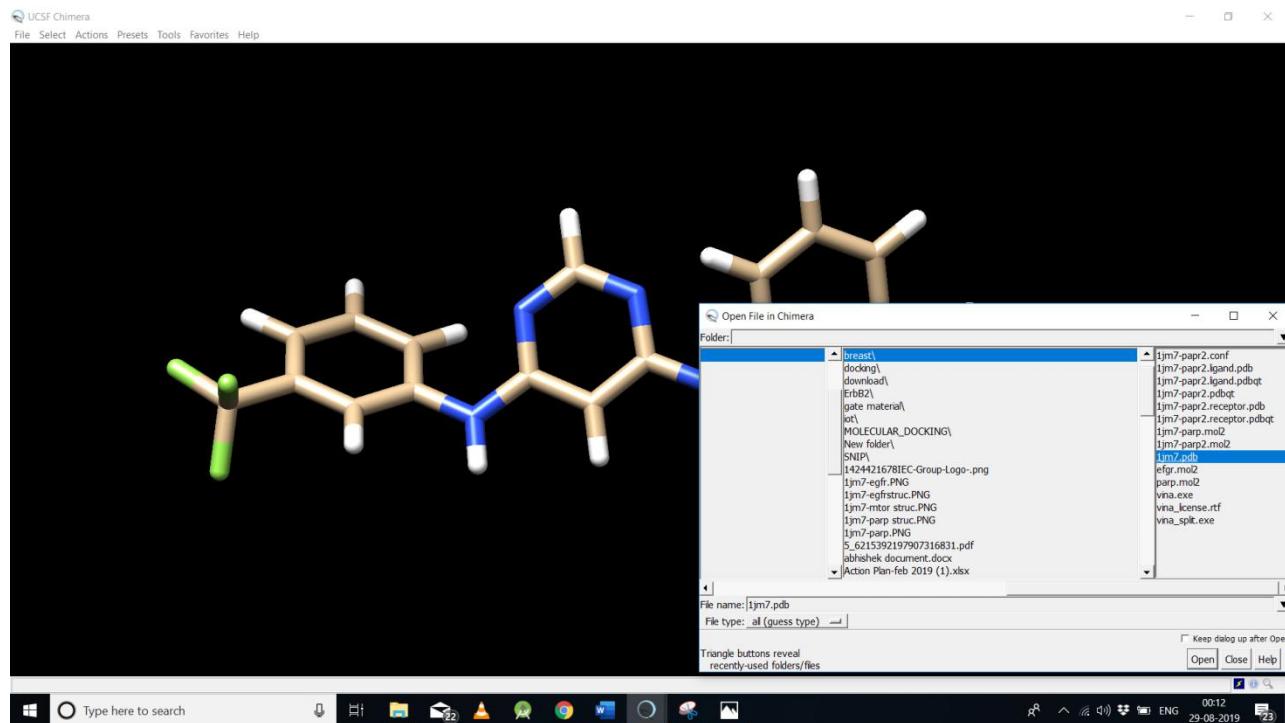
The screenshot shows the UCSF Chimera software interface. The top menu bar includes File, Select, Actions, Presets, Tools, Favorites, and Help. On the left, there is a 'Tool Icons' panel and a 'Scenes' panel containing a 'Save scene...' button. Below these is a 'Named Selections' panel with a 'Name current selection...' button. On the right, a vertical list of files is displayed:

- parp.mol2
- 1jm7-papr2.ligand.pdb
- 1jm7-papr2.receptor.pdb
- 1jm7-parp2.mol2
- 1jm7.pdb
- 1JM7-PARP.mol2
- 1jm7.pdb
- PARP.mol2
- egfr.mol2
- 1jm7-tarie.ligand.ligand.pdb
- 1jm7-egfr.ligand.pdb
- 1jm7-egfr.receptor.pdb
- 1jm7-tari.mol2
- egfr.mol2
- 1jm7-tarie.ligand.receptor.pdb
- 1jh7str.mol2
- tari.mol2
- 1jm7-tarie.ligand.pdb
- 1jm7-tarie.receptor.pdb
- 3EDR.mol2
- 1jm7-2egf.ligand.pdb
- 1im7-egfr.ligand.pdb



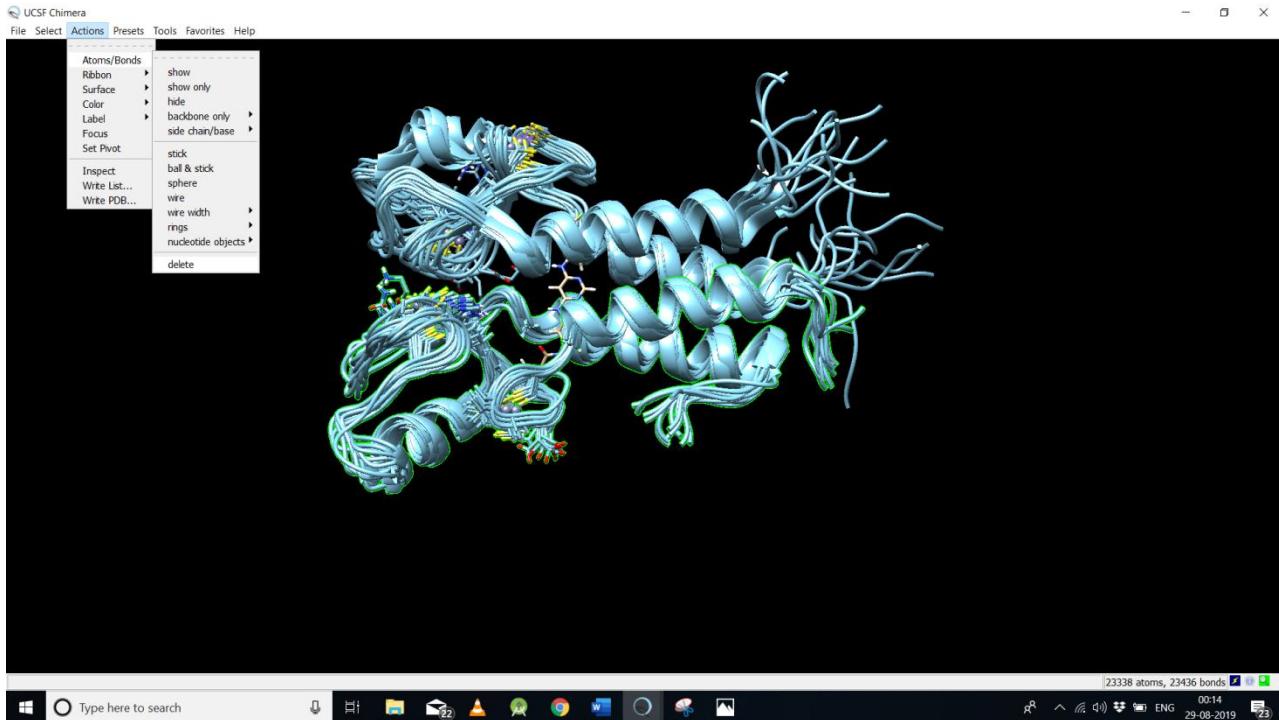


2. Then we extract the protein BRAC1 (1jm7) which we extracted from the pdb databases which is responsible for the breast cancer. And open the same protein in pdb format in the above inhibitor.

