*Biomedical & Pharmacology Journal*, June 2024. Vol. **17**(2), p. 965-997

# The Binding Capacity of the Lead Phytochemical Molecule to Cancer Cell Target Proteins and its Potential Anticancer Properties with Respect to Standard Drugs

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https://dx.doi.org/10.13005/bpj/2916

(Received: 05 September 2022; accepted: 10 April 2023)

**Molecular docking is an important tool for connecting molecular biological structure to computer-aided drug design. The purpose of this blind docking experiment is to compare the binding energies of these three drugs and to predict the most likely binding poses of a ligand with a known three dimensional structure of a protein. To substantiate our previous *in vitro* study findings, an *in silico* model was chosen to compare the binding properties of the three drugs. The work is entirely bioinformatics in nature. Blind docking was accomplished with the help of free software/(s). A comparison was made among the three drgus, used primarily in cancer treatment, namely, anastrazole, capecitabine and quercetin. In our *in vitro* study, these three drugs were extremely effective. CB-Dock2 to blind dock, SwissTargetPrediction to choose the targets, PubChem and Protein Data Base to obtain 3D structures of ligand and target respectively were used. Absorption, Distribution, Metabolism, and Excretion (ADME) from SwissADME, drug likeness from MolSoft L.L.C. software, and Liponski's rule was used to check the "Rule of five (RO5)". The crystallographic structures have resolution values ranging from 1 Å to 3 Å. Lipinski's rule of five, Swiss ADME and drug likeness were used to compare the three drugs. For all of the targets studied, quecetin appeared to have the highest AutoDock vina scores. To summarize the current findings and publicly available data, quercetin is chemoprotective and radioprotective to healthy/ normal cells and it can be used during cancer treatment.**

**Keywords:** Blind docking, Anastrozole, Capecitabine, Querecetin, breast cancer, protein data bank, CB-Dock2, Pubchem.

The most commonly discussed cancer is breast cancer (BC). The current treatment has a short-term effect of slowing tumor development. Patients frequently experience relapses the disease[1]. Cell proliferation and apoptotic pathways fail during this process and cancer takes over. BC is slowed by eating nutritious foods and staying physically fit. Foods high in saturated fat, processed meat and so on raise circulating levels of endogenous estrogens, pro-inflammatory cytokines, and growth factors. These in turn contribute to the development of breast cancer[2]. Natural fruits and vegetables are high in antioxidants and thus protect against the development of BC. Regular consumption of fresh fruits and vegetable, triglycerides, soy products and limited consumption of red wine and carbohydrates raises polyphenol and fibre levels and provides tumorigenesis resistance[3].

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*In silico*/docking approach has been shown to improve the drug discovery process by using free online software (s) in less time as well as understanding and estimating the toxicity and efficiency of the small molecules or drugs[4]. The two of the qualities directly linked to the primary structure are selectivity and affinity. Protein (target) and ligand (drug) interaction will have to overcome difficulties such as toxicity because of non-specific protein binding and insufficient efficacy because of low affinity[5].

Quercetin: The human diet is high in flavonoids which have promising therapeutic properties for a variety of illnesses, including cancer. The flavonoid quercetin has been extensively researched and is found in major amounts in commonly used plants such as *Allium cepa, Brassica, Allium sativum,* spinach and others. According to research, quercetin works well on malaria, inflammations, Alzheimer's, obesity, and breast cancer on par with standard drugs[6]. Based on research findings, quercetin inhibits BC by preventing signal transduction, encouraging cancer cell apoptosis and suppressing cancer cell proliferation and metastasis[7].

Anastrozole: Aromatase inhibitors of type II are non-steroids and anastrozole is a type II potent aromatase inhibitor. Anastrozole binds to the heme ion of aromatase in a reversible manner, lowers the levels of estrone (E1), 17-beta-estradiol (E2) and estrone sulphate (E1S). Aromatase inhibitors are the endocrine therapy of choice for treating breast cancer, particularly in postmenopausal women. Anastrozole is the first-line treatment choice for metastatic situations and postmenopausal women with oestrogen receptor-positive BC[8].

Capecitabine: Synonym Xeloda, is a fluoropyrimidine deoxynucleoside carbamate antimetabolic drug. In *in-vivo* conditions, thymidine phosphorylase (dThdPase) converts this drug to 5-fluorouracil (5-FU). It is far more effective as an adjuvant treatment in metastasis and in advanced BC, also referred to as a rescue drug. It can be effective when combined with other medications[9].

The benefits of combination therapy include improved or maintained efficiency, dose and toxicity reduction; and a delay in the development of drug resistance. In our previous study[10], we established that a very low dose of quercetin (16 g/ml) inhibited cell growth, while increasing cell death, arresting cell cycle, inducing mitochondrial depolarization, and expressing caspase in combination with anastrozole and capecitabine. The current study backs up these findings by docking various BC proteins with the three drugs and comparing their efficacy in binding to the targets. Anti-apoptotic proteins, hydrolases, isomerases, oxidoreductases, transcription factors, binding proteins, signaling proteins, and transferases are all included in this category.

## MATERIAL AND METHODS

CB-Dock2 was used to dock the drugs (anastrozole, capecitabine, and quercetin) with the target proteins. Each target protein was docked separately on each of the three ligands. A total 117 proteins were docked. The selected target molecules majorly belong to oxidoreductases/ oxidoreductase inhibitors, hydrolases/hydrolase inhibitors, isomerases, kinase/kinase inhibitors, transferase/transferase inhibitors, hormone, and cell cycle transcription factors, growth factor receptors, apoptosis regulators, and signaling proteins. Small molecules' interaction with targets enables biological functions, interpretation, prediction and drug development process. Blind docking aids in determining the precise binding sides of proteins and predicts the bind poses of any given molecule.

**SwissADME**

*In silico* methods predict Absorption, Distribution, Metabolism, and Excretion (ADME) parameters based on available molecular structure. The SwissADME web tool, which is simple to use, assisted in predicting the physicochemical functions, medicinal chemistry, water solubility, drug-likeness, lipophilicity, and pharmacokinetics. To obtain all these mentioned parameters, the smiles from PubChem for anastrozole, capecitabine, and quercetin were copied and submitted on the SwissADME page. Following completion, the "BOILED-Egg" button was pressed to record the key parameters of gastrointestinal absorption and blood-brain barrier (BBB)[11].

**Drug likeness**

Drug likeness provides a balance between molecule properties and structure, determines the likelihood of a small molecule becoming an oral drug, and identifies the similarities to known drugs.

This tool provides molecular formula, number of (hydrogen) bond donors and acceptors (HBA and HBD), logP, logS, pKA value, molecular weight, BBB, and likeness score after entering the smiles. The higher the probability, the higher the score value of an active drug. The water partition coefficient predicts an oral drug's water solubility. High potency at the biological target is a required quality in drug candidate potency. It summarizes the ligand and lipophilic efficiencies. The number of (hydrogen) bonds versus side chains (alkyl) of a molecule is used to calculate solubility factor. Slower absorption and action result from lower solubility. Too many hydrogen bonds result in low-fat solubility and a failure to penetrate the cell membrane and act inside the cell. The LogP value should be between 0.4 and 5.6, the molecular weight should be from 160 to 480/ mol, and the molar refractivity should be from 40 to 130 with 20 to 70 atoms. The drug molecules' molecular properties and drug likeness were provided by MolSoft L.L.C. software[12].

**Lipinski's rule**

The "Rule of five (RO5)" or "Lipinski's rule" determines whether a predicted molecule adheres to five rules: molecular weight (<500 g/mol), hydrophobicity (Log *P* <5), HBA (no. <10), HBD (no. <5), Polar Surface Area (PSA) (d"140 AÚ) and rotatable bonds (< 10Rot B). It determines the chemical's oral bioavailability as well as its chemical and physical properties. A molecule is predicted to be a drug if it meets at least three of the five rules, and a non-oral drug if it violates more than two rules[13].

**SwissTargetPrediction (STP)**

This tool predicts innate small protein molecule targets. Humans provide the default prediction. STP works by providing smile input or by drawing the 2D structure protein probe molecules from PubChem (both synchronise automatically)[14, 15].

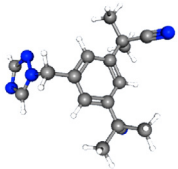
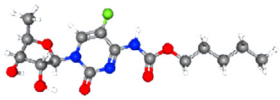
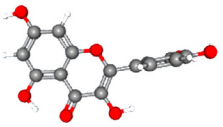
**Ligand and protein selection**

PubChem provided the 3 dimensional (3D) drug structures and isomeric smiles for anastrozole, capecitabine, and quercetin[16-19] and the RCSB protein databank (RCSB PDB) provided the protein targets[20].

**Docking study**

CB-Dock2 was used in this study to detect protein surface curvature (CurPocket) and guide molecular docking by Auto Dock Vina (1.1.2 version). CB-Dock2 has many

**Table 1.** The 3 dimensional structure, molecular weight, formula and canonical smiles of the selected drug

| Name | PubChem id | MW (g/ mol) | Chemical formula | Structure | Smiles |
|---|---|---|---|---|---|
| Anastrozole | 2187 | 293.37 | $C_{17}H_{19}N_5$ |  Anastrozole | CC(C)(C#N)C1=CC (=CC(=C1)CN2C= NC=N2)C(C)(C)C#N |
| Capecitabine | 60953 | 359.35 | $C_{15}H_{22}FN_3O_6$ |  Capecitabine | CCCCCOC(=O) Nc1nc(=O)n(cc1F) [C@@H]1O[C@@H] ([C@H]([C@H]1O)O)C |
| Quercetin | 5280343 | 302.24 | $C_{15}H_{10}O_7$ |  Quercetin | OC1CC(O)C2C(C1) OC(C(C2=O)O)C1C CC(C(C1)O)O |

MW: Molecular Weight, g: gram, 3D: 3 dimensional

benefits over other docking methods[21] available. The four steps involved in quick protein-ligand blind docking are data input and processing; cavity detection, visualization and data analysis. CB-Dock2 examines the ligand for hydrogens, adds hydrogens and partial charges, generates the initial 3D confirmation, adds missing side chain atoms, adds hydrogen atoms, examines the missing residues, and removes the co-crystallized water and hetero groups.

## RESULTS AND DISCUSSION

A library of targets has been collected from the literature search and structures were retrieved from RCSB. The blind docking method is a model that can be preferred for understanding the relation between drug and target at atom level. It describes the ability of a drug or small molecule to bind to a target protein. It is a two-step process that aids in predicting ligand confirmation, position, orientation (pose), and affinity assessment.

The current study focuses on drug molecule interactions with target proteins in BCs. *in vitro* compared the efficiency of purified quercetin from radish leaves and dill weed leaves with anastrozole and capecitabine. Our findings indicated that quercetin, in conjuction with anastrozole and capecitabine, could reduce the toxic burden at a low concentration (16 µg/ml)[10].

**Table 2.** Physicochemical properties of anastrozole, capecitabine and quercetin from SwissADME

| Property | Anastrozole | Capecitabine | Quercetin |
|---|---|---|---|
| Molecular weight (g/mol) | 293.37 | 359.35 g/mol | 302.24 g/mol |
| Fraction Csp3 | 0.41 | 0.67 | 0.00 |
| Number of rotatable bonds | 4 | 8 | 1 |
| Number of HBA | 4 | 8 | 7 |
| Number of HBD | 0 | 3 | 5 |
| TPSA | 78.29 Å | 122.91 Å | 131.36 Å |
| XLogP3 (lipophilicity) | 2.03 | 0.56 | 1.54 |
| Log S (ESOL) | -3.04 | -2.07 | -3.16 |
| GI absorption | High | High | High |
| BBB permeant | Yes | No | No |
| Lipinski | 0 violation | 0 violation | 0 violation |
| Synthetic accessibility | 2.21 | 4.67 | 3.23 |
| Lead-likeness | Yes | No | Yes |
| Bioavailability | 0.55 | 0.55 | 0.55 |

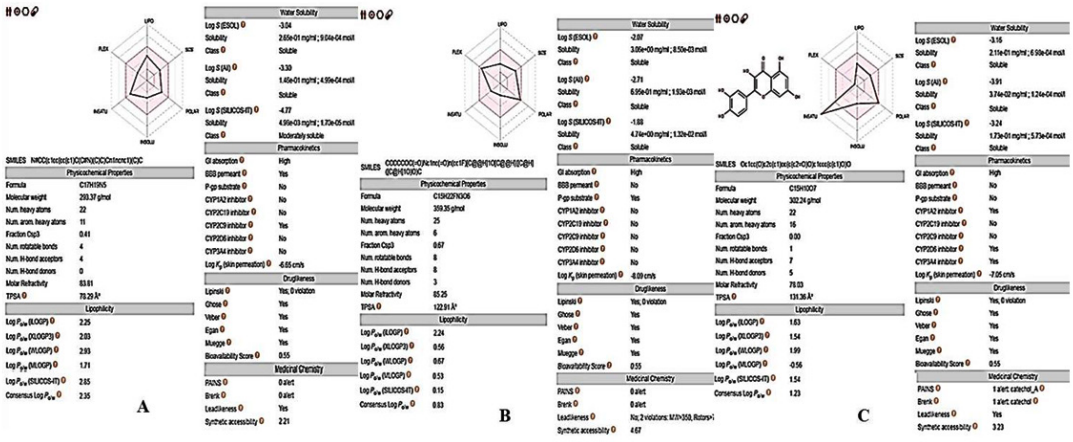



**Fig. 1.** The bioavailability radar from Swiss ADME is presented.
A: Anastrozole, B: Capecitabine, C: Quercetin

Docking experiments were conducted to determine which of the three drugs (anastrozole, capecitabine and quercetin) had the highest binding efficiency (Table 1). The protein targets were classified and docked against the three drug molecules using SwissTarget predictions and published literature.

Molecular weight <5 denotes the light weight of the molecules, that can pass through the target cell's membrane. Lower MW favours oral absorption, and higher molecules choose an alternate route namely through the membranes. The table shows the molecular weight of the selected compounds according to Lipinski's rule. The test compound's bioavailability radar revealed an immediate consideration of drug-likeness (Table 2 and Fig. 1). XlogP (between -0.7 and +5.0), MW (between 150 and 500 g/mol), polarity (TPSA: between 20 and 130 Å; a little higher for quercetin), solubility (Logs: <6), flexibility (rotatable bonds: <9) are the six major properties considered[22].