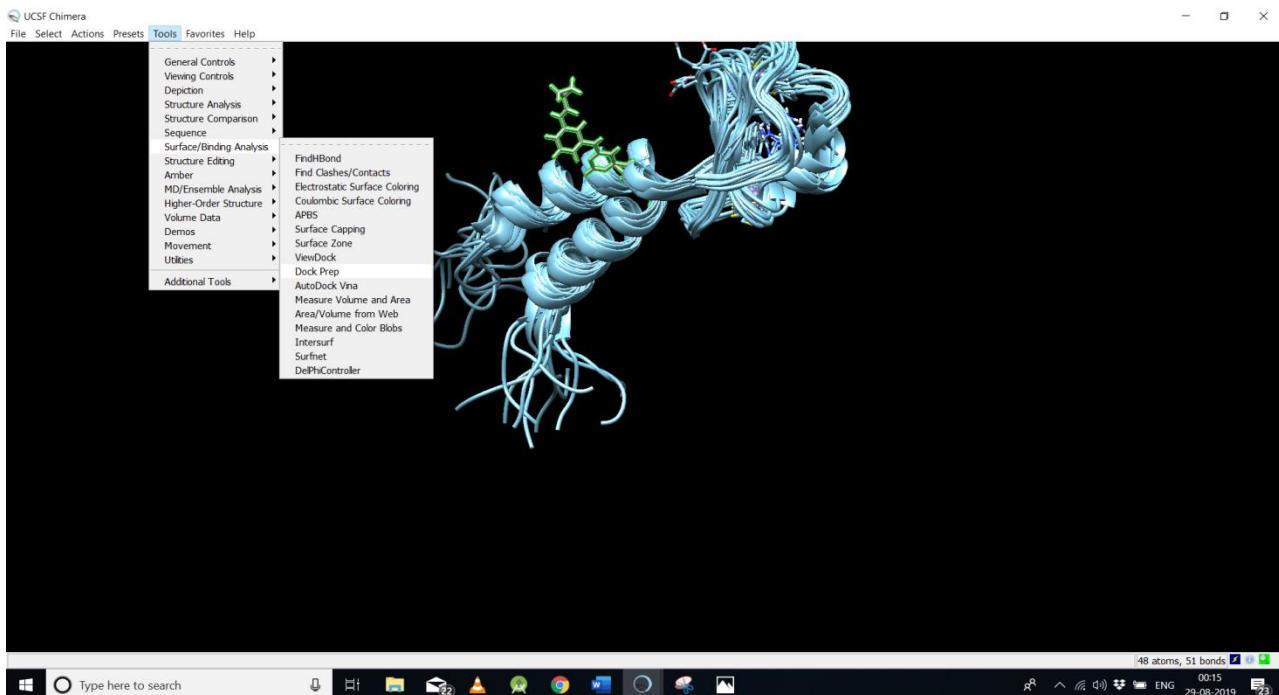


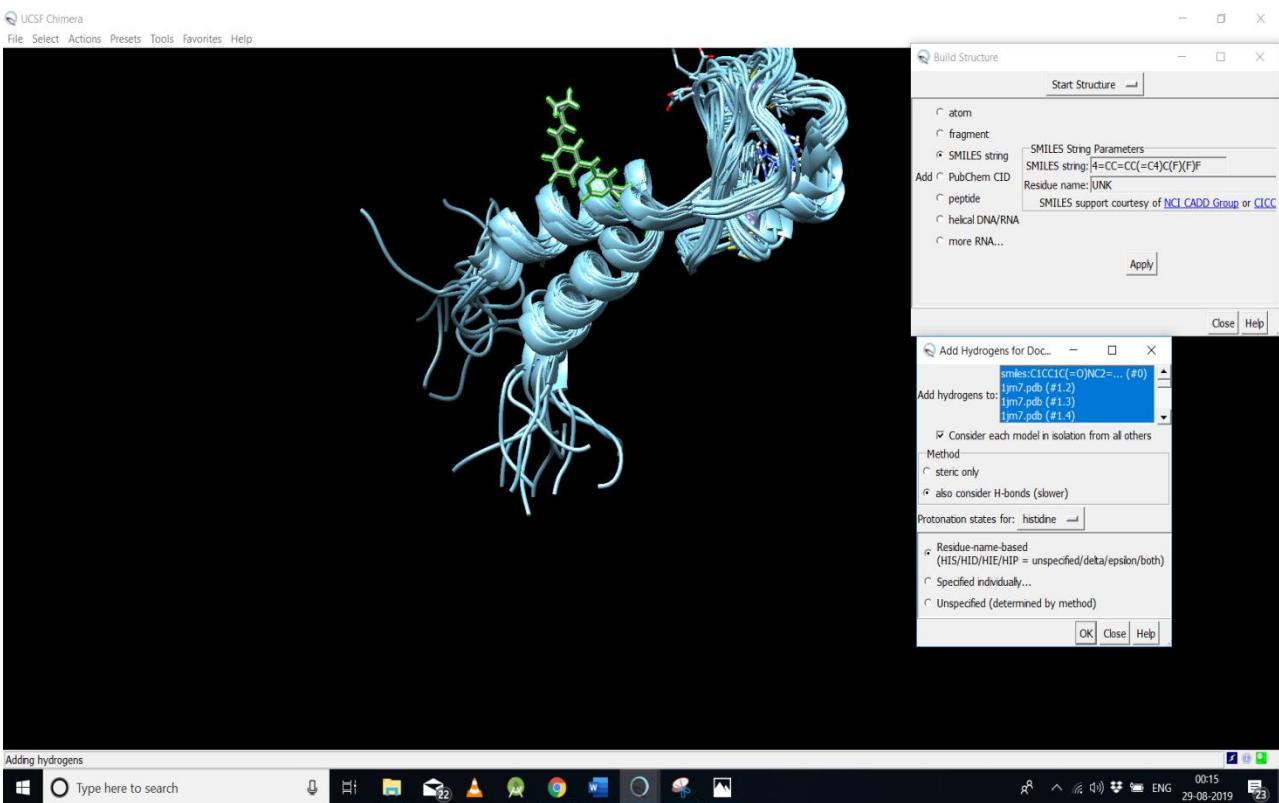
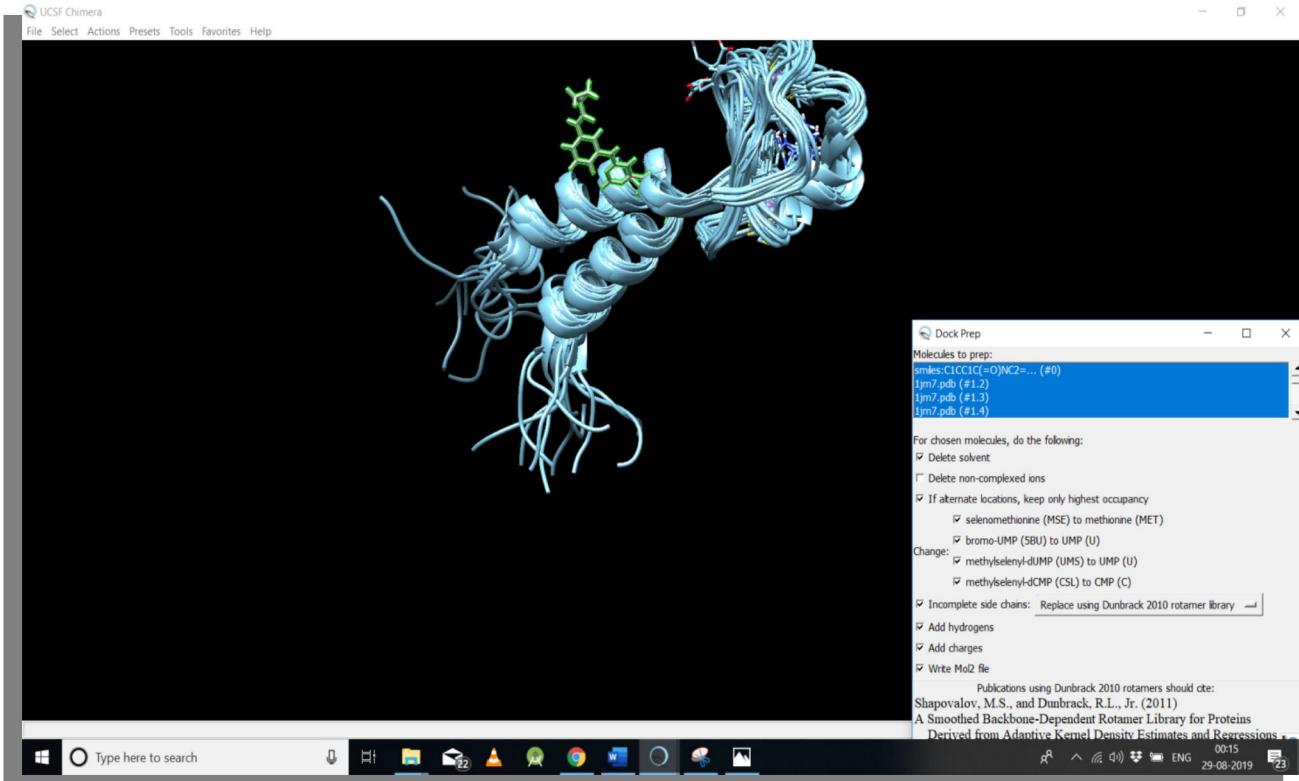
3. Now we open the protein 1jm7 within the chimera studio with the structure of the inhibitor and save the file within the same directory.

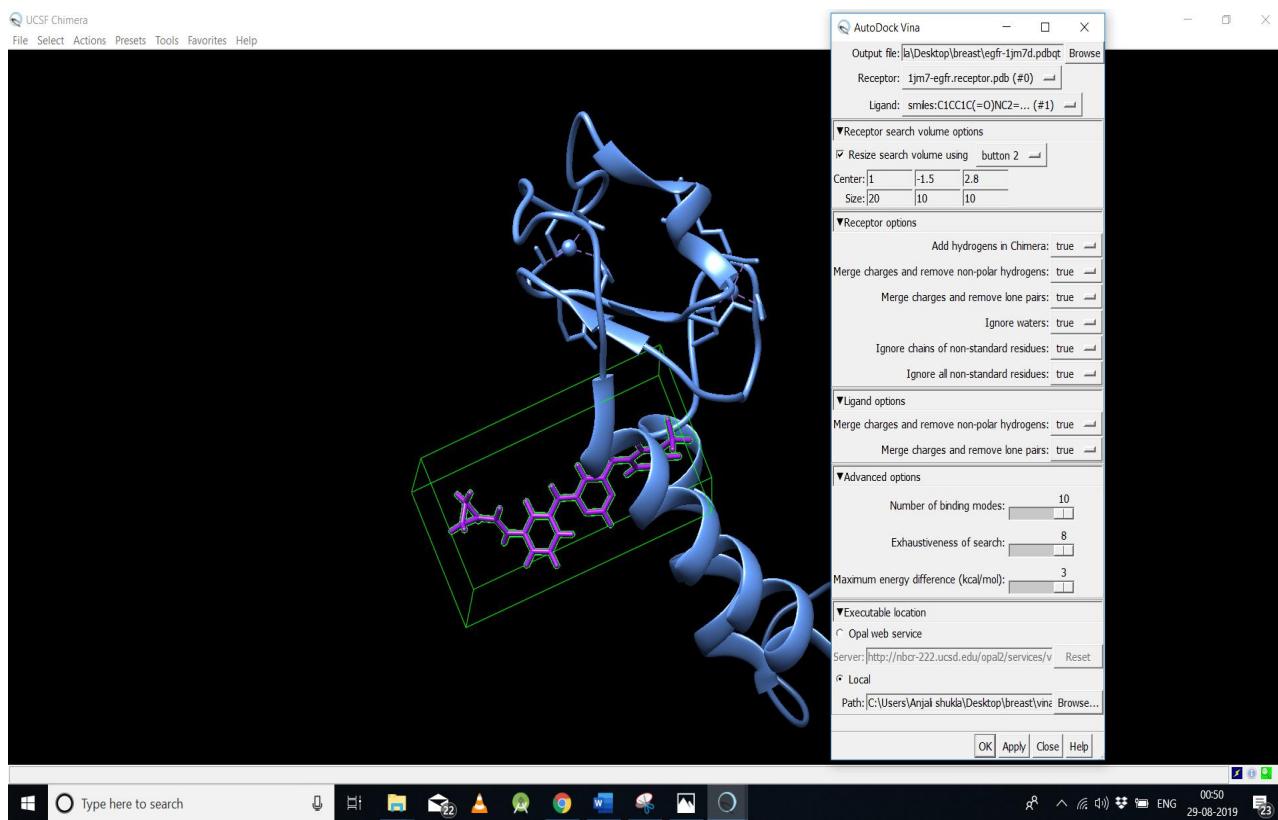
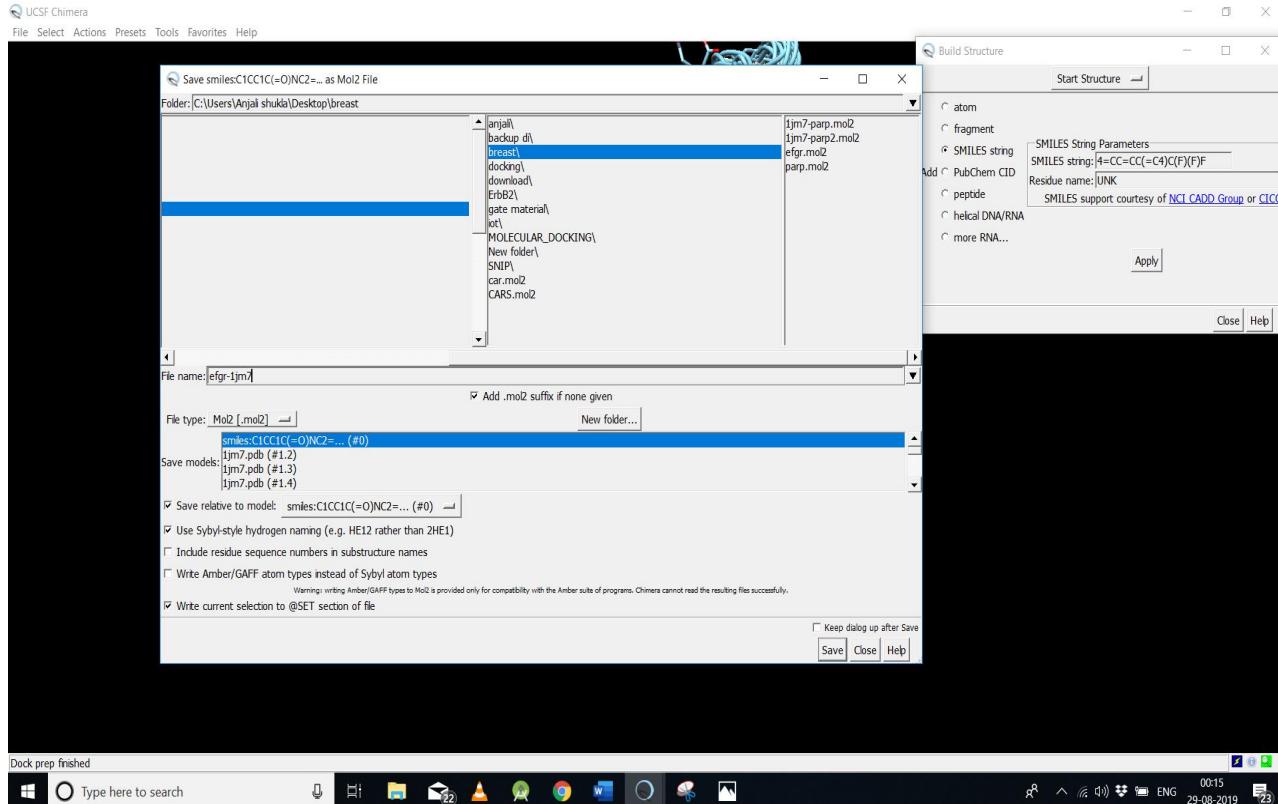
4. Now we go to the dock prepare for the final preparation of the structure and follow the instruction just doing ok.

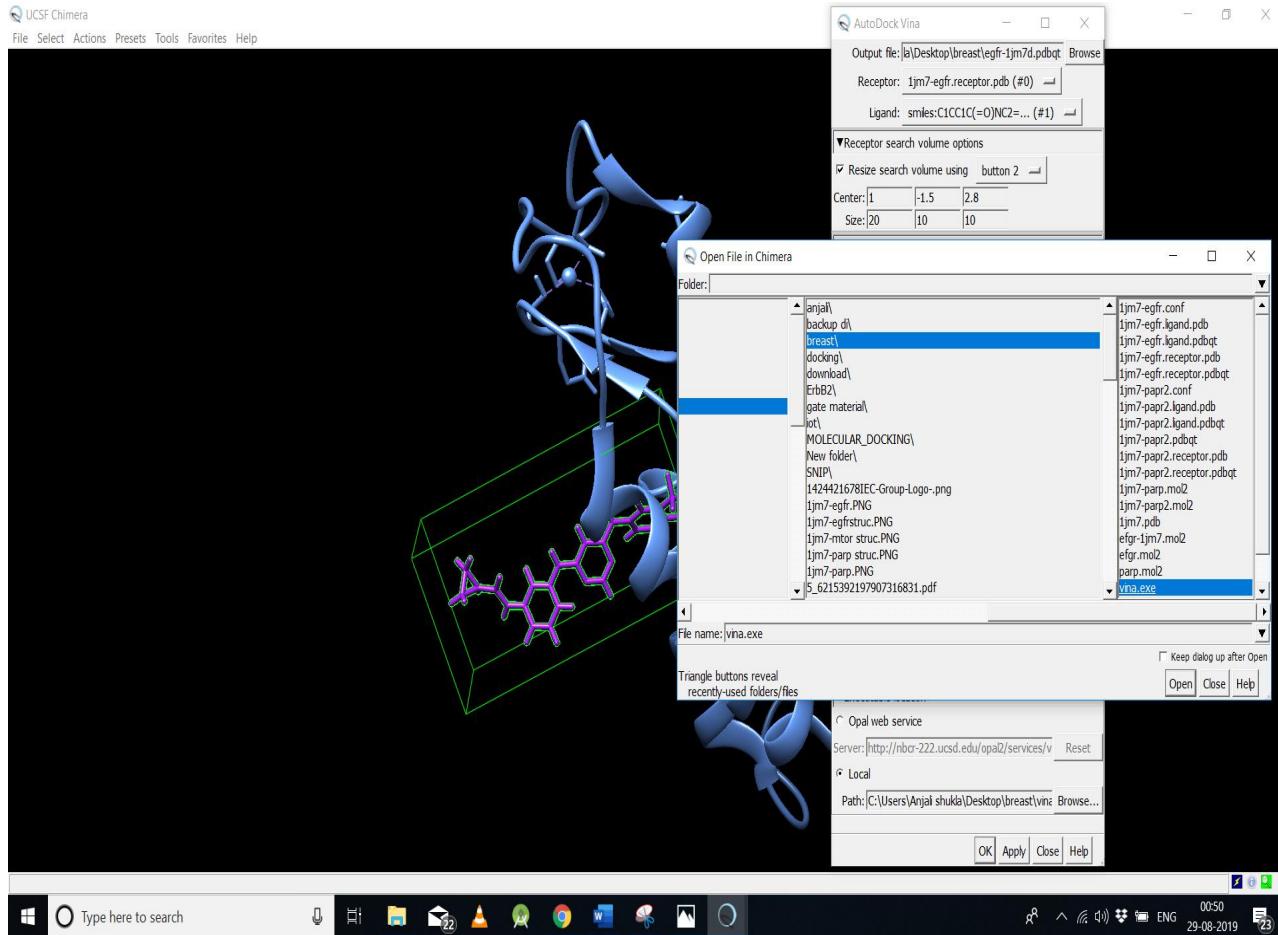


5. Again we go to the action bar and choose the autodock vina and follow the instruction so on, in that we have to set the pocket for the docking. And set the file storage location of local.





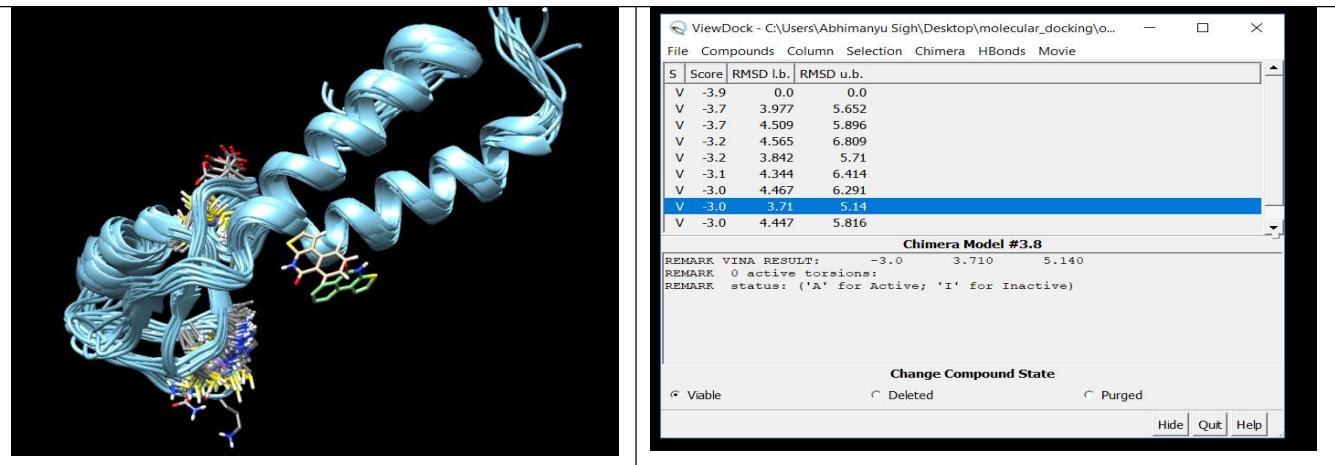




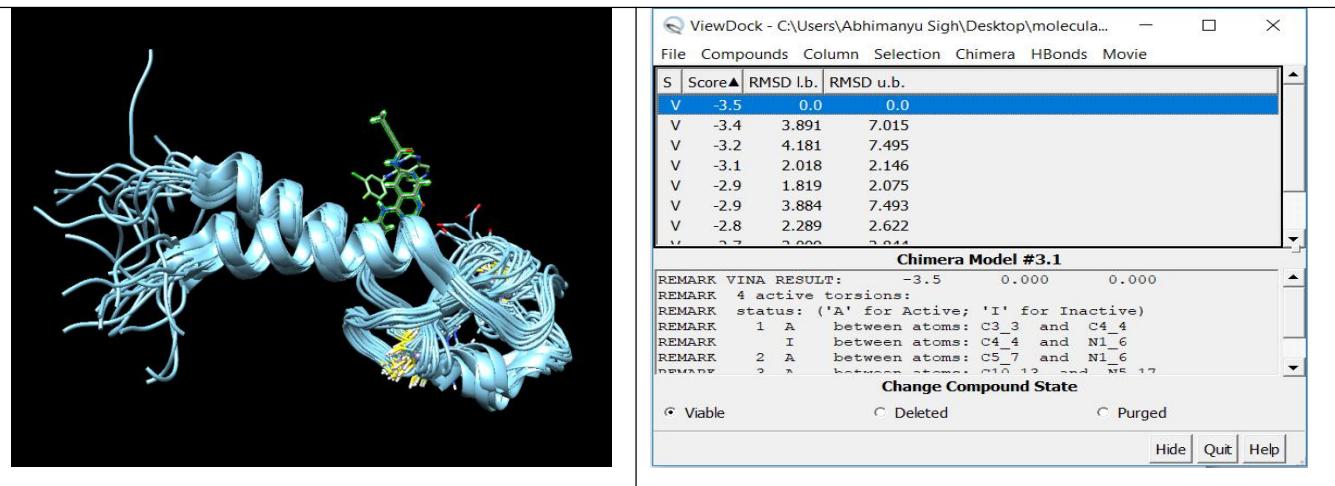
6. The result of the above docking would be shown below with the screenshot result. With the different inhibitor listed above.