The "BOILED-Egg" graphical output predicts two important ADME parameters at the same time: passive gastrointestinal absorption and BBB[15]. While the area in the figure represents passive absorption by GI track (Capecitabine and

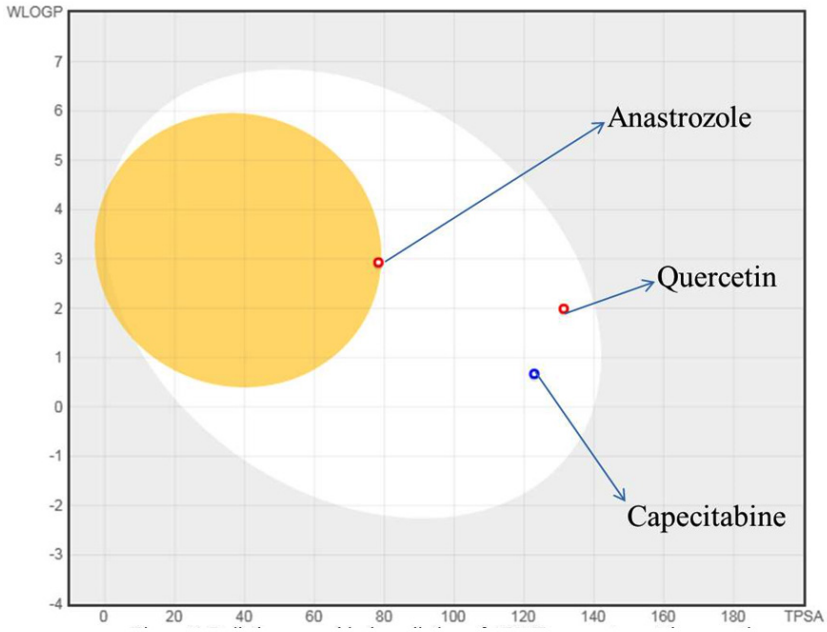



**Fig. 2.** Boiled egg graphical prediction of ADME parameters at the same time

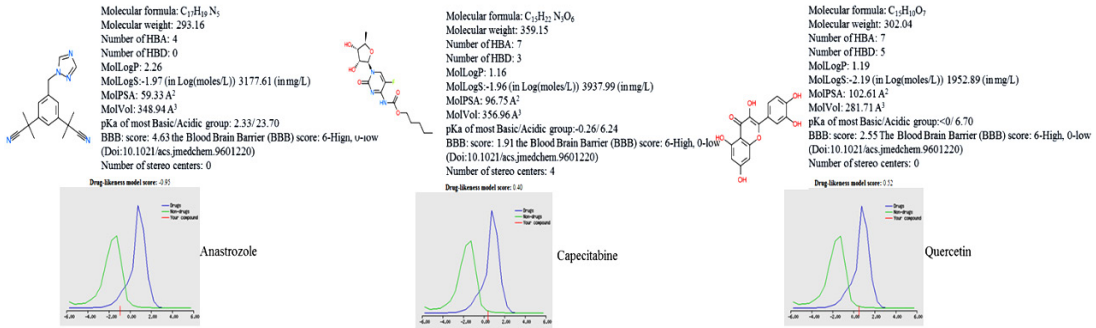



**Fig. 3.** Plotted drug likeness scores of Anastrazole, Capecitabine

Quercetin), the yolk region (Anastrozole) has higher probability of penetrating the brain (Fig. 2).

The molecular properties of Ana, Cap, and Que were predicted using MolSoft. The outcomes are predicted in (Fig. 3). Green and blue lines represent non-drug and drug-like behavior. Non-drug peaks are those with values between zero and negative. Based on their drug-likeness scores, among the three, Capecitabine (positive value of 0.40) and Quercetin (positive value of 0.52) were considered drug molecules, whereas Anastrozole appears to be a non-drug (-0.95).

To modify the action of macromolecule targets, drugs or bioactive molecules shall bind to them. The mapping of targeted bioactive small molecules is an important step in understanding the molecular actions behind their activity and forecasting cross reactivity or potential side effects.

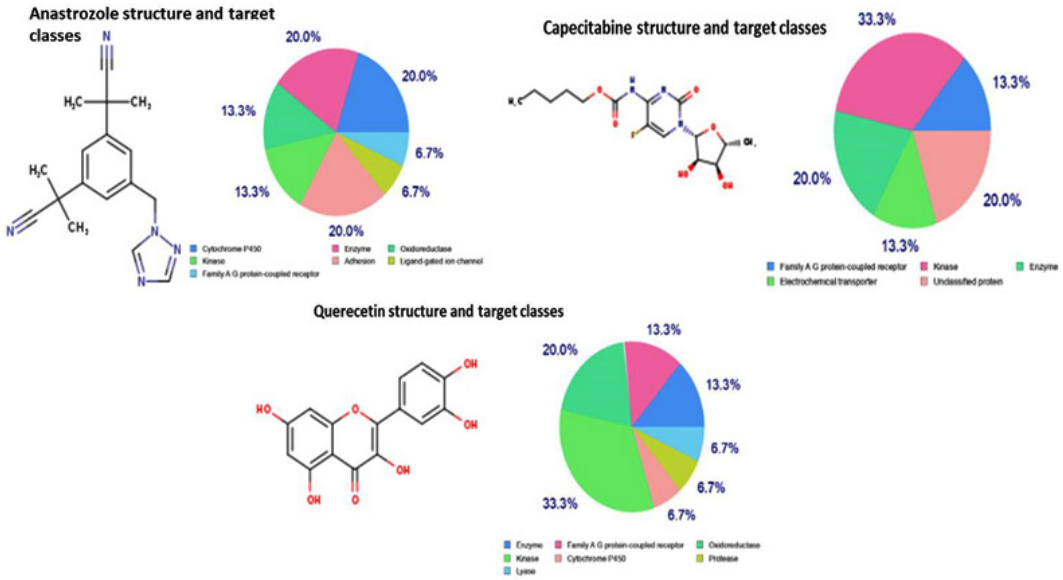



**Fig. 4.** Swiss Target Prediction of the three drugs and their classes in percentages

**Table 3.** Apoptosis target classes used in the present study

| No. | Protein molecule | RCSB id | Length | Resolution | Vina score of the drugs used |
|---|---|---|---|---|---|
| 1. | CASP8 and FADD-like apoptosis regulator | 3H13 | 272 | 2.20 Å | A:-6; C:-6.8; Q:-6.9 |
| 2. | Apoptosis regulator Bcl-X | 2YXJ | 181 | 2.20 Å | A:-7.4; C:-6.9; Q:-7.2 |
| 3. | Apoptosis regulator Bcl-2 | 2O2F | 138 | | A:-7.2; C:-6.9; Q:-7.1 |
| 4. | Apoptosis regulator Bcl-2, Bcl-2-like protein 1 chimera | 4IEH | 169 | 2.10 Å | A:-7.7; C:-6.8; Q:-7.2 |
| 5. | Apoptosis inhibitor survivin | 1E31 | 142 | 2.71 Å | A:-7.1; C:-7.5; Q:-7.5 |
| 6. | Apoptosis regulator Bcl-2 | 2W3L | 144 | 2.10 Å | A:-7.5; C:-7.7; Q:-7.4 |
| 7. | Apoptosis regulator Bcl-X | 2YXJ | 181 | 2.20 Å | A:-7.5; C:-6.9; Q:-7.1 |
| 8. | Mcl-1 | 3KZ0 | 158 | 2.35 Å | A:-7.1; C:-6.2; Q:-6.6 |
| 9. | Bcl-2-like protein 1 | 3ZLN | 181 | 2.29 Å | A:-9.1; C:-7.9; Q:-7.9 |
| 10. | Induced myeloid leukemia cell differentiation protein Mcl-1 | 5IEZ | 159 | 2.60 Å | A:-7.9; C:-7.7; Q:-8.5 |
| 11. | Apoptosis regulator Bcl-2 | 1GJH | 166 | | A:-6.2; C:-6.2; Q:-6.9 |

Å: Angstrom; CASP: Caspase; FADD: Fas-associated death domain; Bcl-X: B-cell lymphoma extra; Bcl 2: B-cell lymphoma 2; Mcl-1: Induced myeloid leukemia cell differentiation protein; A: Anatrozole, C: Capecitabine; Q; Quercetin

**Table 4.** Contact amino acids and varieties of bonds between the target and the ligand molecules belong to apoptotic proteins involved in breast cancer

| PDB | Contact residues, bond pattern and number of bonds | | |
|---|---|---|---|
| | Anastrazole | Capecitabine | Quercetin |
| 3H13 | SER318GLN319PRO332LEU333HIS334ARG337TRP403LEU405TRP466<br>Weak (2), hydrophobic (5) | GLY317SER318GLN319 LEU405CYS406THR407ASN447MET450TYR451ASN454TYR463TYR464VAL465TRP466<br>Weak (3), Hydrogen (8), Hydrophobic (5) | ASN262 TYR360SER411 LEU412LEU413GLN415SER416SER419PRO420SER421LEU42GLN425TYR449TRP453TYR463<br>Weak (3), Hydrogen (9), hydrophobic (9) |
| 2YXJ | THR344LYS345ASN346ASP348GLN351ASP354GLN307THR308TYR311ASP312GLU356ASP357TRP358PHE368LYS374LYS376 LYS379<br>Weak (1), hydrogen (1), hydrophobic, (15)pi-pi (1) | SER164 ARG165ALA168 ALA171THR172TYR120PHE123 GLU124VAL127ASN128 PHE131 ARG132<br>ASP133GLY134VAL135TRP169THR172TYR173ASP176HIS177<br>Weak (3), hydrogen (5), hydrophobic (14), ionic (2) | TYR120PHE123GLU124GLN125VAL127ASN128TRP169THR172TYR173ASP176HIS177PRO116GLY117TYR120ARG165TRP169<br>Hydrogen (3), hydrophobic (10), pi-pi (1) |
| 2O2F | PHE101TYR105ASP108PHE109MET112VAL130GLU133LEU134GLY142ARG143ALA146PHE147 PHE150<br>Hydrophobic (9) | PHE101ASP108PHE109MET112VAL130GLU133LEU134PHE135ARG136ASP137ARG143ALA146PHE147 PHE150<br>Hydrophobic (15), hydrogen (2), weak (1), ionic (1) | GLN96ALA97GLY98ASP100PHE101ARG104TYR105ASP108TRP141GLY142ARG143VAL145<br>Hydrophobic (7), pi-pi (1),weak (1), Hydrogen (2) |
| 4IEH | PHE63TYR67ASP70PHE71MET74VAL92GLU95LEU96GLY104ARG105ALA108PHE109GLU111PHE112VAL115<br>Pi-pi (1), weak (1), Hydrophobic (14) | ALA59ASP62 PHE63ARG66TYR67LEU96ASN102TRP103GLY104ARG105VAL107ALA108PHE157TYR161<br>Pi-pi (1), weak (1), hydrophobic (15), ionic (2) Hydrogen (2) | PHE63ASP70PHE71MET74VAL92GLU95LEU96PHE97ARG105ALA108PHE109GLU111PHE112VAL115<br>Pi-pi (1), weak (3), Hydrophobic (9),Hydrogen (2) |
| 1E31 | PHE13 LEU14LYS15 ARG18GLU40PHE58PHE86VAL89LYS91GLN92PHE93GLU94LEU96LEU104<br>Hydrogen (3),hydrophobic (5), pi-pi (2), ionic (1) | PHE13LEU14LYS15ASP16ARG18GLU40ILE74LYS78PHE86LEU87SER88VAL89LYS90LYS91GLN92PHE93<br>Hydrogen (7), hydrophobic (5), weak (1) | PRO12PHE13LEU14LYS15ARG18GLU40ILE74LYS78PHE86LEU87SER88VAL89LYS90LYS91GLN92PHE93LEU96<br>Hydrogen (7), hydrophobic (4), weak (3), ionic (1), pi-pi (1) |
| 2W3L | LYS22ARG26SER64ARG65ARG68PHE71SER75GLU111GLY114VAL115VAL18GLU119ASN122ASP62ARG66TYR67<br>Hydrogen (2), hydrophobic (6), weak (1), ionic (1), cation pi (1) | LYS22ARG26SER64PHE71SER75GLU111VAL115VAL118ALA59ASP62PHE63ARG66TYR67GLY104 VAL107TYR161<br>Hydrogen (7), hydrophobic (13), ionic (1) | LYS22ARG26ASP61SER64ARG65ARG68PHE71ALA72SER75VAL115VAL118GLU119ASN122ARG66<br>Hydrogen (7), hydrophobic (3), weak (3) |
| 3KZ0 | GLN189ALA190GLN221ARG222GLU225GLN229LEU232PHE273LYS276HIS277LYS279THR280<br>Hydrogen (5), hydrophobic (7), weak (1), ionic (1) | GLN189ALA190THR191LEU232PHE273LYS276HIS277LYS279THR280ASN282GLN283<br>Hydrogen (3), hydrophobic (8) weak (4) | ARG187THR191LYS279GLN283GLU284SER285CYS286ILE287GLU288ARG187ALA190THR191GLU240LYS279GLN283GLU284SER285CYS286ILE287<br>Hydrogen (11), hydrophobic (4), weak (7) |
| 3ZLN | PHE97ARG102PHE105SER106ASP107LEU108THR109GLU129LEU130ARG132GLY138ARG139ALA142SER145PHE146<br>Hydrogen (2), ionic (3), hydrophobic (11),pi-pi (1), weak (1) | LYS16LYS20PHE97GLU98ARG102ARG103PHE105SER106ASP107LEU108THR109LEU130ALA142SER145PHE146GLY148ALA149<br>Ionic (3), weak (4), hydrogen (6),hydrophobic (13),cation pi (1) | LYS20PHE97GLU98LEU99ARG102ARG103ASP107LEU108THR109LEU130ALA142PHE143SER145PHE146 ALA149<br>Ionic (2), cation (1),Hydrogen (8),hydrophobic (11), weak (1) |
| 5IEZ | HIS224ALA227PHE228MET231LEU235LEU246VAL249METT250VAL253PHE254ARG263THR266LEU267PHE270<br>Hydrogen (20, weak (1), hydrophobic (13) | ASN239GLU240ASN282GLN283GLU284SER285CYS286ChainB:GLU173ARG176GLN177LEU179GLU180SER183ARG184GLY200ARG201SER202GLU288<br>Hydrogen (7),hydrophobic (4), weak (5) | ASN239GLU240LYS279ASN282GLN283GLU284SER285ChainB:ASP172GLU173TYR175ARG176GLN177LEU179GLU180SER183ARG184GLY200ARG201SER202GLU288<br>Hydrophobic (3), weak (4), Hydrogen (7) |
| 1GJH | HIS3ALA4GLY5ARG6THR7GLY8TYR9HIS186GLN190GLY193GLY194TRP195ASP196ALA197<br>Hydrogen (2), cation pi (1), hydrophobic (7) | HIS3ALA4GLY5TYR9ASP10ASN11ASN182HIS186ILE189GLN190GLY193 GLY194TRP195<br>Pi-pi (1), hydrogen (6) hydrophobic (5) | HIS3ALA4GLY5GLY8TYR9ASP10ASN11HIS186ILE189GLN190GLY193GLY194TRP195ASP196ALA197<br>Hydrogen (3), pi-pi (1), hydrophobic (2) |

The targeted classes for the three drugs tested were provided by SwissTargetPrediction (Fig. 4). The choice of a protein for docking research is critical, particularly its resolution. A crystal structure contains either protein or nucleic acid. The obtained data from these crystals is the measure of resolution. Majorly, the crystallographic structures have resolution values between 1 Å and 3 Å.