Result of vina

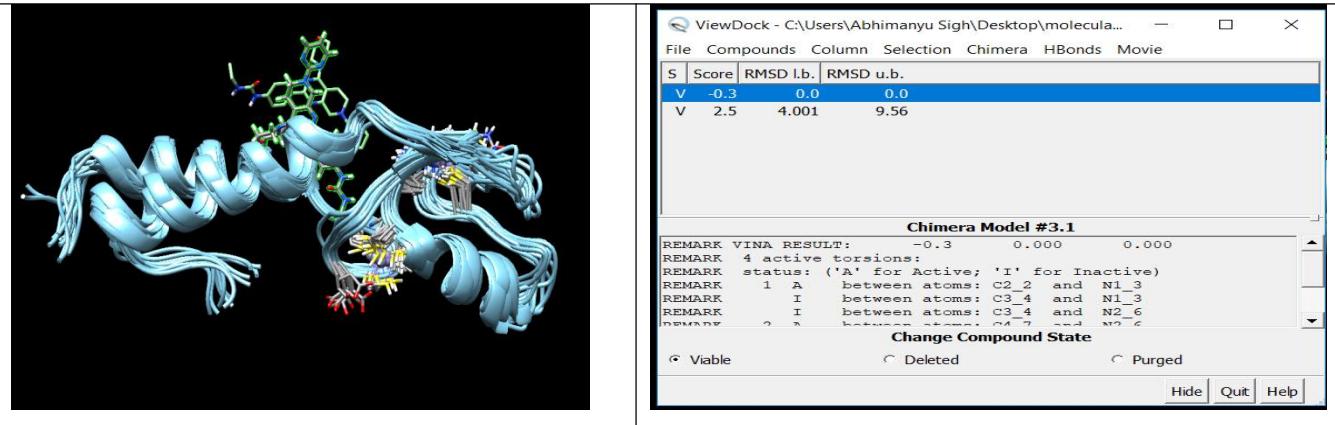
1. PARP1



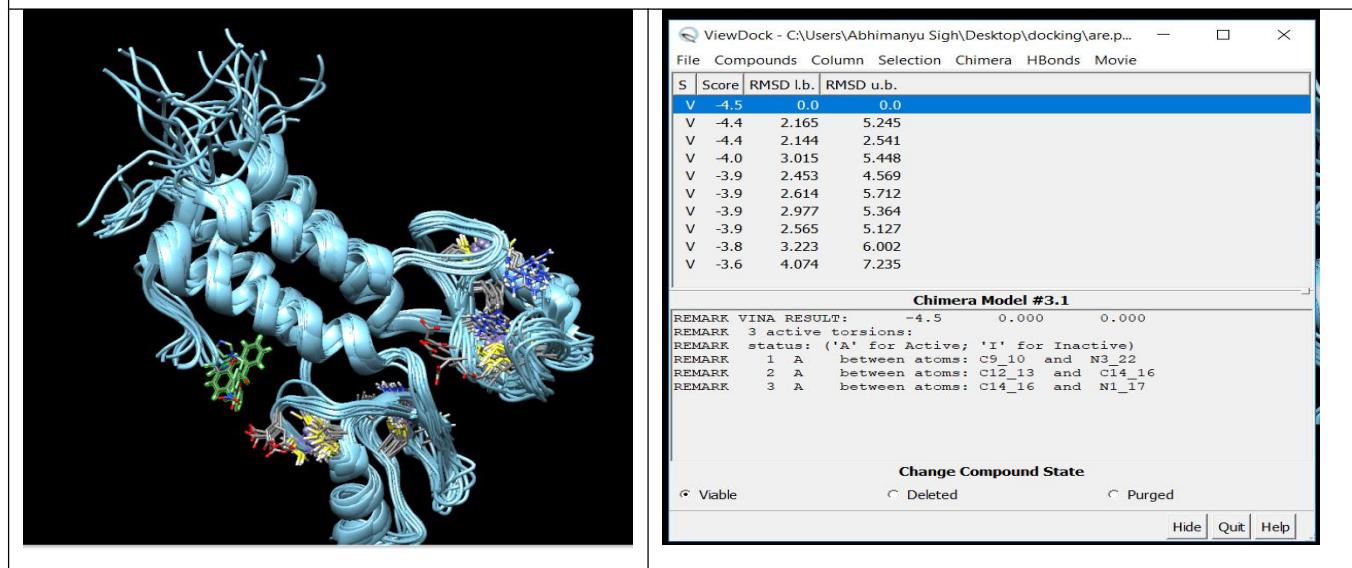
2. Tyrosine kinase Inhibitor (egfr)



MTOR



Aromatase



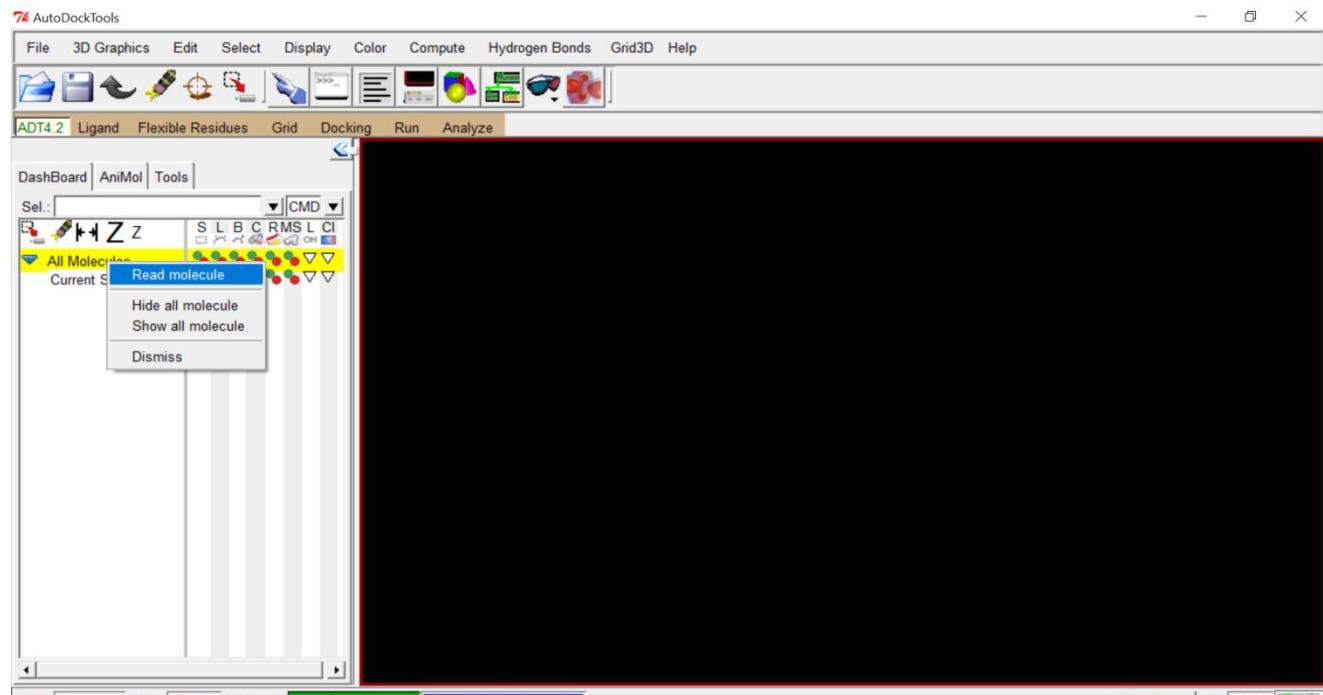
Scoring of inhibitor

Docked	SCORE	RMSD l.b.	RMSD u.b
1JM7-PARP	-3.9	0	0
1JM7-EGFR	-3.5	0	0
1JM7-MTOR	-0.3	0	0
1JM7-AROMATASE	-4.5	0	0

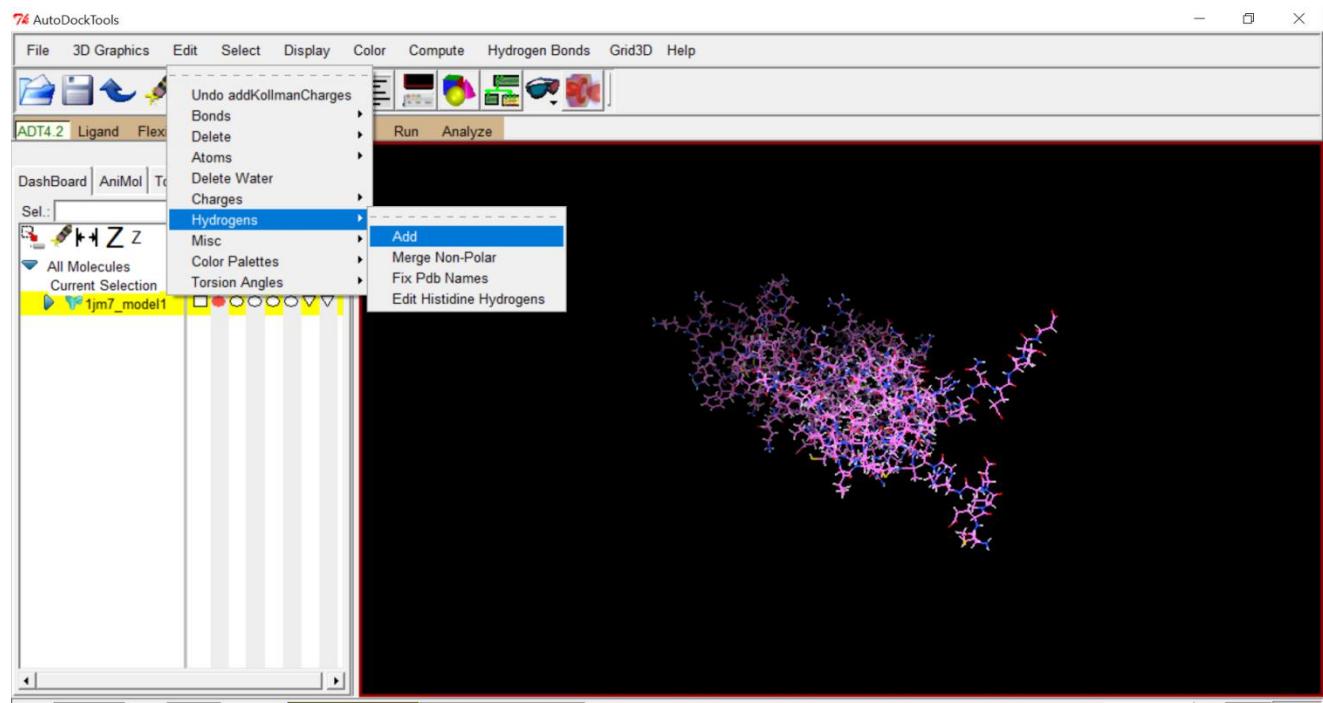
Autodock analysis

1- open ADT:

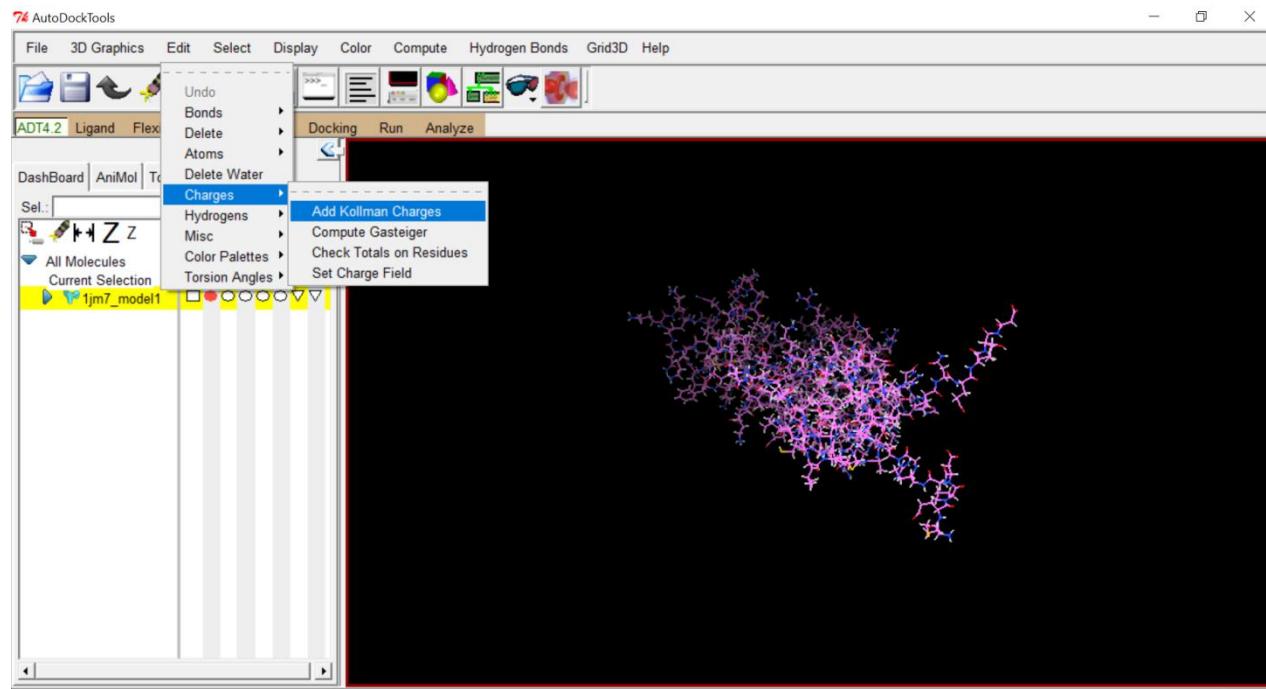
File > Read Molecule> Select Protein File (“.pdb” file)



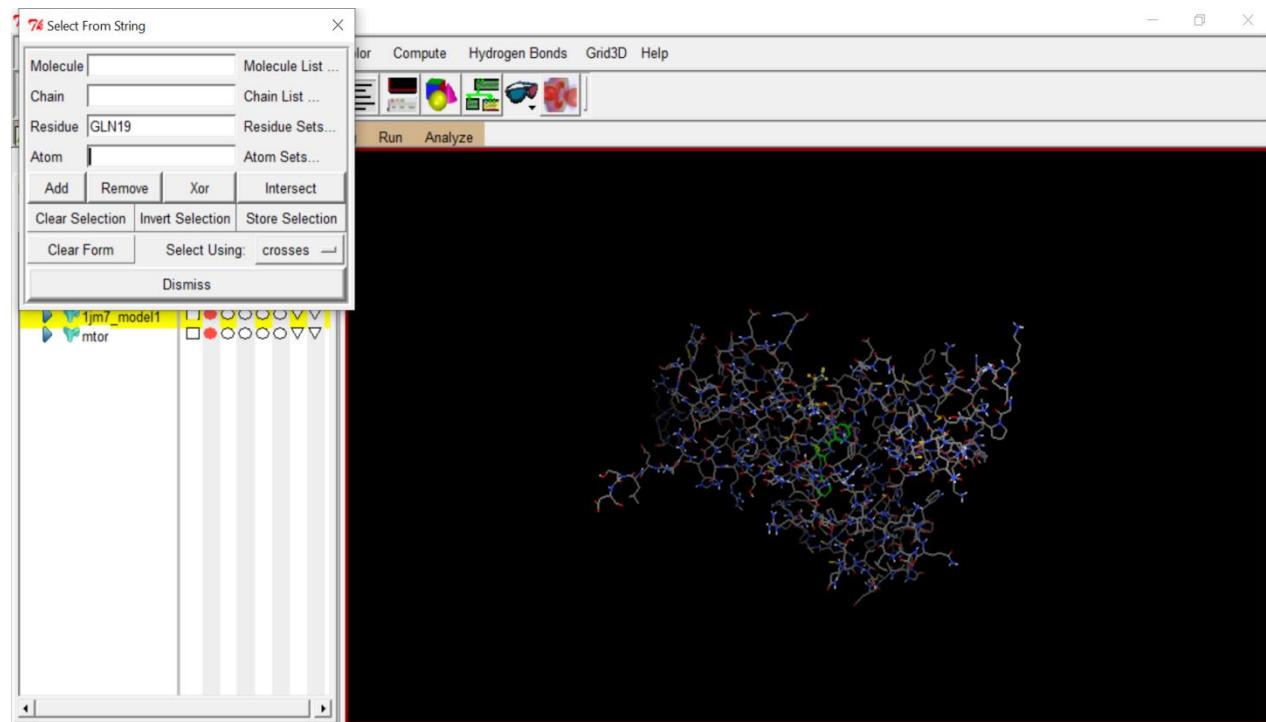
2- Edit > Hydrogens >Add>>>>> Polar Only >OK



3- Edit > Charges > Add Kolman Charges> Ok



4- Edit > Select > Select from string > select HETATOM



5- Prepare the ligand in pdbqt formate in OPENBABEL

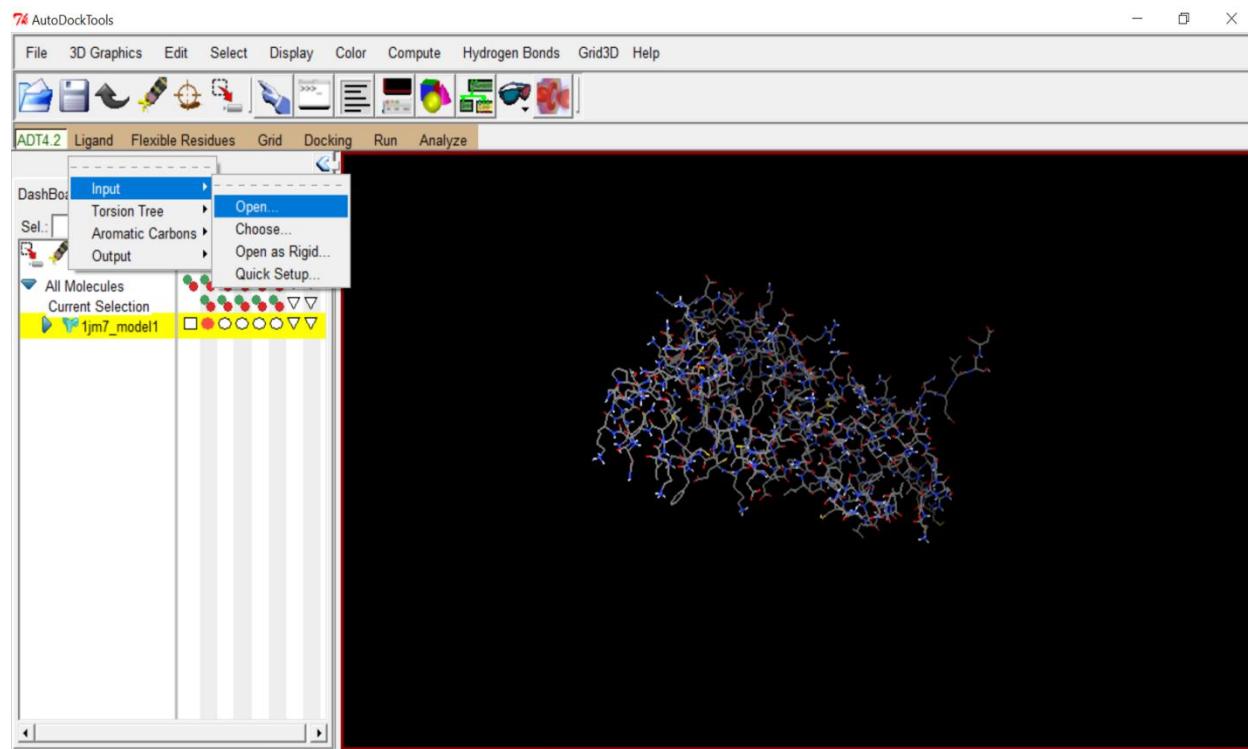
The screenshot shows the OpenBabelGUI interface. On the left, the "INPUT FORMAT" section shows a file named "59239114.sdf" in MDL MOL format. The "CONVERT" button is highlighted in blue. On the right, the "OUTPUT FORMAT" section shows the converted file in AutoDock PDQT format, with the output file path set to "D:\Saura\motor\motor.pdbqt". The output text includes REMARK sections and a detailed atom list.

```

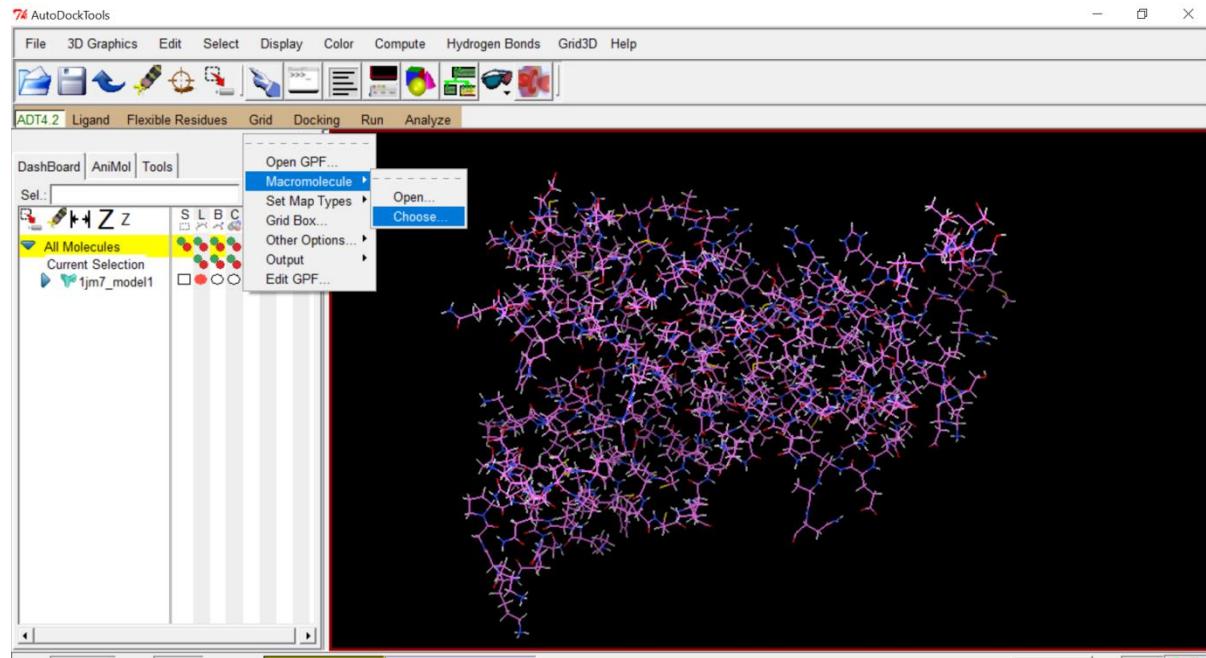
REMARK Name = 59239114
REMARK 5 active torsions:
REMARK status: ('A' for Active; 'I' for Inactive)
REMARK 1 A between atoms: N_9 and C_31
REMARK 2 A between atoms: N_10 and C_34
REMARK 3 A between atoms: C_11 and C_21
REMARK 4 A between atoms: C_22 and C_24
REMARK 5 A between atoms: C_34 and C_35
REMARK
REMARK x y z vdW Elec
REMARK q Type
REMARK
ROOT
ATOM 1 O UNL 1 -1.237 5.778 0.766
0.00 0.00 -0.376 OA
ATOM 2 C UNL 1 -2.098 4.898 1.486
0.00 0.00 +0.179 C
ATOM 3 C UNL 1 -1.529 3.489 1.466
0.00 0.00 +0.135 C
ATOM 4 N UNL 1 -1.304 3.051 0.079
0.00 0.00 -0.308 N
ATOM 5 C UNL 1 -1.052 1.673 -0.014
0.00 0.00 +0.129 A
ATOM 6 C UNL 1 -2.115 0.806 -0.185
0.00 0.00 +0.017 A
ATOM 7 C UNL 1 -1.798 -0.539 -0.298
0.00 0.00 +0.067 A
ATOM 8 C UNL 1 -2.885 -1.547 -0.577
0.00 0.00 -0.225 C