**Apoptotic proteins as targets**

A few anit-apoptotic proteins will be targeted to gain insight into the drug's mode of action. With a few exceptions, anastrozole had higher vina scores than the other two with apoptotic proteins studied in the present work (Tables 3 and 4, Fig. 5).

Tumor cells escape, protect and develop drug resistance by avoiding receptor mediated apoptosis. C-FLIP (Cellular FLICE like inhibitory protein) is a key regulator protein in the extrinsic cell death pathway (FADD-like IL-1beta-converting enzyme inhibitory protein). Overexpression of c-FLIP protects the tumor cells. This is a capable caspase activation initiator and cell death inhibitor as well as an enhancer of procaspase-8 activation. Bcl-2 and Bcl-xL overexpression in cancer cells confers a survival benefit over standard chemotherapy (anti-apoptotic or pro-survival proteins). Survivin, a mitotic spindle fiber-associated protein, acts as an apoptosis activator. Myeloid cell Leukemia-1 is a Bcl-2 anti-apoptotic member. Anti-apoptotic protein over-expression promotes cell survival and proliferation. Targeting these proteins will aid in the development of new drugs and drug combinations[20].

**Hydrolases as targets**

The vina scores of quercetin seem to be the highest among the three drugs tested by docking for hydrolases (Tables 5, 6) (Fig. 6)[20]. DPP-4 is a cell surface protein that either suppresses or activates tumors. MMP-9 is essential in inflammatory and oncological disorders. ADAMTSs are members of extracellular zinc metalloproteinase family. Chemokine receptors are cell migration receptors linked to cancer metastasis. VEGF is a type of angiogenesis factor. Chemokine receptors regulate cell migration, cancer, immune responses, inflammation, and so on. Butyrylcholinesterase (BChE) and its genes are found in a variety of human cancers. Tumorigenesis, cell proliferation, and cell differentiation have all linked to it. DHS36 interacts with RNA and DNA G-quadruples to control transcription and post-transcriptional regulation. Cysteine protease relates to the mammalian interleukin-1 beta converting enzyme (ICE). Caspases, the cysteine proteases, are key role players in apoptosis and inflammation. MMP-

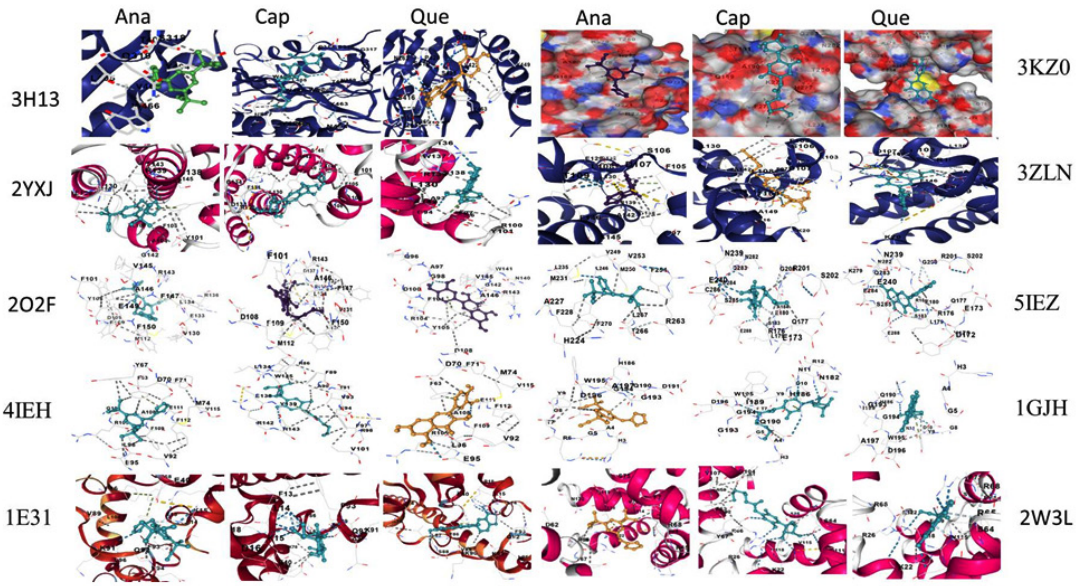



**Fig. 5.** Docking profile of protein and ligand binding of the apoptotic proteins studied. Ana: Anastrazole, Cap: Capecitabine and Que: Quercetin

9 is a protein that is participates in inflammation, wound healing, tumour growth and metastasis[20].

**Isomerases as targets**

The vina scores of quercetin were the highest of the three drugs tested (Tables 7, 8) (Fig. 7)[20]. Type IIA DNA topoisomerases are required for the maintenance of higher order DNA structure. The double standard DNA is covalently joined by human topoisomerase I. Type II topoisomerases (TOP2s) cleaves both the DNA duplex and cause cancer cell death. Kinase complexed mTOR is an important growth and proliferation regulator. DNA topoisomerases, particularly type IIA topoisomerases, have been identified as anti-bacterial and anti-cancer drug targets. Topoisomerase-targeting anticancer drugs work by poisoning topoisomerase, causing replication fork arrest and double-strand break formation[20].

**Oxidoreductases as targets**

The vina score of quercetin is the highest among the tested drugs against the goals of oxidoreductases (Tables 9, 10) (Fig. 8)[20]. Myeloperoxidase (MPO), a neutrophilic enzyme, promotes oxidative stress in a number of inflammatory pathologies. Catalysis of human cytochrome P450 aromatase enzyme results to form estrogens from androgens. Human Aldehyde dehydrogenase 1A3's expression is more in cancers. COX takes charge of the increased production of prostaglandins during inflammation. P450 1A2 is accountable for the activation of carcinogenic compounds. Increased GSH levels in tumor cells are linked to tumor progression and resistance to chemotherapeutic drugs. Cancer cells show elevated levels of FTO expression. eNOS is involved in promotion or inhibition of cancer

**Table 5.** Hydrolases target classes used in the present study

| No. | Protein molecule | RCSB id | Length | Resolution | Vina score of the drugs used |
|---|---|---|---|---|---|
| 1. | Dipeptidyl peptidase 4 soluble form | 4A5S | 740 | 1.62 Å | A:-8;C:-7.2;Q:-9 |
| 2. | Matrix metalloproteinase-9, | 5TH6 | 231 | 1.70 Å | A:-7.3;C:-7.0;Q:-8.6 |
| 3. | A disintegrin and metalloproteinase with thrombospondin motifs 4 | 4WKE | 235 | 1.62 Å | A:-7.4;C:-7.5;Q:-8.6 |
| 4. | C-X-C chemokine receptor type 4, Lysozyme Chimera | 3OE0 | 499 | 2.90 Å | A:-7.9;C:-8.1;Q:-8.2 |
| 5. | protein (vascular endothelial growth factor) | 1VPP | 102 | 1.90 Å | A:-6.5;C:-6.6;Q:-6.7 |
| 6. | NHE-RF1 | 4JL7 | 91 | 1.16 Å | A:-6.7;C:-6.2;Q:-6.7 |
| 7. | Apopain | 1PAU | 147 | 2.50 Å | A:-5.8;C:-6;Q:-6 |
| 8. | Caspase-8 | 1QTN | 164 | 1.20 Å | A:-6.7;C:-7.2;Q:-7.2 |
| 9. | Matrix metalloproteinase-9 (EC 3.4.24.35) (MMP-9) (92 kDa type IV collagenase) (92 kDa gelatinase) (Gelatinase B) (GELB) | 2OVX | 159 | 2.00 Å | A:-8.1;C:-8.6;Q:-10.4 |
| 10. | DEAH (Asp-Glu-Ala-His) box polypeptide 36 | 5VHE | 933 | 3.79 Å | A:-8.5;C:-8.4;Q:-8.9 |
| 11. | Cholinesterase | 4BDS | 529 | 2.10 Å | A:-8.9;C:-8.2;Q:-9.3 |
| 12. | C-X-C chemokine receptor type 4, Lysozyme Chimera | 3ODU | 502 | 2.50 Å | A:-8.3;C:-7.9;Q:-8.3 |
| 13. | C-X-C chemokine receptor type 4, Lysozyme Chimera | 3OE9 | 499 | 3.10 Å | A:-8.2;C:-7.2;Q:-8.1 |
| 14. | C-X-C chemokine receptor type 4, Lysozyme Chimera | 3OE8 | 502 | 3.10 Å | A:-8.6;C:-7.6;Q:-8.2 |
| 15. | C-X-C chemokine receptor type 4/Endolysin chimeric protein | 4RWS | 498 | 3.10 Å | A:-7.5;C:-7.1;Q:-8.2 |
| 16. | Beta-secretase 1 | 4IVT | 433 | 1.60 Å | A:-7.4;C:-7.1;Q:-7.8 |

NHE-RF1: Sodium (+)/Hydrogen (+) exchange regulatory cofactor 1; A: Anatrozole, C: Capecitabine; Q; Quercetin

**Table 6.** Contact amino acids and varieties of bonds between the target and the ligand molecules belong to hydrolases involved in breast cancer.

| PDB | Contact residues, bond pattern and number of bonds | | |
|---|---|---|---|
| | Anastrazole | Capecitabine | Quercetin |
| 4A5S | PRO475GLY476MET509PRO 510SER511LYS512GLN527ILE 529ASP556VAL558PHE559A RG560LEU561ASN562ALA56 4THR565 Ionic (2), hydrogen (5), weak (3), hydrophobic (4) | GLN314MET325HIS345ILE346G LU347ET348SER349THR350THR 351GLY52LYS373ILE375SER376 ASN377GLU378GLY380PHE387 LYS392CS394PHE396ASP588HIS 592 Cation pi (1), ionic (2), hydrogen (8), weak (3), Hydrophobic (9) | PRO475GLY476MET509PRO510 SER511LYS512GLN527ILE529AS P556VAL558PHE559ARG560LEU 561ASN562ALA564THR565 Ionic (2), hydrogen (17), Hydrophobic (11), weak (6) |
| 5TH6 | ARG143LEU147LEU212SER3 94PHE396LEU397PHE425TH R426GLU427GLY428PRO429 PRO430ARG143LEU212PHE3 96PHE425THR426GLU427GL Y428PRO429PRO430 Cation pi (2), hydrophobic (12), weak (2), hydrogen (4) | ARG143LEU147LEU212GLY213S ER394PHE396LEU397PHE425T HR426GLU427GLY428PRO429P RO430LEU431ARG143ALA146L EU147ALA150PHE396GLU427G LY428PRO429PRO430LEU431 Cation pi (2), hydrophobic (20), weak (2), hydrogen (3) | LEU397VAL398HIS401PRO415GL U416ALA417LEU418MET419TYR 420PRO421MET422TYR423ARG 424THR426GLY428PRO429PRO4 30HIS432 Hydrophobic (7), hydrogen (9) weak (6) |
| 4WKE | THR326ASP328THR329LEU3 30GLY331THR358HIS361VAL 390ALA392PRO393VAL394M ET395 Cation pi (3), hydrogen (4), weak hydrogen (1), hydrophobic (5) | GLY323ASP328THR329LEU330 GLY33MET332PHE357THR358H IS361GLU362HIS365HIS371HIS 389VAL390ALA392PRO393VAL 394MET395ALA396VAL398 Hydrogen (9),weak hydrogen (3), hydrophobic (8) | ASP328THR329LEU330GLY331M ET332PHE357THR358HIS361GL U362HIS365HIS371HIS389VAL39 0MET391ALA392PRO393VAL394 MET395ALA396VAL398 hydrogen (8), weak hydrogen (6), hydrophobic (4), pi-pi (1) |
| 3OE0 | ALA137ILE138ALA141LYS225 LEU226ASN1002GLU1005VA L1094THR1157TRP1158ASP 1159TYR1161LYS234 LYS236 Hydrogen (4), hydrophobic (6) weak hydrogen (2) | ARG30GLU32ASN33PHE36ASN 37LEU41ASP97ALA98ARG183IL E185CYS186ASP187LYS282SE R285 ILE286ARG1 Hydrogen (7), hydrophobic (13), ionic interaction (4), weak hydrogen (1) | ALA137ILE138ALA141LEU226AL A1093VAL1094GLY1156THR115 7TRP1158ASP1159GLY231HIS232L YS234ARG235LYS236ALA237L EU238 Hydrogen (9), pi-pi sticking (1), hydrophobic (6),weak hydrogen (5) |
| 1VPP | ASP34ILE35PHE36TYR39PRO 40GLU42ILE43TYR45PHE47S ER50GLU64LYS107 Hydrogen (1), pi-pi sticking (1), hydrophobic (9), ionic interaction (2), weak hydrogen (1) | GLU64ChainW:ASP34ILE35PHE 36ILE43GLU44TYR45ILE46PHE4 7SER50CYS51 Hydrogen (10), pi-pi sticking (1), hydrophobic (5), weak hydrogen (1) | ILE35PHE36TYR39PRO40ASP41G LU2ILE43TYR45ILE46PHE47SER5 0 PRO85GLU64 Hydrogen (2), hydrophobic (9),weak hydrogen (2) |
| 3OE8 | LEU41TYR45PHE93TRP94AS P97ALA98TRP102VAL112HIS 113TYR116CYS186ASP187AR G188 SER285 GLU288 Hydrogen bond (1), pi-pi sticking (1), hydrophobic (4), ionic interaction (1),Weak hydrogen (1) | HIS113TYR116THR117LEU120T YR121LEU167ASP171ARG188TY R190PHE199GLN200HIS203TYR 255GLY258ILE259ASP262SER26 3HIS281ILE284GLU288 Weak hydrogen (2), ionic interaction (1), hydrophobic (15), Hydrogen (8), cation-pi (1) | TYR45PHE93TRP94ASP97TRP10 2CYS109VAL112HIS113TYR116A RG188HIS281ILE284SER285 GLU288 Hydrogen (6), pi-pi sticking (3), hydrophobic (6),weak (2) |
| 4JL7 | LYS19ASN22GLY23TYR24GLY 25PHE26LEU28HIS72VAL75V AL76ILE79 ARG80 Weak hydrogen (1), hydrophobic (7), cation-pi interaction (1) hydrogen bond (1) | ASN22GLY23TYR24GLY25PHE26 HIS27LEU28LEU41GLU43VAL76 ILE79 Weak hydrogen (2), hydrophobic (6), hydrogen (3) | LYS19GLY23TYR24PHE26HIS27L EU28HIS72VAL76ILE79ARG80AL A81ALA82LEU83 ASN84 Weak hydrogen (3), hydrophobic (9), hydrogen (6), cation-pi interaction (2), pi-pi (1) |
| 3OE9 | LEU41TYR45PHE93TRP94AS P97TRP102VAL112HIS113TY R116CYS186ASP187ARG188 SER285GLU288 Ionic (2), hydrophobic (6), hydrogen (4), pi-pi (2) | TRP94ASP97HIS113TYR116THR 117LEU120TYR121ASP171ARG1 83CYS186ASP187ARG188GLN2 00HIS203TYR255GLU288 Weak hydrogen (6), ionic interaction (1), hydrophobic (15), hydrogen (7) | LEU41TYR45TRP94ASP97ALA98C YS109VAL112HIS113TYR116ARG 183CYS186ARG188ILE284SER28 5ILE286GLU288 Weak hydrogen (3), ionic interaction (1), hydrophobic (4), Hydrogen (9), pi-pi (2) |
| 4RWS | HIS113TYR116THR117LEU12 0TYR121ASP171ARG188TYR 190VAL196PHE199GLN200HI S203LEU1GLY2CYS5 Weak hydrogen (2), ionic (3), hydrophobic (7), hydrogen (7), cation-pi (1) | ALA137ILE138ALA141THR142LY S225LEU226ASN1002ILE1003AL A1093VAL1094ALA1097TRP115 8ASP1159SER1162SER1164GLY 231LYS234 LYS236Weak hydrogen (2) hydrophobic (12), hydrogen (3) | HIS113TYR116THR117LEU120TY R121ASP171CYS186CYS187ARG 188TYR190PHE199GLN200GLN2 02HIS203LEU1GLY2CYS5 Weak hydrogen (2) hydrophobic (7) , hydrogen (6) |
| 3ODU | LEU41TYR45PHE93TRP94AS | GLU31GLU32ASN33ASN37LYS3 | GLU32LEU41TYR45PHE93TRP94 |

| | | | |
|---|---|---|---|
| | P97ALA98TRP102CYS109VAL 112HIS113TYR116CYS186AS P187ARG188SER285GLU288 Weak hydrogen (1), ionic (5), hydrophobic (8), Hydrogen (2), pi-pi (1) | 8LEU41TYR45TRP94ASP97ALA9 8VAL112HIS113TYR116CYS186 HIS281LYS282SER285GLU288 Ionic (1), hydrogen (3), hydrophobic (8), weak hydrogen (5) | ASP97ALA98TRP102VAL112HIS1 13TYR116ARG188SER285 GLU288 Hydrogen (4), hydrophobic (7), weak hydrogen (1), pi-pi (1) |
| 4BDS | ASP70GLY78SER79TRP82AS N83GLY115GLY116GLY117T HR120TYR128GLU197SER19 8ALA199ALA328PHE329TYR 332TRP430MET437HIS438GL Y439TYR440ILE442 Ionic (3), pi-pi (1) hydrophobic(7), weak hydrogen (5), hydrogen (10) | TRP82GLY115GLY116GLY117GL N119THR120GLU197SER198AL A199THR284PRO285LEU286SE R287VAL288ASN289PHE329HIS 438GLY439 Hydrophobic (14), weak hydrogen (3), hydrogen (11) | GLN67ASN68ILE69ASP70TRP82A SN83PRO84TYR114GLY115GLY1 16THR120GLY121TYR128GLU19 7SER198TYR332HIS438GLY439IL E442 Ionic (1), hydrophobic (4), weak hydrogen (5), hydrogen (10), pi-pi (2) |
| 5HVE | LYS78GLU79GLU81ARG82AR G85LYS847TRP887GLN922T HR929TRP935ILE936ILE937P HE938GLN939 Ionic (3), hydrophobic (7), weak hydrogen (3), hydrogen (4) | PHE579ASN584ILE585SER586T HR636PRO637LEU638GLU639G LU640GLU701PRO702PHE729L YS844HIS891LEU892LYS893 MET894 Ionic (3), hydrophobic (4), weak hydrogen (1), hydrogen (6) | LEU343PRO637LEU638GLU639G LU640LEU641GLU701PRO702HI S703PHE729LYS844HIS891 LEU892 Ionic (1), cation-pi (1), hydrophobic (7), weak hydrogen (2), hydrogen (10) |
| 1PAU | THR177HIS237ChainB:TRP34 0ARG341PHE381SER381PHE 381ASP381PHE381ASP502G LU503VAL504 Hydrogen (6), ionic (1), cation pi (1), hydrophobic (6), weak hydrogen (4) | MET176THR177HIS237GLY238P HE244CYS285GLY287THR288Ch ainB:TYR338TRP340SER381ASP 381PHE381ASP502GLU503VAL 504 Hydrogen (5), hydrophobic (16), weak hydrogen (2) | ChainA:GLU191THR192ASN195L EU196ChainB:LYS358ALA361ASP 362LYS363PHE400TYR401 Hydrogen (6), hydrophobic (9), ionic (1), weak hydrogen (2) |
| 1QTN | LYS253 LEU254 HIS255 SER256ILE257ARG258HIS317 GLY318ASP319TYR324CYS36 0GLY362ASP363THR503 Ionic (1), cation pi (2), weak hydrogen (3), hydrophobic (11), hydrogen (3) | LYS320GLY321PRO332ILE333TY R334THR337SER338THR341GL N361GLU396PHE399LEU401ME T403ASN407GLN465THR467 THR469Hydrogen (10), hydrophobic (7), weak hydrogen (5) | LYS253LEU254SER256ILE257AR G258HIS317GLY318ASP319TYR3 24CYS360GLY362ARG413GLU50 2THR503 Cation-pi (1), ionic (1), hydrogen (11), weak hydrogen (3), hydrophobic (6) |
| 2OVX | GLN126VAL167GLN169HIS1 75GLY176ASP177GLY197ILE 198ASP201HIS203TRP124TY R160SER161ARG162ASP163 Hydrogen (6), ionic (4), hydrophobic (5), weak hydrogen (2) | GLY186LEU187LEU188ALA189L EU397VAL398HIS401GLN402HI S405HIS411GLU416ALA417LEU 418TYR420PRO421MET422TYR 423ARG424THR426PRO430 Hydrophobic (8), hydrogen (3), weak hydrogen (2) | LEU188LEU397VAL398HIS401GL N402PRO415GLU416ALA417LEU 418TYR420PRO421MET422TYR4 23ARG424THR426GLU427GLY42 8PRO429PRO430 Hydrogen (8), weak hydrogen (3), hydrophobic (7) |

etiology. Cyclooxygenase 1 is an anti-inflammatory responsive enzyme. Aromatase inhibitors are thus first-line therapy for estrogen-dependent breast cancer.

**Proteins as targets**

Table 11 provides the vina score comparison; wherein, quercetin showed the highest vina score for protein binding targets and table 12 shows the contact residues and bonds (Tables 11, 12) (Fig. 9)[20]. Overexpressed HSP90 aids transformation by stabilizing the mutated and overexpressed onco-proteins identifed in BC cells. Carcinoma-associated antigen is the epithelial cell adhesion molecule (EpCAM). HER 2, a member of an oncogenic protein family, involves in development and progression of breast cancers that are aggressive. Methenyltetrahydrofolate Synthetase regulates carbon flow by one-carbon metabolic network, which provides vital constituents for cell growth and proliferation; reserve has been shown to arrest the cell growth. ALDH1A3 is overexpressed and important for tumor cell's vitality. HER 2 stimulates cell propagation in tissues. ER binds to either of structurally and functionally distinct ERs (ER*á* and ER*â*). PKC delta's C2 domain is activated by diacylglycerol, and functions as a tumor suppressor, a regulator of cell cycle progression (positive) and a regulator of apoptosis (positive or negative). Estrogen Receptor alpha LBD, (a novel isoform of ERá), promotes endocrine resistance and cancer proliferation (breast). Ephrin type-A receptor 2 (EphA2) (a receptor tyrosine kinase), overexpresses in breast cancers (human) and involves in a variety of

serious progressions related to malignant breast progressions, including proliferation, migration, survival, invasion, metastasis, drug resistance, and angiogenesis[20].

**Signal proteins as targets**

With a minor difference, among the three drugs, quercetin's vina score is the highest (Tables 13, 14) (Fig. 10) for signaling proteins[20]. EGFR

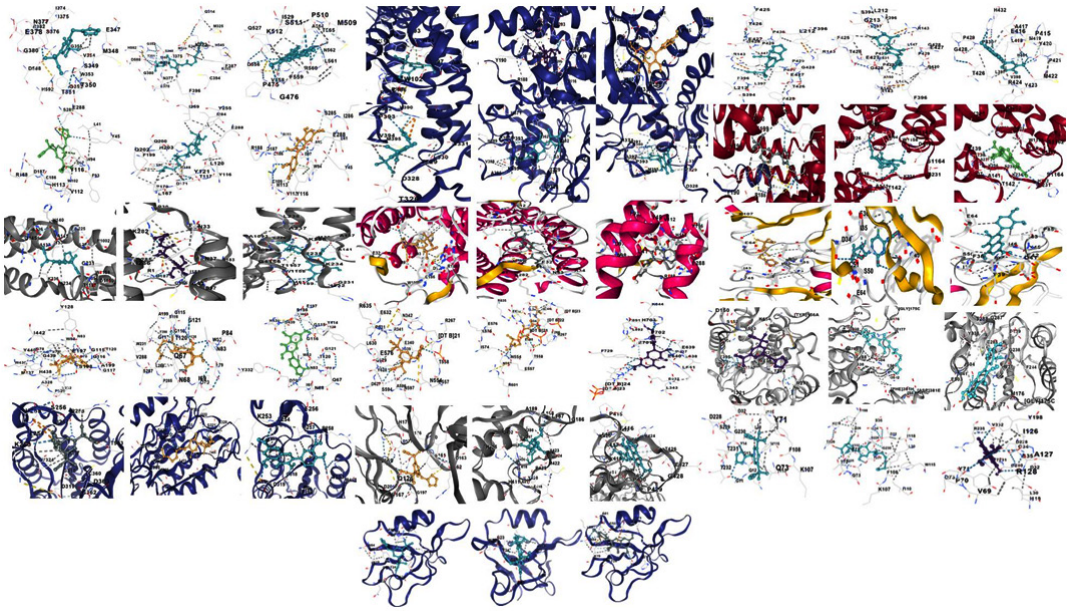


**Fig. 6.** Docking poses of hydrolases with the ligannds
First lane from left to right: (1-3) Ana: 4A5S, Cap: 4A5S, Que:4A5S; (4-6) Ana:3OE8, Cap:3OE8, Que: 3OE8; (7-9) Ana:5TH6, Cap:5TH6, Que:5TH6
Second lane from left to right: (1-3) Ana: 3OE9, Cap: 3OE9, Que:3OE9; (4-6) Ana:4WKE, Cap:4WKE, Que: 4WKE; (7-9) Ana:4RWS, Cap:4RWS, Que:4RWS
Third lane: from left to right: (1-3) Ana: 3OE0, Cap: 3OE0, Que:3OE0; (4-6) Ana:3ODU, Cap:3ODU, Que: 3ODU; (7-9) Ana1:VPP, Cap:1VPP. Que:1VPP
Fourth lane from left to right: (1-3) Ana:4BDS , Cap:4BDS , Que:4BDS; (4-6) Ana:5VHE, Cap:5VHE, Que: 5VHE; (7-9) Ana:1PAU, Cap:1PAU, Que:1PAU
Fifth lane from left to right: (1-3) Ana: 1QTN, Cap: 1QTN, Que:1QTN; (4-6) Ana:2OVX, Cap:2OVX, Que: 2OVX; (7-9) Ana:4IVT, Cap:4IVT, Que:4IVT
Last lane Ana:4JL7, Cap:4JL7, Que:4JL7

**Table 7.** Isomerases target classes used in the present study

| No. | Protein molecule | RCSB id | Length | Resolution | Vina score of the drugs used |
|---|---|---|---|---|---|
| 1. | Peptidyl-prolyl cis-trans isomerase FKBP5 | 4DRH | 144 | 2.30 Å | A:-8.4; C:-8.5;Q:-8.4 |
| 2. | DNA topoisomerase 2-beta | 3QX3 | 803 | 2.16 Å | A:-8.5;C:-7.8;Q:-9 |
| 3. | DNA topoisomerase I | 1K4T | 592 | 2.10 Å | A:-8.5;C:-8.4;Q:-9.1 |
| 4. | DNA topoisomerase II, alpha isozyme | 1ZXM | 400 | 1.87 Å | A:-8.9;C:-8.5;Q:-10.1 |
| 5. | DNA topoisomerase I | 1T8I | 592 | 3.00 Å | A:-8.3;C:-8.2;Q:-8.9 |

FKBP5: FK506-binding protein 5; A: Anatrozole, C: Capecitabine; Q; Quercetin

promotes tumorigenesis by regulating epithelial tissue development and homeostasis. â-arrestin regulates cell proliferation, migration, promotes cell invasion, sends anti-apoptotic survival signals, influences tumor growth rate, metastatic potential, angiogenesis, and drug resistance. CXCL12, secreted by carcinoma-associated fibroblasts (CAFs), directly stimulates tumor growth by acting through CXCR4, which is articulated by BC cells and promotes invasiveness. During tumor development, CXCL12 also acts as a chemo-attractant. In malignant tumors, its expression promotes and contributes for tumor growth and metastasis. CCR5 may indirectly affect cancer development by regulating the antitumor immune response[20].