```

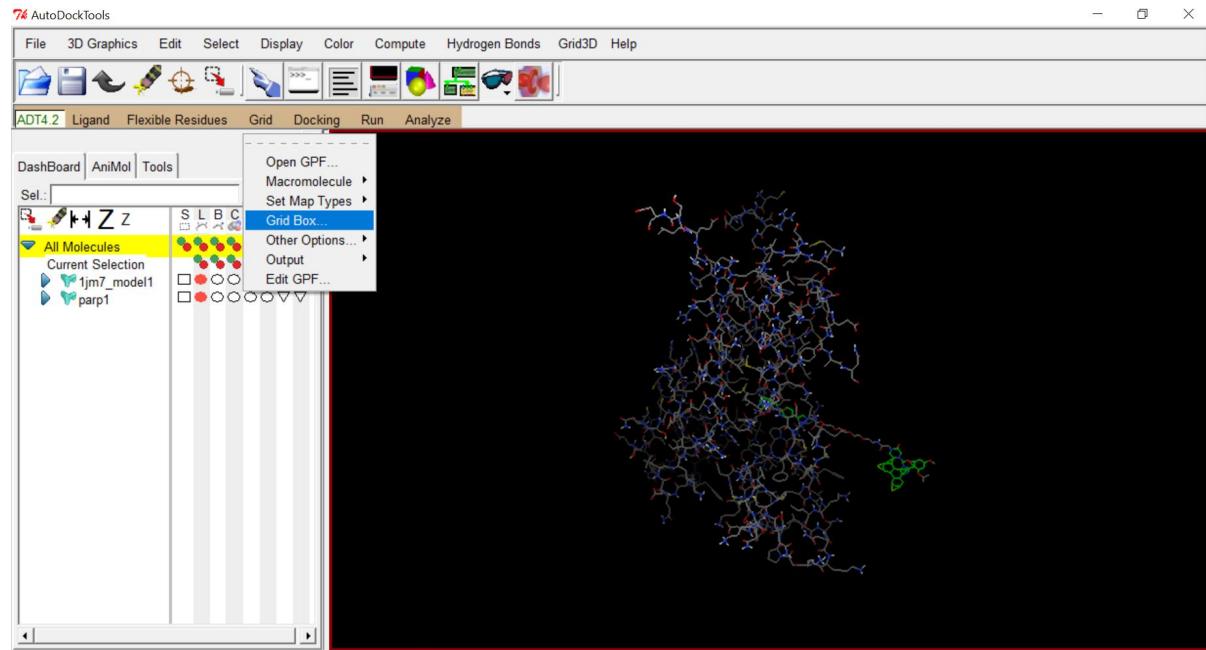
6- Add ligand to the protein Ligand > Input > Open> Select Ligand File (“.pdb” file) > OK



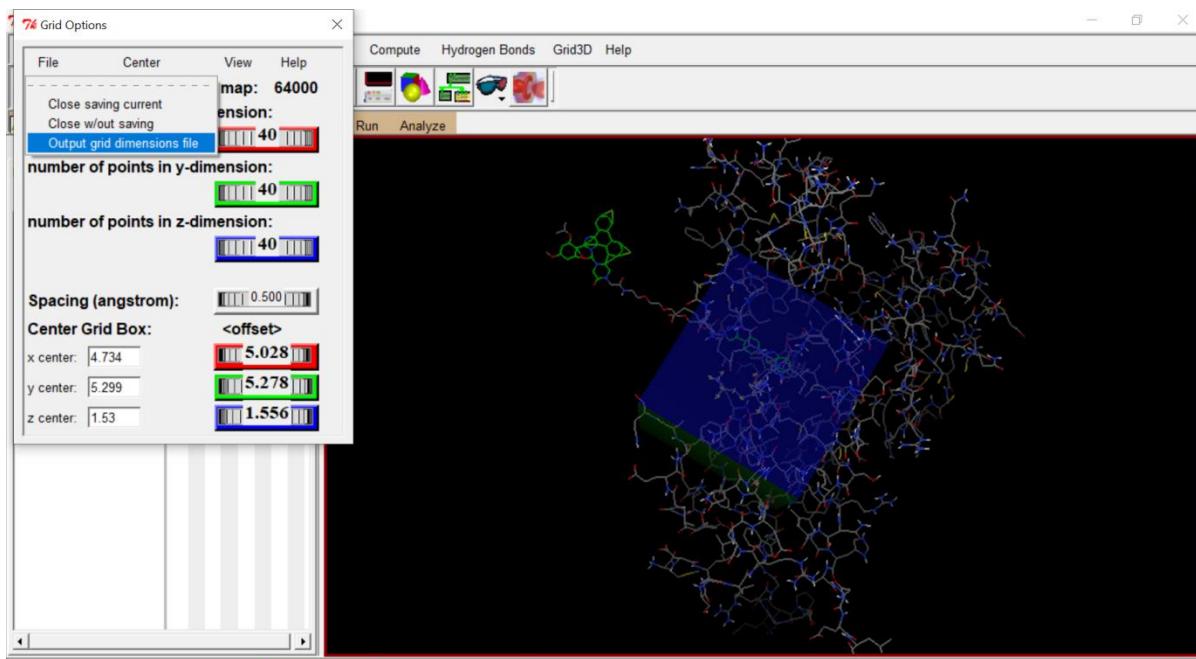
7- Now we go to run autogrid first, Grid > Macromole > Choose > Click (Protein) > Select Molecule > OK > save



8- Grid > GridBox> Set the BOX> File > Close Saving Current

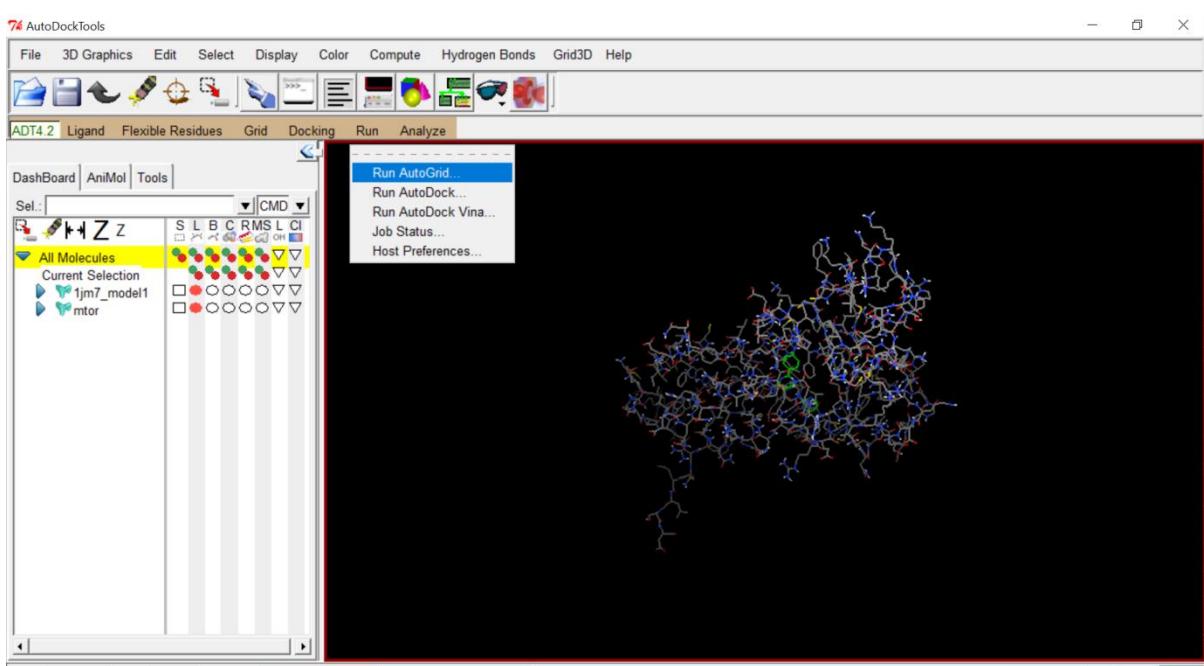


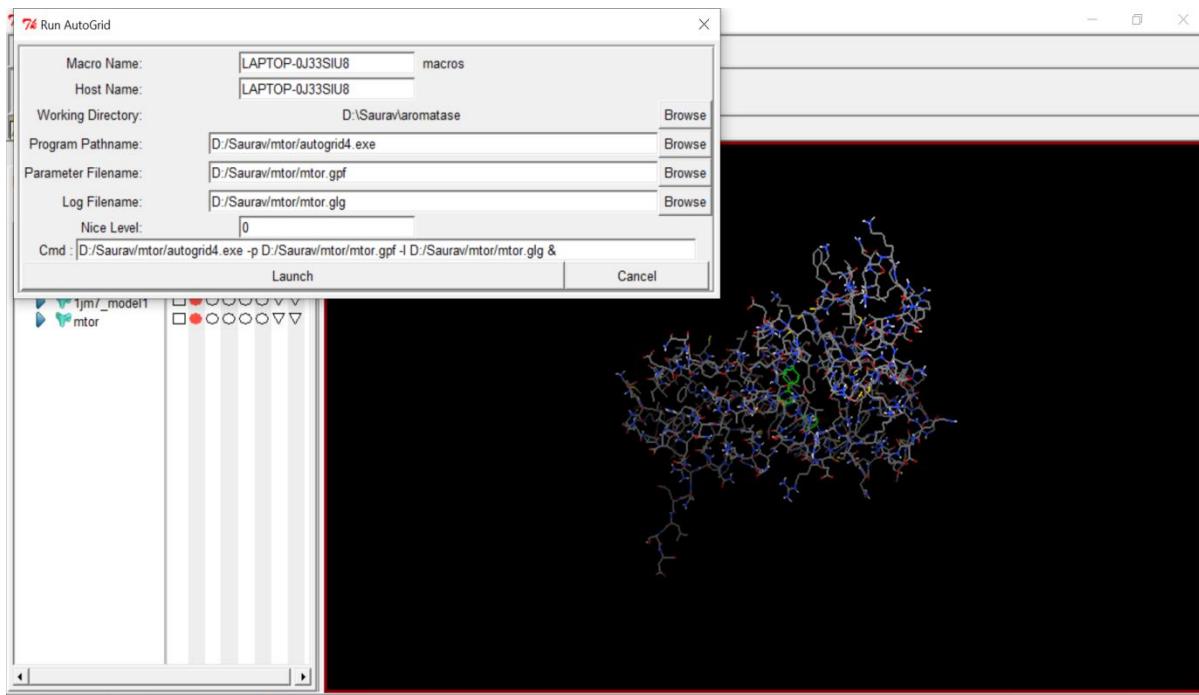
9- Grid > Output > Save GPF > grid.gpf > save



10- Run > Run AutoGrid:

- Select Program Pathname: 'autogrid4.exe' (i.e. C:\Program Files (x86)\The Scripps Research Institute\Autodock\4.2.6)
- Select Parameter Filename: 'grid.gpf' (you should select it based on your workfolder path)
- Launch!

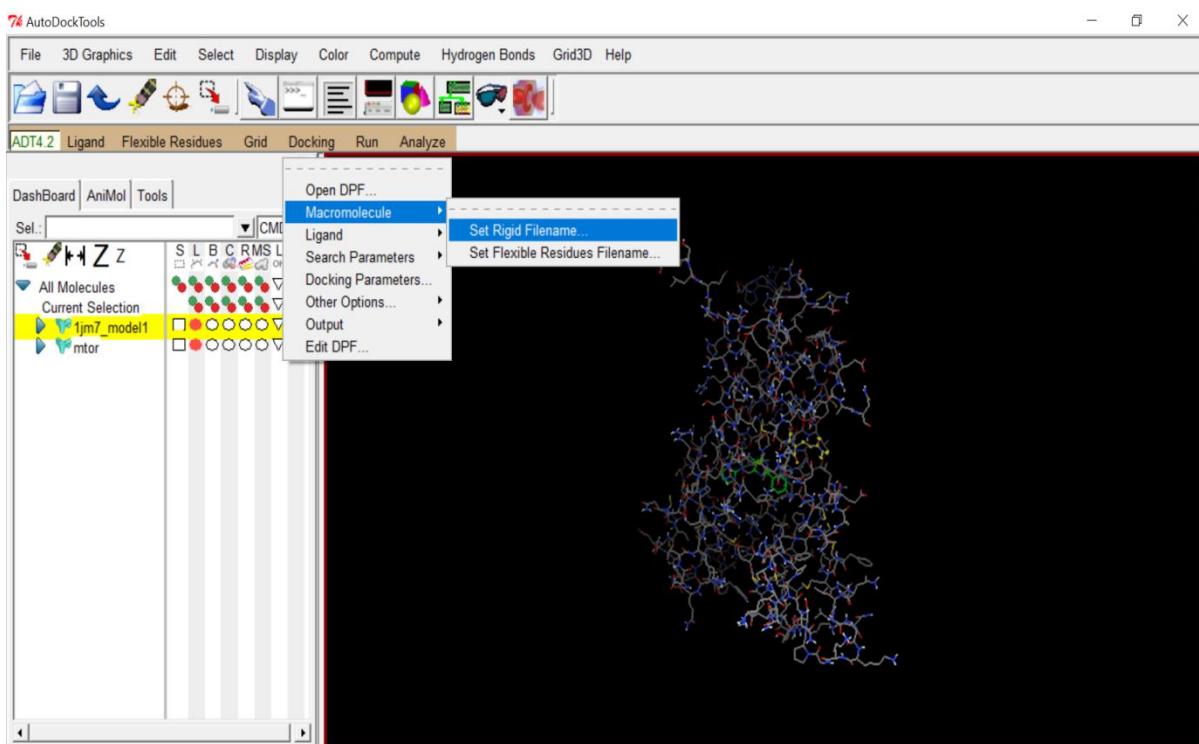




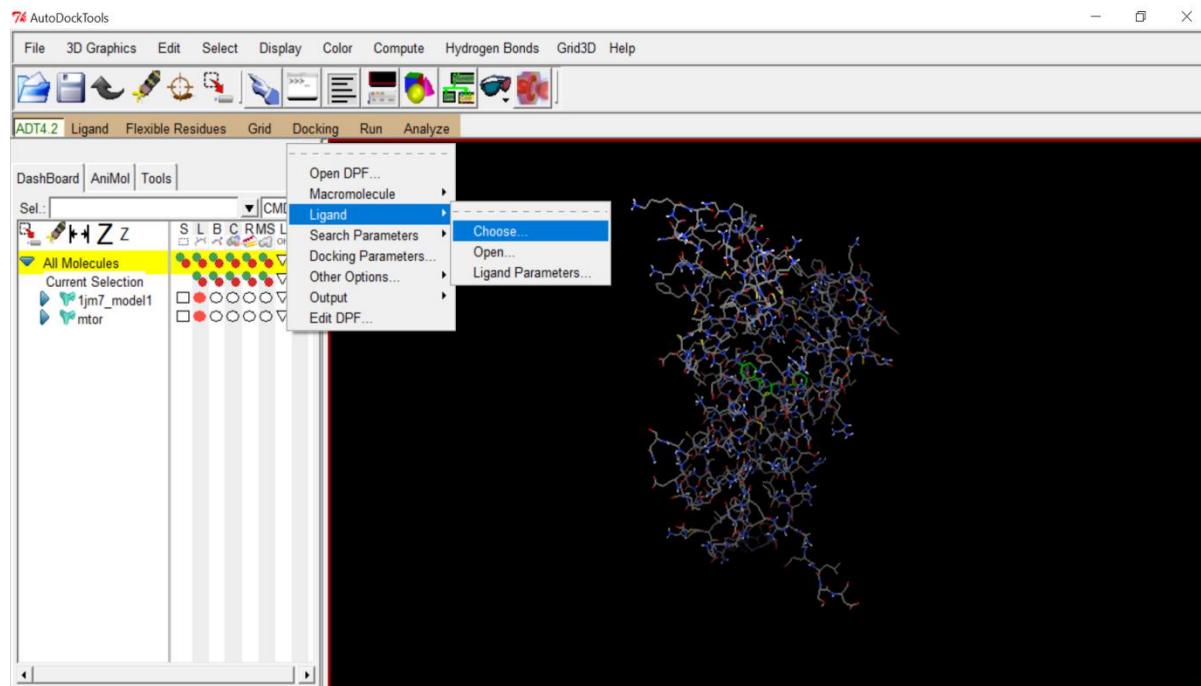
After having finished above steps following the below ways:

Run ADT:

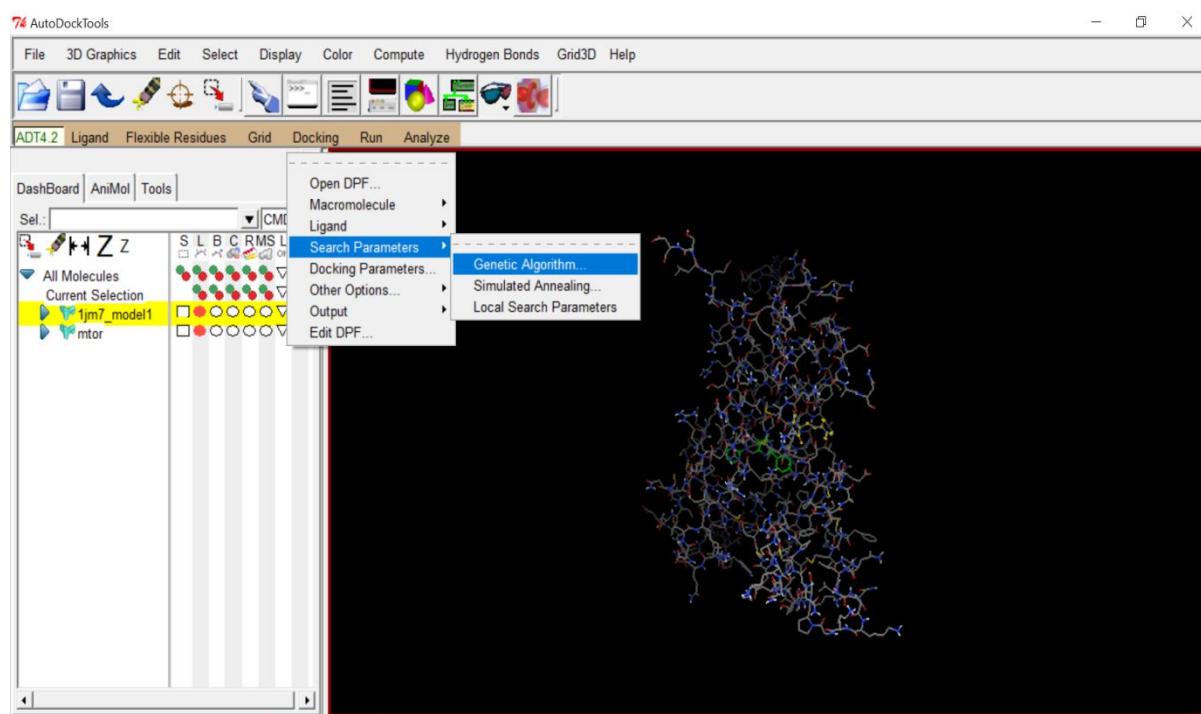
1- Docking > Macromolecule > Set Rigid filename > Select ‘Protein.pdbqt’ > Open



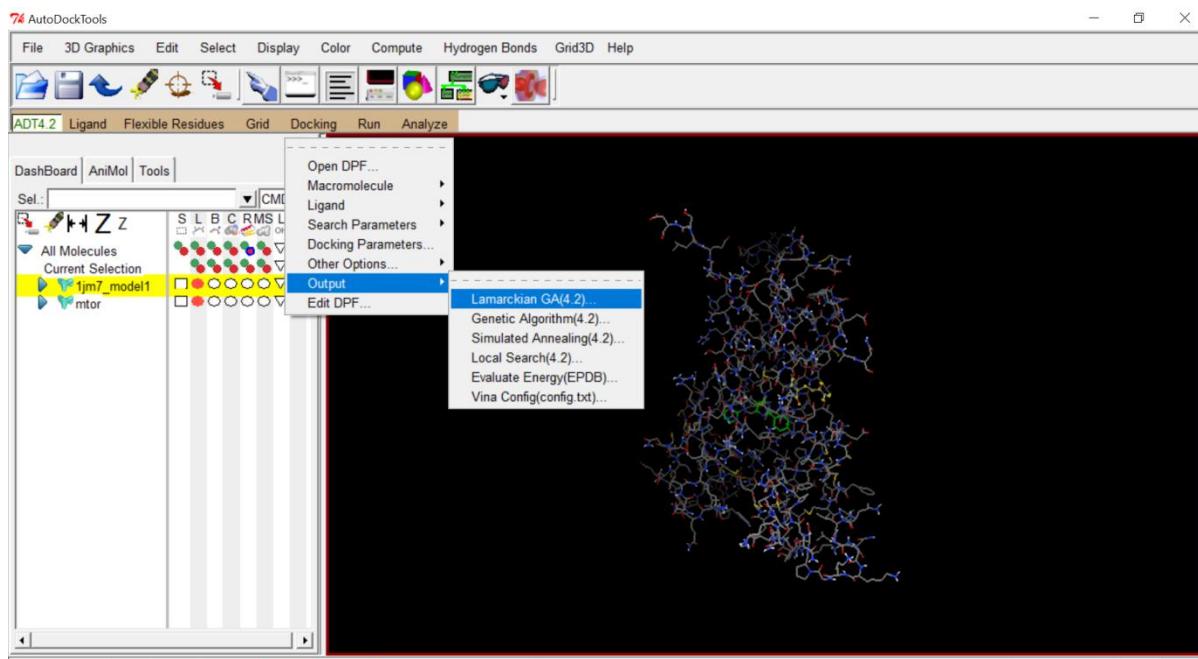
2- Docking > Ligand > Choose > Click ‘Ligand’ > Select Ligand > Accept