**Transcription factors as targets**

Vina score of quercetin seemed to be the highest when compared to the three drugs (Tables 15, 16 and Fig. 11) for transcription factors[20]. Drug activation of ER beta significantly inhibits cancer cell growth. HIF-1 activates cancer cell survival genes and allows them to grow in the hostile hypoxic tumor environment. Increased tumor HIF-1alpha has been linked to aggressive tumor growth, angiogenesis, and poor prognosis. Rb C-terminal domain (RbC) is required for growth inhibition. Above 66% of breast carcinomas express Erá, and majority ER+ tumors also express progesterone receptors (PRs). Chemotherapy is rendered less effective due to ER mutations. Patients with advanced disease condition will

**Table 8.** Contact amino acids and varieties of bonds between the target and the ligand molecules belong to isomerases involved in breast cancer

| PDB | Contact residues and bond pattern | | |
|---|---|---|---|
| | Anastrazole | Capecitabine | Quercetin |
| IZXM | ASN91ALA92ASP94ASN95ARG98ASN120ILE125ILE141PHE142THR147SER148SER149ASN150THR159GLY161ALA167LYS168THR215ILE217TYR34<br>Hydrogen (8), weak hydrogen(2), Hydrophobic (12) | TYR34GLU87ASN91ASP94ASN95ARG98ILE125ILE141PHE142THR147SER148SER149ASN150THR159GLY161ARG162ASN163GLY164TYR165GLY166ALA167LYS168GLN376LYS378<br>Hydrogen (13), weak hydrogen (5), ionic (1) hydrophobic (8) | ASN91ALA92ASP94ASN95ARG98ASN120LYS123GLY124ILE125ILE141PHE142THR147SER148SER149ASN150GLY164ALA167LYS168THR181TYR214THR215<br>Hydrogen (19), weak hydrogen (6), hydrophobic (6) |
| 1K4T | LYS354ILE355GLU356PRO357PRO358PHE361LYS374ARG375ARG376ILE377TRP416GLU418ASN419ILE420SER423LYS425TYR426<br>Hydrogen (3), hydrophobic (8), weak hydrogen (3), ionic (2), pi-pi (3) | LYS202TRP203LYS204TRP205TRP206LYS347GLU348ARG349ASN430SER432SER433ARG434ARG749GLU750ALA753ILE756ASP757<br>Hydrogen (27), hydrophobic (9), weak hydrogen (10), ionic (1) (1), pi-pi (16) | ASN352LYS354ILE355 GLU356PHE361LYS374ARG375ILE377TRP416GLU418ASN419ILE420LYS425TYR426ILE427<br>Hydrogen (24), hydrophobic (5), weak hydrogen (11), ionic (2), pi-pi (11) |
| 3QX3 | ARG503GLY776GLU777GLN778ALA779MET782<br>Weak hydrogen (2), hydrgoen (9), hydrophobic (3), pi-pi (4) | GLU477GLY478ASP479LEU502ARG503GLY504MET782<br>Weak hydrogen (7), hydrogen (19), hydrophobic (3), pi-pi (4) | LYS456GLY478ASP479SER480LEU502ARG503GLY504GLN778MET782<br>Weak hydrogen (11), hydrogen (16), Hydrophobic (1), pi-pi (4), ionic (1) |
| 4DRH | TYR57PHE67ASP68HIS71PHE77TYR113PRO120PHE130ChainE:SER2035TYR2038PHE2039LEU2097THR2098TRP2101ASP2102TYR2105<br>Ionic (2), hydrogen (1), weak hydrogen (3), hydrophobic (10) | TYR57ASP68SER70HIS71PHE77PRO120ChainE:LEU2031GLU2032SER2035PHE2039LEU2097THR2098TRP2101ASP2102TYR2104TYR2105PHE2108<br>Ionic (1), hydrogen (5), weak hydrogen (4), Hydrophobic (15), pi-pi (1) | ASP68HIS71PHE77VAL78GLN85ChainB:LEU2031GLU2032SER2035PHE2039LEU2097THR2098GLN2099TRP2101ASP2102TYR2104TYR2105PHE2108<br>Ionic (2), hydrogen (4), weak hydrogen (5), Hydrophobic (8), pi-pi (1) |
| 1T81 | ASN352LYS354ILE355GLU356PRO357PRO358PHE361LYS374ARG375ILE377TRP416GLU418ASN419LYS425TYR426<br>Weak hydrogen (4), hydrogen (16), ionic (2), pi-pi (9), hydrophobic (8) | ILE355GLU356PRO357PRO358PHE361GLY363ARG364HIS367LYS374ARG375ILE377TRP416GLU418ASN419ILE420GLN421SER423LYS425<br>Weak hydrogen(6), hydrogen (21), ionic (2), pi-pi (11), hydrophoic (12) | ASN352GLU356PRO357LEU373LYS374ARG375ARG376ILE377TRP416GLU418ASN419ILE420LYS425TYR426ILE427<br>Weak hydrogen (6), hydrogen (18), ionic (1), pi-pi (13), hydrophobic (4) |

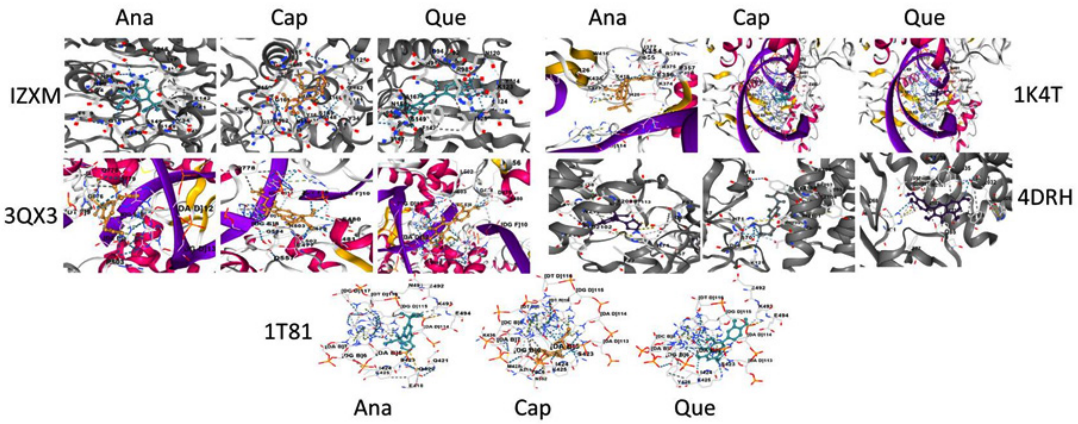



**Fig. 7.** Interaction between the isomerase targets and ligands
Top panel from left to right: Ana: IZXM, Cap: IZXM, Que: IZXM; Ana:1K4T, Cap:1K4T, Que: 1K4T
Middle panel from left to right: Ana:3QX3, Cap:3QX3, Que:3QX3; Ana: 4DRH, Cap:4DRH, Que:4DRH
Last panel from left to right: Ana:1T81, Cap:1T81, Que:1T81

**Table 9.** Oxidoreductases target classes used in the present study; A: Anatrozole, C: Capecitabine; Q; Quercetin

| No. | Protein molecule | RCSB id | Length | Resolution | Vina score of the drugs used |
|---|---|---|---|---|---|
| 1. | Prostaglandin G/H synthase 2 | 3LN1 | 587 | 2.40 Å | A:-8.5;C:-8.3;Q:-9.8 |
| 2. | prostaglandin h2 synthase-1 | 1EQH | 580 | 2.70 Å | A:-8.0;C:-8.0;Q:-9.2 |
| 3. | Corticosteroid 11-beta-dehydrogenase isozyme 1 | 2ILT | 275 | 2.30 Å | A:-8.1;C:-8.6;Q:-8.8 |
| 4. | Prostaglandin G/H synthase 2 | 5KIR | 551 | 2.70 Å | A:-8.7;C:-8.4;Q:-9.5 |
| 5. | myeloperoxidase light chain | 4C1M | 108 | 2.00 Å | A:-8.1;C:-8.1;Q:-9.6 |
| 6. | Cytochrome P450 19A1 | 3S7S | 503 | 3.21 Å | A:-8.4;C:-7.6;Q:-8 |
| 7. | Aldehyde dehydrogenase family 1 member A3 | 6TRY | 512 | 2.90 Å | A:-8.3;C:-8.3;Q:-8.9 |
| 8. | endothelial Nitric-oxide synthase | 1M9K | 415 | 2.01 Å | A:-7.5;C:-7.8;Q:-9.5 |
| 9. | Cytochrome P450 2C9 | 1R9O | 477 | 2.00 Å | A:-8.3;C:-7.8;Q:-8.2 |
| 10. | Inducible nitric oxide synthase | 4NOS | 427 | 2.25 Å | A:-8.5;C:-7.6;Q:-9.3 |
| 11. | Cyclooxygenase-2 | 4COX | 587 | 2.90 Å | A:-8.4;C:-8.6;Q:-9.5 |
| 12. | Cytochrome P450 1A1 | 6DWN | 491 | 3.00 Å | A:-8.3;C:-8.6;Q:-10.5 |
| 13. | Cytochrome P450 1A2 | 2HI4 | 495 | 1.95 Å | A:-8.6;C:-9;Q:-9.8 |
| 14. | Polyphenol oxidase | 2Y9X | 391 | 2.78 Å | A:-8.2;C:-7.6;Q:-9 |
| 15. | Glutathione reductase | 3DK8 | 478 | 1.10 Å | A:-6.9:C:-7.9;Q:-8.9 |
| 16. | Protein fto | 3LFM | 494 | 2.50 Å | A:-7.8;C:-7;Q:-7.7 |
| 17. | Prostaglandin G/H synthase 1 | 2OYE | 600 | 2.85 Å | A:-8;C:-8.1;Q:-9.1 |
| 18. | Cytochrome P450 19A1 | 3EQM | 503 | 2.90 Å | A:-8.2;C:-7.7;Q:-8 |
| 19. | Cytochrome P450 21-hydroxylase | 4Y8W | 482 | 2.64 Å | A:-8;C:-7.9;Q:-8.7 |
| 20. | Aldehyde dehydrogenase family 1 member A3 | 6TE5 | 512 | 3.25 Å | A:-8.2;C:-8.3;Q:-8.9 |
| 21. | Aldehyde dehydrogenase family 1 member A3 | 7A6Q | 512 | 2.95 Å | A:-8.3;C:-8.1;Q:-9 |
| 22. | Prostaglandin h2 synthase-1 | 1EQG | 580 | 2.61 Å | A:-7.6;C:-8;Q:-9.2 |
| 23. | Aldehyde dehydrogenase family 1 member A3 | 5FHZ | 529 | 2.90 Å | A:-8.2;C:-8.4;Q:-9.1 |

**Table 10.** Contact amino acids and varieties of bonds between the target and the ligand molecules belong to oxidoreductases involved in breast cancer

| PDB | Contact residues, bond pattern and number of bonds | | |
|---|---|---|---|
| | Anastrazole | Capecitabine | Quercetin |
| 1EQH | PHE142SER143VAL145ARG374ASN375ARG376PHE142SER143VAL145LEU224GLY225HIS226ARG374ASN375ARG376<br>Hydrogen (3), hydrophobic (5) | PHE142SER143VAL145GLY225HIS226GLY227VAL228TYR373ARG374ASN375ARG376GLY533GLY536ASN537PRO538TRP139PHE142VAL145LEU224GLY225HIS226ARG374<br>Hydrogen (7), weak hydrogen (2), hydrophobic (7) | ALA199ALA202GLN203THR206HIS207PHE210THR212LEU295ASN382TYR385HIS386TRP387HIS388LEU390MET391ILE444<br>Hydrogen (7), weak hydrogen (3), hydrophobic (10), cation pi (1) pi-pi (2) |
| 2ILT | THR40GLY41ALA42LYS44GLY45ILE46GLY47ARG48ASN119HIS120ILE121VAL168SER169SER170TYR183LYS187LEU215GLY216LEU217ILE218THR220ALA223<br>Hydrogen (6), Hydrophobic (8), weak hydrogen (2) | GLY41ALA42LYS44GLY45ILE46GLY47ARG48ASN119HIS120ILE121VAL168SER169SER170LEU171ALA172TYR177TYR183LEU215GLY216LEU217ILE218THR220THR222ALA223<br>Hydrogen(11), Hydrophobic (10), weak hydrogen (4) | THR40GLY41ALA42LYS44GLY45ILE46GLY47ARG48ASN119HIS120ILE121VAL168SER169SER170TYR183LYS187LEU215GLY216LEU217ILE218THR220ALA223<br>Hydrogen (12), Hydrophobic (4), weak hydrogen (5) |
| 3lN1 | HIS75ARG106GLN178TYR334VAL335LEU338SER339TYR341LEU345LEU370TYR371TRP373ARG499ALA502ILE503PHE504MET508VAL509GLU510GLY512ALA513SER516LEU517<br>Hydrophobic (8), weak hydrogen (1), hydrogen (6) | ASN19CYS21CYS22ASN24PRO25CYS26ARG29GLY30GLU31CYS32TYR120GLY121TYR122LEU138PRO139PRO140VAL141ALA142CYS145GLN447GLU451LYS454ARG455GLN313<br>Hydrophobic (11), weak hydrogen (4), hydrogen (9) | ASN19CYS21CYS22ASN24CYS26GLN27ARG29GLY30GLU31CYS32MET33TYR116GLY121LEU138PRO139PRO140VAL141ALA142GLN447GLU451LYS454ARG455<br>Ionic (4), Hydrophobic (6), weak hydrogen (4), hydrogen (19) |
| 4C1M | ALA28PHE29VAL30ARG31PRO34ALA35ARG31ALA152THR159ILE160ARG161ASN162ARG323THR159ILE160ARG323<br>Hydrophobic (8), hydrogen bonds (3) | MET87GLY90GLN91ASP94HIS95GLU102PHE146PHE147ARG239TYR296PHE332ARG333TYR334GLY335HIS336LEU406PHE407LEU415LEU417LEU420ARG424<br>Hydrophobic (7), weak hydrogen (2), ionic (2)hydrogen (6), cation pi (2) | PHE86MET87GLY90GLN91ASP94HIS95ASP98PHE99THR100ARG239GLU242TYR296THR329ASN330PHE332ARG333TYR334GLY335HIS336LEU338<br>Cation-pi (1), weak hydrogen (2), Hydrophobic (8), hydrogen (8), ionic (1), pi-pi (1) |
| 5KIR | CYS36HIS39PRO40 CYS41GLN42ASN43ARG44GLY45VAL46CYS47TYR130LYS137ALA151LEU152PRO153GLN461GLU465LYS468 ARG469<br>Hydrophobi (10), hydrogen (5), weak hydrogen (2), ionic (2) | TRP323GLN327ASN34CYS36HIS39PRO40CYS41GLN42ARG44GLY45VAL46CYS47MET48SER49TYR130GLY135TYR136LEU152PRO153PRO154VAL155PRO156GLN461GLU465<br>Hydrophobic (9), hydrogen (8), weak hydrogen (4), ionic (1) | ASN34CYS36HIS39CYS41ARG44GLY45VAL46CYS47MET48TYR130GLY135TYR136LEU152PRO153PRO154VAL155PRO156GLN461GLU465<br>Hydrophobic (5), hydrogen (10), weak hydrogen (1), ionic (1) |
| 1EQG | PHE142SER143VAL145LEU224GLY225HIS226ARG374ASN375ARG376ChainB:PHE142SER143VAL145ARG374ASN375ARG376<br>Hydrogen (4), hydrophobic (4) | PHE142SER143VAL145GLY225HIS226GLY227VAL228TYR373ARG374ASN375ARG376GLY533GLY536ASN537PRO538TRP139PHE142SER143VAL145LEU224GLY225HIS226ARG374ASN375ARG376<br>Hydrogen (9), hydrophobic (9), cation pi (1), weak hydrogen (2) | ALA199PHE200ALA202GLN203THR206HIS207PHE210THR212LEU295ASN382TYR385HIS386TRP387HIS388LEU390MET391ILE444VAL447<br>Hydrogen (11), hydrophobic (6) pi-pi (1), weak hydrogen (1) |
| 3S7S | ARG115ILE132 ILE133TRP141ARG145PHE148LEU152TRP224GLU302MET303ILE305ALA306ASP309THR310ARG435GLY436CYS437ALA438GLY439<br>Cation pi (1), hydrophobic (18), hydrogen (8) | ARG115ILE132ILE133PHE134PHE148LEU152TRP224GLU302MET303ALA306VAL370LEU372VAL373MET374PHE430ARG435GLY436CYS437ALA438GLY439LEU477<br>Hydrophobic (18), weak hydrogen (2) hydrogen (11) | ARG115ILE132ILE133TRP141ARG145LEU152PHE203MET303ALA306ALA307THR310MET311VAL370ARG435GLY436CYS437ALA438GLY439ILE442ALA443MET446<br>Cation pi (1), hydrophobic (6), weak hydrogen (3)hydrogen bonds (13) |
| 1R9O | ARG97ILE112VAL113PHE114TRP120ALA297THR301LEU362SER365LEU366HIS368PHE428SER429ARG433ILE434CYS435VAL436 | ARG97ILE112VAL113ARG124ILE205GLY296ALA297GLU300THR301THR304LEU361LEU362LEU366PHE428ARG433ILE434CYS435VAL436GLY437 | ARG97VAL113ALA297GLY298THR301THR302THR305GLN356LEU361LEU362SER365LEU366HIS368LEU391PRO427PHE428SER429ARG433CYS435ALA441 |