3- Docking > Search Parameters > Genetic Algorithm > Accept

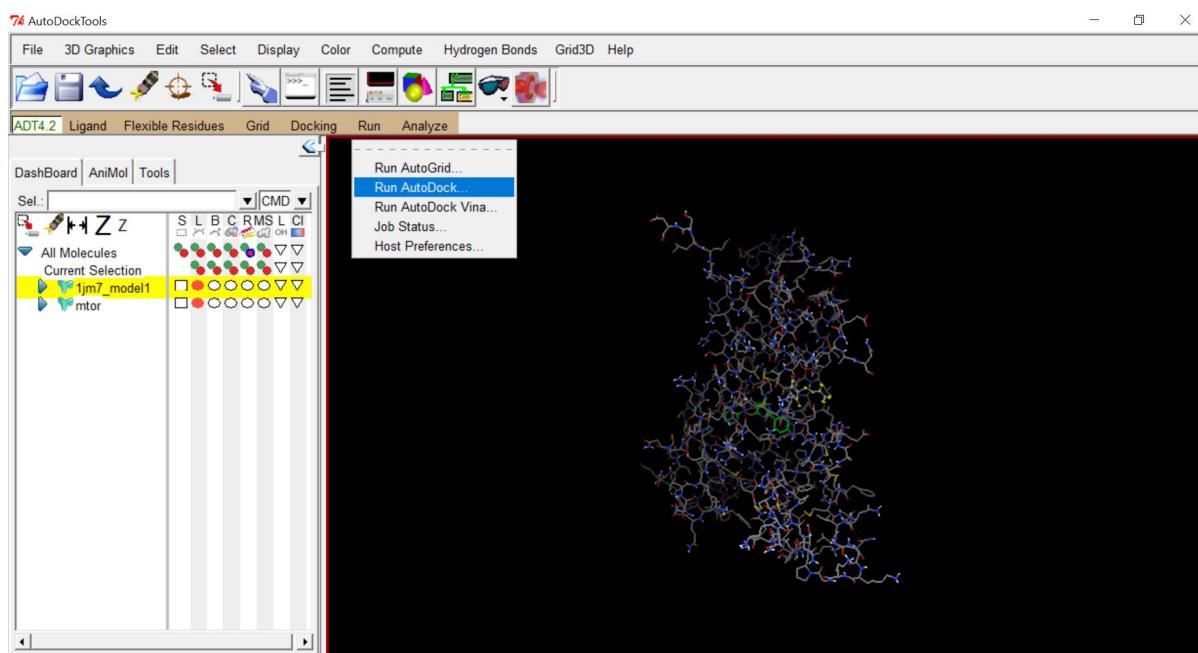


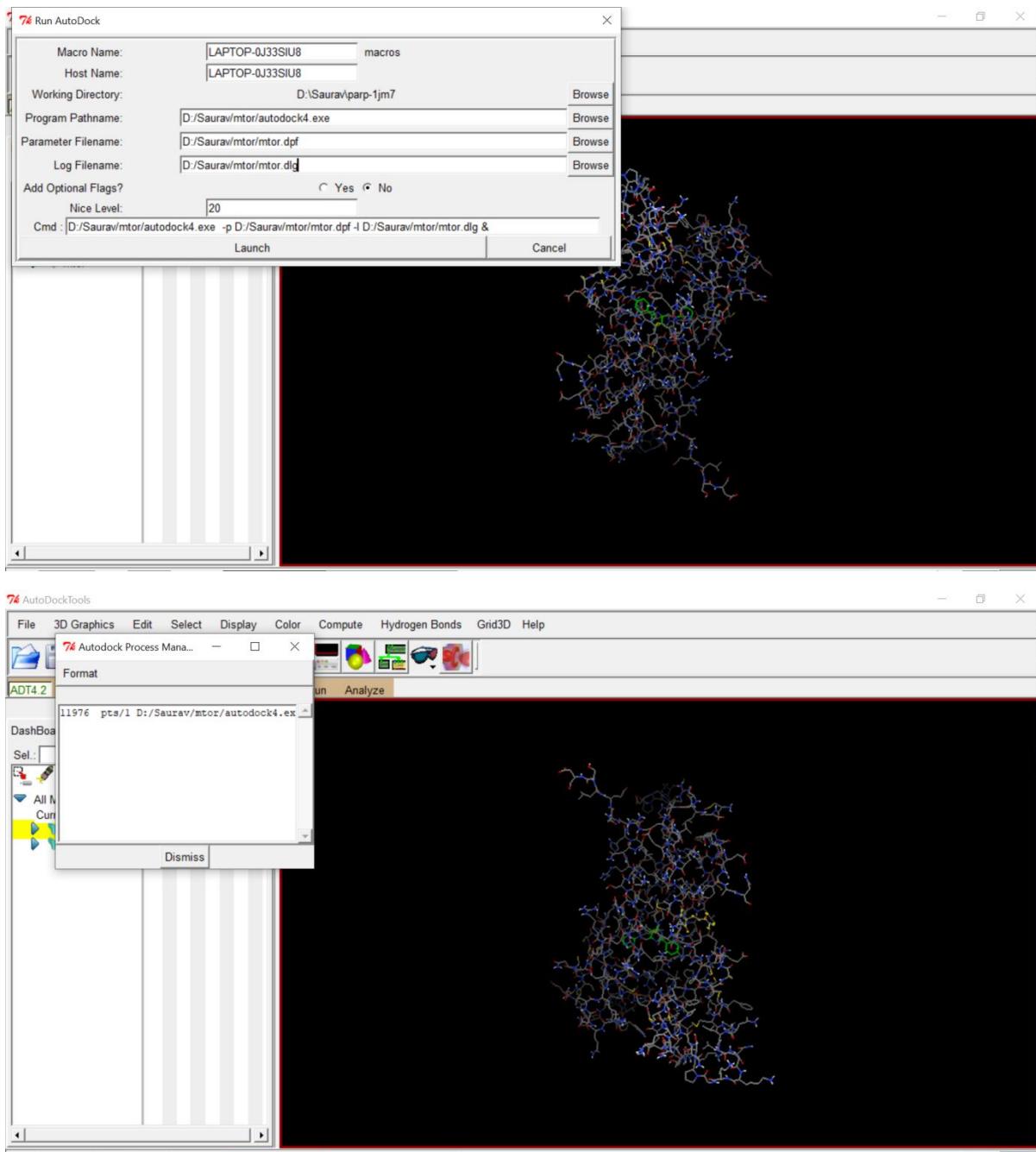
4- Docking > Output > Lamarckian GA> Save file as ‘dock.dpf’



5- Run > Run AutoDock

- Select Program Pathname: ‘autodock4.exe’ (C:\Program Files (x86)\The Scripps Research Institute\Autodock\4.2.6)
- Select Parameter Filename: ‘dock.dpf’ (Based on you workfolder path)
- Launch!





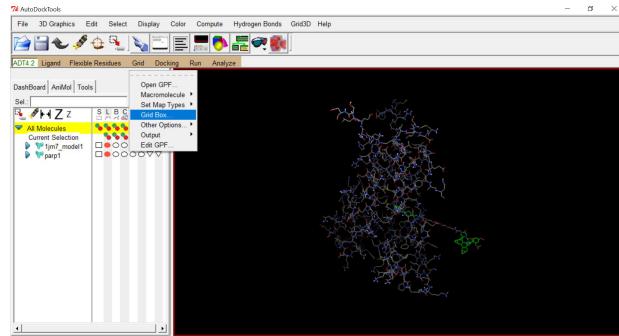
Please wait for finishing and don't dismiss it!!

Docking result analysis:

Go to the workspace in which files are saving and there you found files.dlg which contain lots of binding energy information there you search for binding result and this table will give you the exact docking energy.

Result of autodock

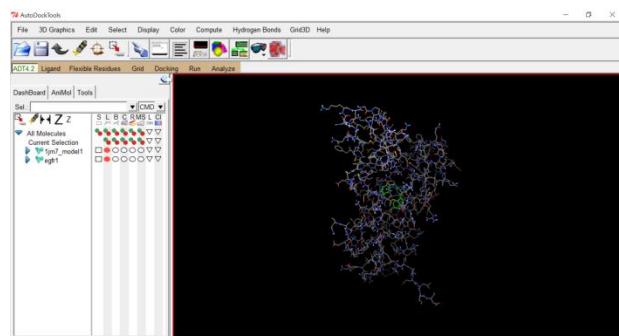
1 PARP1



Binding score

Rank	Sub-Rank	Run	Binding Energy	Cluster RMSD	Reference RMSD	Grep Pattern
1	1	1	-3.70	0.00	14.19	RANKING
1	2	7	-3.61	0.21	14.18	RANKING
2	1	9	-3.54	0.00	11.68	RANKING
2	2	3	-3.54	0.07	11.70	RANKING
2	3	2	-3.54	0.01	11.68	RANKING
2	4	10	-3.53	0.09	11.70	RANKING
2	5	5	-3.53	0.04	11.68	RANKING
2	6	4	-3.50	0.17	11.65	RANKING
3	1	8	-3.41	0.00	13.15	RANKING
3	2	6	-3.41	0.16	13.12	RANKING

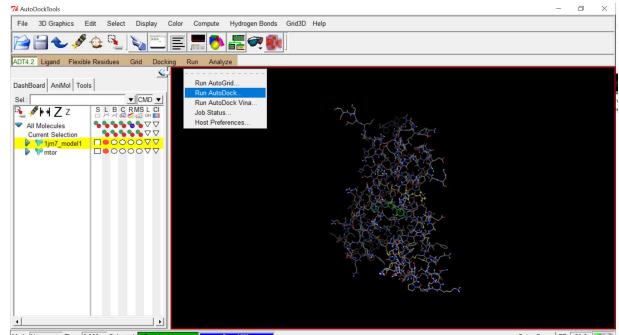
2 Tyrosine kinase Inhibitor (egfr)



Binding score

Rank	Sub-Rank	Run	Binding Energy	Cluster RMSD	Reference RMSD	Grep Pattern
1	1	2	-3.48	0.00	14.47	RANKING
2	1	6	-3.08	0.00	14.69	RANKING
3	1	8	-3.03	0.00	13.66	RANKING
4	1	7	-2.82	0.00	12.85	RANKING
5	1	4	-2.55	0.00	14.06	RANKING
6	1	9	-2.49	0.00	13.55	RANKING
7	1	3	-2.12	0.00	14.05	RANKING
7	2	10	-1.83	1.65	13.80	RANKING
8	1	1	-2.03	0.00	14.54	RANKING
9	1	5	-1.47	0.00	15.14	RANKING

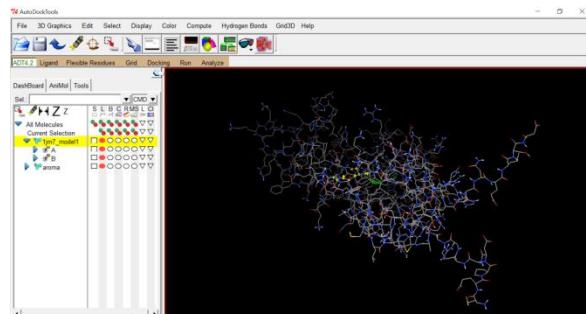
3 mtor



Binding energy

Rank	Sub-Rank	Run	Binding Energy	Cluster RMSD	Reference RMSD	Grep Pattern
1	1	1	-0.70	0.00	14.19	RANKING
1	2	7	-0.61	0.21	14.18	RANKING
2	1	9	-0.54	0.00	11.68	RANKING
2	2	3	-0.54	0.07	11.70	RANKING
2	3	2	-0.54	0.01	11.68	RANKING
2	4	10	-0.53	0.09	11.70	RANKING
2	5	5	-0.53	0.04	11.68	RANKING
2	6	4	-0.50	0.17	11.65	RANKING
3	1	8	-0.41	0.00	13.15	RANKING
3	2	6	-0.41	0.16	13.12	RANKING

4 Aromatase



Binding energy

Rank	Sub-Rank	Run	Binding Energy	Cluster RMSD	Reference RMSD	Grep Pattern
1	1	10	-5.74	0.00	12.86	RANKING
1	2	6	-5.69	0.40	12.86	RANKING
2	1	9	-5.62	0.00	13.71	RANKING
2	2	5	-5.40	1.89	14.08	RANKING
2	3	1	-5.28	0.42	13.89	RANKING
2	4	8	-5.11	1.98	14.12	RANKING
3	1	3	-5.22	0.00	14.09	RANKING
3	2	4	-5.07	0.94	14.31	RANKING
4	1	7	-5.13	0.00	14.58	RANKING
4	2	2	-4.89	1.29	14.23	RANKING

Scoring of inhibitor

Docked compound	SCORE	RMSD l.b.	RMSD u.b
1JM7-PARP	-3.7	0	14.19
1JM7-EGFR	-3.48	0	14.47
1JM7-MTOR	-0.70	0	14.19
1JM7-AROMATASE	-5.74	0	12.86

Conclusion:

Printed above is telling you the pose SCORE, the energy (the more negative the value, the better the interaction, which is assumed to be the dG), and then, RMSD's they only tell you the structural difference between your first pose and the following poses when compared to the best one.

HENCE, by performing the docking of inhibitors with same protein to two different dock tool one can predict the most suitable drug for a disease and here AROMATASE is the most suitable inhibitor for breast cancer.

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