| | | | |
|---|---|---|---|
| | Pi-pi stacking (1) Hydrophobic (18) | ALA477<br>Hydrophobic (12), weak hydrogen (3), hydrogen (9) | LEU445<br>Hydrophobic (8), weak hydrogen (4), hydrogen (14) |
| 6TE5 | ARG276ASN485GLY486ARG487TYR492ALA495GLU496HIS168ILE171ARG276THR278ASN485GLY486LEU494ALA495GLU496TYR497THR498GLU499VAL500<br>Hydrogen (9), ionic (6), hydrophobic (4), weak hydrogen (4) | LYS266ARG276VAL277THR278ASN485GLY486ALA495GLU496THR498GLU499VAL500LYS266LYS275ARG276VAL277THR278ASN485GLY486ARG487TYR492ALA495GLU496<br>Weak hydrogen (7), hydrogen (14), ionic (3), hydrophobic (10) | LYS266VAL277THR278GLY479ASN485GLY486ARG487GLU496LYS266LYS275ARG276VAL277THR278ASN485LEU494ALA495GLU496THR498GLU499VAL500<br>Hydrophobic (6), ionic (2), weak hydrogen (5), hydrogen (17) |
| 2Y9X | PHE97TYR101ALA104PHE105LEU108VAL126GLU129LEU130GLY138ARG139ALA142PHE143SER145 PHE146<br>Hydrophobic (8), weak hydrogen (3), hydrogen (6), ionic (3) | GLN307THR308TYR311ASP312VAL313SER352ASP353ASP354GLU356ASP357TRP358SER375LYS376LYS379SER380ASP336GLN351ASP353 ASP354GLU356<br>Hydrophobic (8), weak hydrogen (1), hydrogen (7), ionic (2) | SER2ASP3LYS5ASP336SER337PRO338TYR343ASN346GLN347ASP348PRO349GLN351TYR311ASP312SER375LYS376GLU377GLU378ASN57LEU59ASP60GLY61TYR62<br>Hydrophobic (2), weak hydrogen (7), ionic (1)hydrogen (13) |
| 6TRY | PRO179TRP180ASN181GLN208PHE255GLY257SER258VAL261GLY282GLN312CYS313CYS314ILE357ASP358LYS360GLN361LYS364GLU411PHE413<br>Hydrophobic (7), ionic (4), hydrogen (1) | LYS266ARG276VAL277ASN485GLY486ARG487TYR492ALA495GLU496ChainB:LYS25LYS266LYS275ARG276VAL277THR278ASN485GLY486ALA495GLU496THR498GLU499 VAL500<br>Hydrophobic (8), weak hydrogen (4), ionic (2), hydrogen (8) | HIS168ARG276LEU494ALA495GLU496THR498GLU499VAL500ChainB:GLY479ASN485GLY486ARG487GLU491TYR492ALA493LEU494 ALA495GLU496<br>Pi-pi stacking (1), hydrophobic (3), weak hydrogen (3), hydrogen (15), ionic (2) |
| 3EQM | ARG115ILE132ILE133TRP141ARG145PHE148LEU152TRP224GLU302MET303ILE305ALA306ASP309THR310ARG435GLY436CYS437ALA438GLY439<br>Cation pi (1), hydrogen (9), hydrophobic (16) | ARG115ILE132ILE133PHE134ARG145PHE148LEU152TRP224GLU302MET303ALA306VAL370LEU372VAL373MET374PHE430GLY436CYS437ALA438GLY439LEU477<br>Hydrogen (15),weak hydrogen (2),hydrophobic (18) | ARG192GLN218PHE221ASP222GLN225PRO308ASP309THR310VAL313ILE474SER478HIS480ASP482GLU483THR484<br>Pi-pi (2), cation pi (1), hydrogen (7,weak hydrogen (3),hydrophobic (6), ionic (1) |
| 3lFM | ILE85THR92PRO93VAL94ARG96TYR106TYR108LEU109LEU203ALA227VAL228SER229TRP230HIS231HIS232ASP233GLU234ARG322<br>Pi-pi stacking (2), hydrophobic (9), weak hydrogen (3), hydrogen (2), ionic (5) | ILE85THR92PRO93VAL94ARG96TYR106TYR108LEU109LEU203ALA227VAL228SER229HIS231HIS232ASP233GLU234ARG322<br>Pi-pi stacking (2), hydrophobic (5), weak hydrogen (2), hydrogen (8), ionic (3) | ILE85ARG96TYR106TYR108LEU109LEU203ASN205VAL228SER229TRP230HIS231HIS232ASP233GLU234THR320ARG322<br>Cation-pi (1), pi-pi stacking (2), hydrophobic (5),weak hydrogen (4), hydrogen (9), ionic (2) |
| 4COX | CYS36ASN39PRO40CYS41GLN42ASN43ARG44GLY45GLU46CYS47ASP125TYR130ALA151LEU152PRO153GLN461GLU465LYS468ARG469<br>Ionic (3), hydrophobic (5), weak hydrogen (2), hydrogen (4) | ASN34CYS36CYS37SER38ASN39CYS47MET48SER49TYR130GLY135TYR136LYS137SER138PRO153PRO154VAL155ALA156CYS159GLY164GLN461TRP323GLN327THR331LEU334SER548THR549 GLY551<br>Hydrophobic(6), weak hydrogen (2), ionic (1) hydrogen (7) | ASN34CYS36CYS37SER38ASN39CYS41GLN42ARG44GLY45GLU46CYS47MET48TYR130GLY135PRO153PRO154VAL155ALA156CYS159 GLY164GLN461<br>Hydrophobic (9), weak hydrogen (5), pi-pi (2), cation pi (1), hydrogen (11) |
| 1M9K | GLN90GLY92PRO93ALA181PRO182ARG183CYS184MET339ASP444TRP447ASN466TYR467PHE468ALA472PHE473ARG474TYR475<br>Hydrophobic (8), ionic (2), cation pi (1), hydrogen (2) | TRP74TRP445PHE460HIS461GLN462ChainB:SER102VAL104GLN247ARG250ALA266ARG365ASN366ASP369HIS371ARG372ALA446TRP447<br>Hydrophobic (9), ionic (1), hydrogen (4), weak hydrogen (3) | VAL71LYS72ASN73VAL76SER78ILE79THR80ASP82MET428LYS429LEU431GLU432GLU434GLN435GY439GLY440CYS441PRO442GLN62GLU463MET464VAL465<br>Hydrophobic (11), ionic (1), hydrogen (14), weak hydrogen (5) |
| 2HI4 | ARG108LEU123THR124PHE125TRP133ARG137ALA317THR321LEU382PHE384THR385ILE386HIS388GLN411LEU450PHE451GLY452ARG456ARG457 | ARG108THR124PHE125THR223PHE226VAL227PHE256PHE260GLY316ALA317ASP320THR321LEU382PHE384THR385ILE386HIS388GLN411LEU450P | ARG108ILE117THR118SER122THR124PHE125THR223PHE226VAL227PHE256PHE260ASN312ASP313GLY316ALA317ASP320THR321LEU382ILE386LEU49 |

| | | | |
|---|---|---|---|
| | CYS458ILE459LEU497<br>Cation-pi (1), hydrophobic (13),weak hydrogen (1), hydrogen (9) | HE451GLY452ARG456ARG457CYS458ILE459LEU497THR498<br>Hydrophobic (19), weak hydrogen (4), hydrogen (9) | 7THR498<br>Hydrophobic (18), weak hydrogen (1), hydrogen (8), pi-pi (1) |
| 4NOS | TRP90TRP461PHE476HIS477ChainD:SER118ILE119MET120ARG199ARG381ASP385ARG388ILE462TRP463VAL465PRO467<br>Pi-pi stacking (1), cation-pi (2), hydrophobic (9),weak hydrogen (3), ionic (2), hydrogen (5) | LEU125ALA197PRO198ARG199CYS200ILE201GLY202MET355PHE369TRP372TYR373MET374GLU377TRP463PHE488TYR489TYR490TYR491<br>Pi-pi (2), cation pi(1), hydrophobic (7), weak hydrogen (1), hydrogen (5) | GLY117SER118MET120ARG381ILE462TRP463VAL465ChainB:LYS88TRP90TRP461VAL475PHE476HIS477GLN478GLU479MET480<br>Pi-pi stacking (3), cation-pi (1), hydrophobic (6), weak hydrogen (5), hydrogen (8) |
| 3DK8 | CYS58CYS63VAL64LYS66LYS67TYR197LEU337LEU338THR339PRO340PRO368THR369VAL370PHE372ASP441LEU444GLN445<br>Hydrophobic (1), hydrogen (7), ionic (3) | GLY27GLY28GLY29SER30GLY31GLU50SER51HIS52LYS53GLY55GLY56THR57CYS58CYS63ALA155THR156GLY157GLY158TYR197ARG291ASN294ASP331LEU337LEU338THR339ALA342<br>Hydrophobic (5),weak hydrogen (4), hydrogen (8) ionic (2) | GLY27GLY28GLY29SER30GLY31GLY32GLU50SER51HIS52GLY55GLY56THR57CYS58VAL61CYS63ALA155THR156GLY157GLY158GLY330ASP331LEU337LEU338THR339ALA342<br>Hydrophobic (2), weak hydrogen (4), hydrogen (13), ionic (1) |
| 2OYE | CYS36TYR39PRO40CYS41GLN44GLY45ILE46CYS47THR129TYR130ASP135ILE151LEU152PRO153GLN461GLU465ARG469<br>Ionic (1), weak hydrogen (1), hydrogen (2),Hydrophobic (9) | ASN34CYS36TYR39PRO40CYS41GLN42HIS43GLN44GLY45ILE46CYS47VAL48TYR130ASP135TYR136LEU152PRO153SER154PRO156GLN461GLU465LYS468ARG469<br>Ionic (1), weak hydrogen (5), hydrogen (7),Hydrophobic (7) | ALA199PHE200ALA202GLN203THR206HIS207PHE210LYS211THR212ASN382TYR385HIS386TRP387HIS388LEU390MET391VAL447<br>Weak hydrogen (3), hydrogen (9),Hydrophobic (8), pi-pi (1), cation-pi (1) |

have a high mutation rate. NFêB encourages the development of an autonomous (hormone-independent), aggressive, high-grade, and late-stage tumor phenotype. The ERá's anti-cancer properties are based on the sealing of its ligand binding domain[20].

**Transferases as targets**

Quercetin's vina score is highest, with the proteins belonging to transferases (Table 17, 18) (Fig. 12a and 12b). Somatic genetic alterations most frequently activate CDK4 and cyclin D1 in a variety of tumor types. CDK4 is a genetically validated therapeutic target, since CDK4/ cyclin D1 pathway is important in oncogenesis. The estrogen receptor (ER) is overexpressed in breast cancer. In ER alpha-positive human breast cancer cells, stromal cell-derived factor 1 (SDF-1), (cytokine stimulator for growth) is a genuine goal of estrogen's action. Cyclin-Dependent Kinases (CDKs) have been proposed as novel and promising target for cancer therapy. These, in conjugation with cyclins, show an important role in cell cycle advancement. CDK dysregulation results in increased cell propagation, has been established in a number of cancers, no exception to BC. CDK1 selective inhibition is linked to potent anti-cancer outcomes either combined with other therapeutics or alone. VEGF promotes vessel proliferation, invasion and survival and endothelial cell proliferation. Tumor cell shape, proliferation, motility, progression and metastasis depend on overexpressed Rho-associated protein kinase 1. Cyclin-dependent kinases (CDKs) regulate cell cycle, apoptosis, transcription and neuronal functions. EphA2 Receptor Protein Kinase regulates cytoskeleton dynamics, cell adhesion, proliferation, differentiation, and metastasis. JAK2 regulates gene expression in the G1 cell cycle, proliferation, oncogenesis, anti-apoptosis, angiogenesis and metastasis. EphA2 tyrosine kinase is involved in angiogenesis, cancer, and inflammation[20].

The EphA4 receptor, (Eph receptor tyrosine kinases family member), is a well-known cell functions (cell adhesion, invasion and migration) regulator. These events occur due to modification of actin cytoskeleton organization. In a variety of cell types, FKBP1 is identified as NF-êB signaling regulator (nuclear factor binding near the ê light-chain in B-cells). As a result, FKBP51

is proposed as a target to treat NF-êB-mediated inflammation and cancer. Cancer relies heavily on p38 activity. p38 mitogen-activated protein kinases (MAPKs) are important in cancer cellular responses, proliferation, survival, cell cycle and migration. The growth factor-activated Ser/Thr kinase p90 ribosomal protein kinase 2 (RSK2) is involved in cell multiplication and tumor promoter-induced cell transformation. Cell growth, motility, survival, metabolism, and angiogenesis are all regulated by human PI3K gamma. CDKs (Cyclin-dependent kinases) play critical role in cell cycle progress and RNA transcription. GSTP-silencing effectively suppressed cell proliferation while not

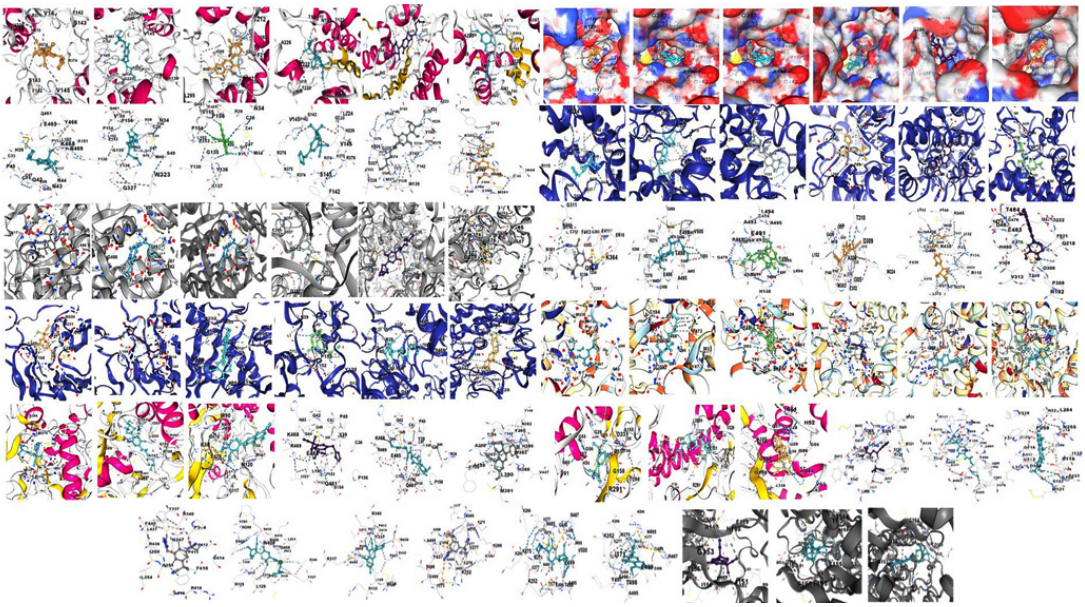


**Fig. 8.** Docking poses of oxidoreductases with Anastrazole, Capecitabine and Quercetin ligands
First lane: 1EQH, 2ILT, 3LN1, 4C1M; Second lane: 5KIR, 1EQG, 3S7S, 1R9O; Third lane: 6TE5, 2Y9X, 6TRY, 3EQM; Fourth lane: 3LFM, 4COX, 1M9K, 2HI4; Fifth lane: 4NOS, 2OYE, 3DK8, 6DWN; Last lane: 4Y8W, 7A6Q, 5FHZ

**Table 11.** Protein binding target classes used in the present study; A: Anatrozole, C: Capecitabine; Q; Quercetin

| No. | Protein Molecule | RCSB id | Length | Resolution | Vina score of the drugs used |
|---|---|---|---|---|---|
| | | EphA2: ephrin type-A receptor 2 | | | |
| 1. | Estrogen receptor | 4PPS | 244 | 1.93 Å | A:-7.2;C:-7.5;Q:-7.7 |
| 2. | Estrogen receptor | 4PP6 | 244 | 2.20 Å | A:-7.3;C:-7.2;Q:-8.4 |
| 3. | Protein kinase C, delta type | 1YRK | 126 | 1.70 Å | A:-6.3;C:-6.4;Q:-7.1 |
| 4. | Estrogen receptor beta | 4J26 | 240 | 2.30 Å | A:-6.9;C:-7.4;Q:-7.7 |
| 5. | estrogen receptor alpha (hER alpha) (protein (estrogen receptor alpha) | 3ERT | 261 | 1.90 Å | A:-8.1;C:-7.5;Q:-7.8 |
| 6. | EphA2 ectodomain | 2X10 | 545 | 3.00 Å | A:-6.5;C:-5.8;Q:-6.5 |
| 7. | Stress-70 protein, mitochondrial | 3N8E | 182 | 2.80 Å | A:-7.4;C:-7.6;Q:-7.7 |
| 8. | Aldehyde dehydrogenase family 1 member A3 | 6S6W | 489 | 3.25 Å | A:-8.1;C: -8.5; Q:-9.0 |
| 9. | 5,10-Methenyltetrahydrofolate cyclo-ligase | 3HY3 | 203 | 1.80 Å | A:-8.4; C:-7.4; Que:-8.2 |
| 10. | Met and epithelial cell adhesion molecule | 6I07 | 262 | 2.35 Å | A:-6.8; C:-6.9;Q:-7.2 |

**Table 12.** Contact amino acids and varieties of bonds between the target and the ligand molecules belong to binding proteins involved in breast cancer.

| PDB | Contact residues, bond pattern and number of bonds | | |
|---|---|---|---|
| | Anastrazole | Capecitabine | Quercetin |
| 6S6 W | PRO179TRP180ASN181GLY 257SER258THR259GLU260L EU281GLY282GLY283CYS31 3CYS314ALA316GLN361GL U411PHE413 Ionic (2), pi-pi, (1) hydrogen (5), hydrophobic (4), cation-pi (1) | LYS266ARG276VAL277ASN 485GLY486ARG487TYR492 ALA495GLU496ChainB:LYS 266LYS275ARG276VAL277 THR278ASN485ALA495GLU 496THR498GLU499VAL500 Ionic (4), hydrogen (12), hydrophobic (7), cation-pi (1), weak hydrogen (6) | LYS266LYS275ARG276VAL2 77ASN485ALA495GLU496T HR498GLU499VAL500Chain B:LYS266LYS275ARG276VA L277ASN485GLY486ARG48 7TYR492ALA495GLU496 Ionic (4), hydrogen (14), hydrophobic (3), weak hydrogen (4) |
| 4PPS | MET343LEU346THR347LEU 349ALA350GLU353TRP383L EU384LEU387MET388LEU3 91ARG394PHE404MET421I LE424PHE425LEU428GLY52 1HIS524LEU525 Ionic (2), weak hydrogen (2), hydrogen (3), hydrophobic (23), pi-pi (1) | GLU323PRO324PRO325ILE 326GLU353HIS356MET357 TRP360ILE386LEU387GLY3 90TRP393ARG394GLY442P HE445VAL446LYS449 Hydrogen (2), hydrophobic (18), weak hydrogen (1), cation-pi (1), ioninc (2), pi-pi (1) | MET343LEU346THR347LEU 349ALA350ASP351GLU353L EU384LEU387MET388GLY3 90LEU391ARG394PHE404V AL418MET421ILE424LEU42 8GLY521MET522HIS524LEU 525TYR526MET528 Hydrophobic (13), hydrogen 2 (4), pi-pi (1), ionic (1) |
| 4PP6 | MET343LEU346THR347LEU 349ALA350GLU353TRP383L EU384LEU387MET388LEU3 91ARG394PHE404MET421I LE424PHE425LEU428GLY52 1MET522LEU525LEU540 Hydrophobic (26), hydrogen (1), ionic (3), weak hydrogen (2) | GLU323PRO324PRO325ILE 326GLU353HIS356MET357 TRP360ILE386LEU387GLY3 90TRP393ARG394GLY442P HE445VAL446 LYS449 Hydrophobic (16), pi-pi (1), ionic (2), cation-pi (2), hydrogen (1) | MET343LEU346THR347LEU 349ALA350GLU353LEU384L EU387MET388ILE389LEU39 1ARG394PHE404VAL418ME T421ILE424LEU428LYS520G LY521MET522HIS524LEU52 5MET528 Hydrogen (7), ionic (1), pi-pi (2), hydrophobic (11), weak hydrogen (1) |
| 1YRK | MET32GLU34LYS47LYS48PR O49ASP60HIS62TYR64 ARG67GLN8PRO9TYR10 PHE12 Hydrogen (2), hydrophobic (6), pi-pi (2) | THR50MET51TYR52PRO53 GLU54LYS56SER57THR58P HE59ChainB:GLN8PRO9TY R10VAL11PHE12ALA13 Hydrogen (8), hydrophobic (5), ionic (1), cation-pi (1) | PHE4LYS48PRO49ASP60 ALA61HIS62TYR64ARG67GL U123ChainB:ILE6GLN8PRO9 TYR10PHE12 Hydrogen (7), hydrophobic (5), ionic (1) pi-pi (2),cation-pi (1) weak hydrogen (1) |
| 3ERT | MET343LEU346THR347ALA 350ASP351LEU354TRP383L EU384LEU387MET522LEU5 25MET528LEU536LEU539 Hdrogen (3), hydrophobic (12) | LEU320GLU323PRO324PR O325ILE326LEU327GLU353 LEU354HIS356MET357TRP 360ILE386LEU387GLY390T RP393ARG394GLY442PHE4 45VAL446LYS449 Hydrogen (4), hydrophobic (16), ionic (1), | MET343LEU346THR347LEU 349ALA350ASP351GLU353 TRP383LEU384LEU387MET 388LEU391ARG394PHE404I LE424LEU428GLY521 LEU525MET528 Hydrogen (5), ionic (1), hydrophobic (13), |
| 2X10 | GLN56 ASN57ILE64TYR 65TYR67SER68VAL69 THR101ARG103CYS188VAL 189ALA190LEU191LEU192 Hydrophobic (5), hydrogen (2), weak hydrogen (3) | VAL364THR365CYS366 GLU367PRO378CYS379GLU 380ALA381VAL383ARG384 TYR385 PRO389HIS390 Weak hydrogen (3), Hydrophobic (13) | THR365CYS366PRO378 CYS379GLU380ALA381SER3 82VAL383TYR385PRO389 HIS390 Hydrophobic (7), hydrogen (3), weak hydrogen (4) |
| 3N8E | ILE447GLU448THR449LEU4 50PHE472SER473THR474AL A475GLN479GLN481VAL48 2GLU483ILE484ARG513 ILE518VAL520 Hydrophobic (14), hydrogen (2) | ILE447GLU448THR449LEU4 50PHE472SER473THR474A LA475VAL482GLU483ILE48 4ARG513ILE518VAL520AS N583MET584GLU586 GLY587 Hydrophobic (14), hydrogen (5), weak hydrogen (1), ionic (1) | ILE447GLU448THR449LEU4 50PHE472SER473THR474AL A475GLN479VAL482GLU48 3ILE484ARG513ILE518 VAL520 Hydrophobic (13), hydrogen (7), weak hydrogen (1) |
| 3HY3 | ILE54PHE55LEU56MET58GL U61ILE80PRO81ARG82TYR8 3PHE85THR107TRP109ILE1 11PRO112GLN113PRO135A RG148TYR152TYR153 | LEU56MET58PRO81ARG82 TYR83PHE85THR107TRP10 9ILE111PRO112GLN113GL Y147ARG148GLY149 LYS150GLY151TYR152 | PHE55 LEU56 SER57 MET58GLU61ILE80PRO81A RG82TYR83PHE85THR107T RP109ILE111PRO112GLN11 |

| | | | |
|---|---|---|---|
| | Pi-pi (2), weak hydrogen (1), hydrogen (2), hydrophobic (6) | Pi-pi (2), hydrogen (4), weak hydrogen (1), hydrophobic (9) | 3PRO135ARG148LYS150 TYR152TYR153 Hydrogen (10), weak hydrogen (2), ionic (1),hydrophobic (8), pi-pi (4) |
| 4J26 | ARG466HIS467ASN470LYS4 71ChainB:ARG466HIS467AS N470LYS471MET473GLU47 4LEU477 HIS498 Hydrogen (4), cation-pi (1), weak hydrogen (1), hydrophobic (9) | GLU276PRO277PRO278HIS 279VAL280LYS304GLU305L EU306HIS308MET309TRP3 12VAL338LEU339GLY342T RP345ARG346ILE355TYR39 7LYS401 Hydrogen (2), cation-pi, (1) weak hydrogen (3), hydrophobic (14), pi-pi (1), ionic (2) | MET295LEU298LEU301ALA 302GLU305TRP335MET336 LEU339MET340LEU343ARG 346PHE356ILE373ILE376PH E377LEU380GLY472MET47 3HIS475LEU476 Hydrogen (7), weak hydrogen (2), hydrophobic (20), pi-pi (1), ionic (1) |
| 6I07 | ARG125PRO257PHE259Cha inD:ARG81LEU88GLN89ASN 91GLN111MET115TRP117L YS129 Hydrophobic (4), hydrogen (3), weak hydrogen (2), pi-pi (1) | GLU217LYS221GLU223PRO 244GLY245GLN246THR247 LEU248ILE249TYR250TYR2 51ChainD:LEU88GLN89ASN 90LYS221GLU223PRO244G LY245 Hydrophobic, hydrogen (10), weak hydrogen (4), pi-pi (1) | ASP1ILE2VAL3MET4THR5PR O100ARG101THR102PHE10 3GLY104CYS105CYS171LEU 172LYS173TRP174MET175 ALA188ASP189ASP190 Hydrophobic (3), hydrogen (9), weak hydrogen (4) |

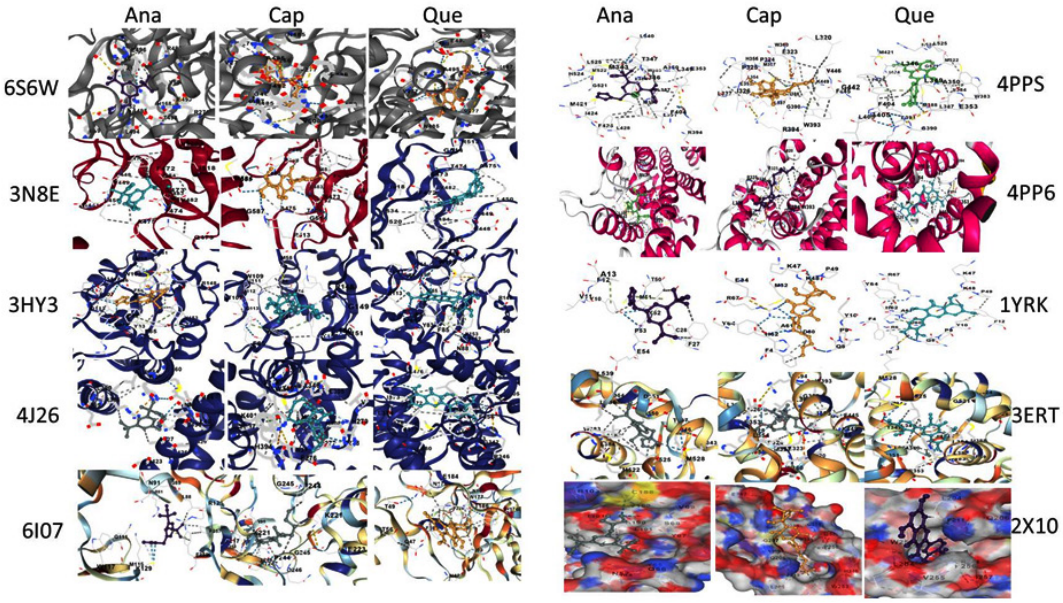



**Fig. 9.** Docking poses of binding proteins with the three ligands

**Table 13.** Signaling protein target classes used in the present study; A: Anatrozole, C: Capecitabine; Q; Quercetin

| No. | Protein molecule | RCSB id | Length | Resolution | Vina score of the drugs used |
|---|---|---|---|---|---|
| 1. | Chimera protein of C-C chemokine receptor type 5 and Rubredoxin | 4MBS | 414 | 2.71 Å | A:-8.6;C:-7.3;Q:-7.9 |
| 2. | epidermal growth factor | 1JL9 | 51 | 3.00 Å | A:-6.2;C:-6.4;Q:-6.4 |
| 3. | Beta-arrestin-2 | 6K3F | 377 | 2.30 Å | A:-8.9;C:-8.2Q:-9 |
| 4. | Stromal cell-derived factor 1 | 2NWG | 68 | 2.07 Å | A:-6.6;C:-5.9;Q:-6.9 |
| 5. | Receptor tyrosine-protein kinase erbB-2 (HER 2) | 5O4G | 606 | 3.00 Å | A:7.4;C:-8; Q-8.4 |

**Table 14.** Contact amino acids and varieties of bonds between the target and the ligand molecules belong signaling involved in breast cancer

| PDB | Contact residues and bond pattern | | |
|---|---|---|---|
| | Anastrazole | Capecitabine | Quercetin |
| 4MBS | TYR37TRP86TYR89LEU104THR105TYR108PHE109THR167CYS178SER179SER180GLN280GLU283 THR284 MET287 Hydrogen (4), hydrophobic (7), ionic (2), weak hydrogen (2), pi-pi (2) | TYR108PHE109PHE112PHE182TYR187LYS191GLN194THR195ILE198TRP248TYR251LEU255ASN258THR259MET279GLU283 Hydrogen (3), hydrophobic (9), weak hydrogen (1) | LEU33TYR37TRP86TYR89THR105TYR108PHE109ASN163THR167ARG168CYS178SER179SER180GLU283THR284MET287 Hydrogen (4), hydrophobic (13), pi-pi (2) weak hydrogen (2) |
| 2NWG | LEU29ASN30THR31PRO32 GLN37ARG20GLU60TYR6 1LYS64ALA65ASN67 Weak hydrogen (3), ionic (2), hydrogen (2), hydrophobic (4) | LYS24HIS25LYS43ChainB:TYR7PRO10CYS11LYS27LEU29ASN30THR31VAL39GLN48 CYS50 Weak hydrogen (1), hydrogen (5), hydrophobic (9), cation-pi (1) | LYS1VAL3SER6TYR7ARG8CYS9PRO10ARG12LYS27LEU29 ASN30THR31LYS24HIS25 ARG41 Weak (1), hydrogen (8), hydrophobic (6), cation-pi (1) |
| 6K3F | ASP27ARG170PHE174HIS212GLU298ASP299THR300ASN301LEU302HIS212GLY213PRO278LEU279LEU280SER281ASP299 THR300ASN301 Ionic (2), cation-pi (1), hydrogen (3), hydrophobic (7), weak hydrogen (1) | ASP27ARG170HIS212PRO278LEU279LEU280GLU298ASP299THR300ASN301LEU302HIS212PRO278LEU279LEU280SER281ASP299 THR300ASN301 Ionic (1), hydrogen (10), hydrophobic (9) | ASN225SER226PRO266SER267ASP30HIS31LEU32ASP33LYS34VAL35ILE120PRO121GLN122ASN123LEU124LYS171 GLN173ILE307 VAL308LYS309GLU310 Ionic (2), cation-pi (1), hydrogen (6), hydrophobic (5), weak (5) |
| 1JL9 | TYR44ILE38GLY39GLU40TYR44ARG45ASP46 Pi-pi (1), ionic (1), weak hydrogen (1), hydrogen (1), hydrophobic (5) | ARG45CYS6PRO7LEU8SER9HIS10ASP11GLY12TYR13CYS14LEU15HIS16ASP17GLY18VAL19CYS20 Hydrogen (6), hydrophobic (5), weak hydrogen (5) | CYS6PRO7LEU8SER9HIS10ASP11GLY12TYR13CYS14LEU15ASP17GLY18 VAL19CYS20 Weak hydrogen (1),hydrophobic (3), hydrogen (7) |
| 5O4G | THR5GLY6THR7ASP8GLN35GLY36GLN59GLN84ASN280TYR281LEU291GLY411ARG412ILE413LEU414GLY417SER441GLY442Hydrogen (6), hydrophobic (8), ionic (2), weak hydrogen (2) | ASP163THR164ASN165ARG166ARG168ALA169TYR32SER91TYR92SER93THR94TRP47 ARG50SER59ASP104SER105 ALA106 TRP107Hydrogen (7), hydrophobic (4), ionic (1), weak hydrogen (3) | THR1VAL3CYS4THR5GLN35PRO278TYR279ASN280TYR281LEU291GY411ARG412ILE413LEU414GLY417GLY440SER441ASN466HIS468 Hydrogen (11), hydrophobic (8), weak hydrogen (8) |

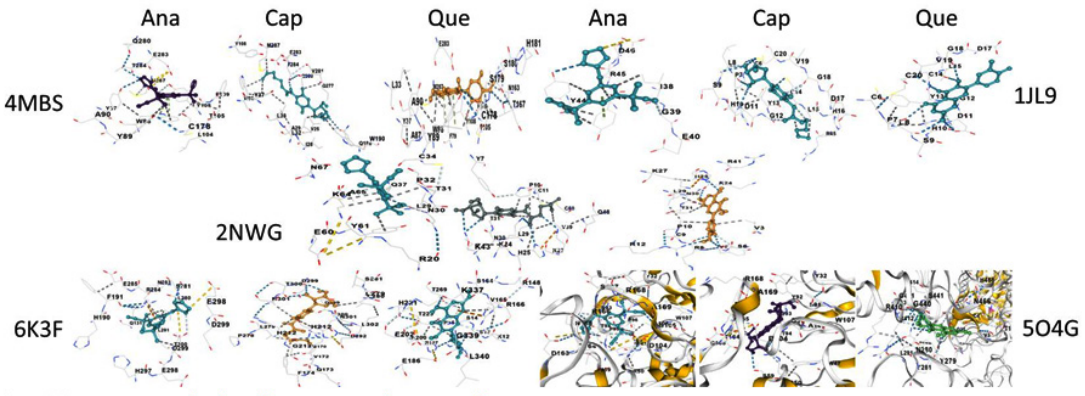



**Fig. 10.** Poses of singling proteins and targets

completely killing the cells. GSTP performs a non-enzyme function in signal transduction via a protein-protein interaction with JNK that guards cancer cells from apoptosis. AKT1 kinase (AKT kinase - a serine/threonine-protein kinase) regulates many signaling downstream pathways participate in cell proliferation, metabolism, survival, growth, and angiogenesis. It belongs to the most commonly triggered multiplying and surviving pathways in cancer. Autophagy and metabolism are both regulated by EGFR. Non-canonical functions are commonly brought by cellular and environmental stresses. These 'stress pathways' are activated in cancer cells and benefit them to survive and resist to therapy. Human IkB kinase beta (IkappaB kinase or IKK) is involved cell proliferation regulation, apoptosis control, angiogenesis promotion and invasion/metastasis stimulation. EGFR regulates EMT (epithelial-mesenchymal transition), cell migration and invasion. Its high expression is a sole predictor of poor diagnosis in Inflammatory Breast Cancer (IBC) and by rewiring apoptotic signaling networks in Triple Negative Breast Cancer (TNBC), its inhibition improves chemosensitivity[20].

Upregulation of intra-cellular signaling paths, PI3K/Akt/mTOR pathway, considering an example, promotes cancer growth and development by driving cellular proliferation, resulting in un-checked cell growth. VEGFR-2 regulates tumor angiogenesis directly. The VEGF/VEGFR-2 system is essential for cancer cell division and survival as an autocrine/paracrine process. Breast cancers overexpress the HER2 receptor, and HER2 overexpression is linked to aggressive tumor growth and metastasis. Cyclin-dependent kinase 6 (CDK6) is vital in cell cycle progression regulation. Recently, it was shown that CDK6 plays a transcriptional lead in tumor angiogenesis. NMPRTases are important in the salvage pathway of NAD+ biosynthesis. FK866 (a potent NMPRTase inhibitor) reduces cellular NAD+ levels and induces apoptosis in tumors. The MAPK signaling pathway connects extracellular signals to the intracellular process that regulates growth, proliferation, migration, and apoptosis[20].

Docking simplified the analysis of protein-ligand interactions. Hydrogen, weak hydrogen, hydrophobic, ionic, pi-pi sticking, covalent, and van der Waals interactions are examples of interactions[23]. The study highlights the main bond pattern *viz.,* hydrogen, hydrophobic, in addition to weak hydrogen bonds and limited cation-pi, pi-pi sticking, and ionic interactions. These bonds have a significant correlation with the vina score of the respective drug and its counterpart ligand. Furthermore, the energies were high due to the increased hydrogen and hydrophobic interactions.

Among the transferase target classes investigated in this study, cyclin-dependent kinase had the highest vina score with quercetin when compared to the other two drugs. The first higher class is (1XO2), which is followed by (1DI8), which has more hydrogen and hydrophobic bonds, considered as predominant in this class. Chronic inflammation is distinguished by the production of reactive nitrogen and oxygen species. These

**Table 15.** Transcription factor target classes used in the present study; A: Anatrozole, C: Capecitabine; Q; Quercetin

| No. | Protein molecule | RCSB id | Length | Resolution | Vina score of the drugs used |
|---|---|---|---|---|---|
| 1. | Estrogen receptor | 7JHD | 251 | 2.40 Å | A:-7.3;C:-7.7;Q:-8.3 |
| 2. | Estrogen receptor | 6SBO | 260 | 1.48 Å | A:-7.9;C:-7.1;Q:-8.4 |
| 3. | Transcription factor Dp-1 | 2AZE | 155 | 2.55 Å | A:-7.1;C:-7.2;Q:-7.7 |
| 4. | Protein (nuclear factor kappa-b (Nf-kB) | 1NFK | 325 | 2.30 Å | A:-8.3;C:-8.4;Q:-9.6 |
| 5. | Progesterone receptor | 4OAR | 258 | 2.41 Å | A:-7.9;C:-7.8;Q:-8.1 |
| 6. | Estrogen receptor beta | 2I0G | 257 | 2.50 Å | A:-8.6;C:-7.8;Q:-8.8 |
| 7. | Estrogen receptor beta | 5TOA | 249 | 2.50 Å | A:-7.4;C:-7.3;Q:-8.9 |
| 8. | Hypoxia-inducible factor 1 alpha inhibitor | 1YCI | 349 | 2.70 Å | A:-8.1;C:-6.7;Q:-7.4 |
| 9. | Stromal cell-derived factor 1 alpha | 2J7Z | 68 | 1.95 Å | A:-6.2;C:-5.9;Q:-6.7 |

**Table 16.** Poses, contact amino acids and varieties of bonds between the target and the ligand molecules belong to transcription factors involved in breast cancer

| PDB | Contact residues and bond pattern | | |
|---|---|---|---|
| | Anastrazole | Capecitabine | Quercetin |
| 5TOA | GLU276 PRO277PRO278 HIS279VAL280LEU301GLU305HIS308MET309TRP312VAL338LEU339GLY342TRP345ARG346PHE356ALA357PRO358 TYR397LYS401 Hydrophobic (7), weak hydrogen (4), hydrophobic (6), ionic (1) | GLU276PRO277PRO278 HIS279VAL280LYS304GLU305LEU306HIS308MET309TRP312VAL338LEU339GLY342TRP345ARG346HIS394 TYR397LYS401 Pi-pi (2) Hydrogen (4), weak hydrogen (2), hydrophobic (12), ionic (1) | MET295LEU298THR 299LEU301ALA302GLU305MET336LEU339MET340LEU343ARG346PHE356ILE373ILE376PHE377LEU380GLY472MET473HIS475LEU476 MET479VAL485 Hydrogen (8), weak hydrogen (2), hydrophobic (13), ionic (1) |
| 1YCI | TYR93PHE100LEU101TYR102 TYR145GLN147LEU186LEU188VAL195THR196PRO197HIS199ASP201PHE207ARG238ILE281ASN294 TRP296 Ionic (4), hydrophobic (10), hydrogen (2), pi-pi (1), weak hydrogen (5) | TYR102TYR145GLN147 LEU186LEU188THR196HIS199ASP201GLU202GLN203PHE207ARG238ILE281ASN294TRP296 Pi-pi (1), cation-pi (1), hydrogen (3), hydrophobic (7) | TYR93SER94PHE100 LEU101TYR102TYR103SER118TYR145GLN147LEU188THR196HIS199ASP201 ASN205PHE207LYS214HIS279ILE281ASN294 TRP296 Ionic (1), hydrophobic (13), weak hydrogen(4), hydrogen (6), cation-pi (1) |
| 2I0G | MET295LEU298THR299LEU301ALA302GLU305TRP335MET336LEU339MET340LEU343ARG346PHE356ILE373ILE376PHE377LEU380GLY472HIS475LEU476VAL487 Ionic (2), hydrophobic (19), hydrogen (1), pi-pi (1), weak hydrogen (2) | GLU276 PRO277PRO278 HIS279GLU305LEU306HIS308MET309VAL338LEU339GLY342TRP345ARG346HIS394TYR397LYS401 Ionic (1), hydrophobic (17), hydrogen (6), weak hydrogen (1), pi-pi (1) | MET295LEU298THR 299LEU301ALA302GLU305MET336LEU339MET340LEU343ARG346PHE356ILE373ILE376PHE377LEU380GLY472MET473HIS475LEU476 MET479 Ionic (1), hydrophobic (14), hydrogen (8), pi-pi (1), weak hydrogen (1) |
| 1NFK | BLYS249VAL251ARG252LEU269ASP271LYS275PRO300 THR301ASP302VAL303HIS304ARG305GLN306VAL310 Pi-pi (6), cation-pi (2) hydrogen (11) weak hydrogen(4), hydrophobic (4), ionic (2) | ARG161GLY162ASN164 PRO165GLY166LEU167SER171LEU173ALA174TYR175LEU176GLN177PHE217THR226ARG228 Pi-pi (13), ionic (3), hydrogen (23) weak hydrogen(13) hydrophobic (11) | GLY162ASN164PRO 165GLY166LEU167SER171LEU173ALA174TYR175LEU176GLN177PHE217PHE225THR226ARG227ARG228GLU230 Pi-pi (9), ionic (3), hydrogen (21), weak hydrogen (10), hydrophobic (4) |
| 2AZE | PHE233LEU259PRO260PHE261ILE262ASP295ASP296ILE297SER235GLN241ALA267PRO268PRO269ChainC:SER834ILE835GLY836GLU837SER838 THR841 Weak hydrogen (2), hydrophobic (7) ionic (2), hydrogen (6) | PHE233VAL237LEU259 PRO260PHE261ILE262ASP295ASP296ILE297LEU234SER235SER240GLN241ALA244ChainC:SER834ILE835GLY836 GLU837SER838THR841 Hydrogen (6), weak hydrogen (2), hydrophobic (14) | PHE233VAL237LEU259 PRO260ASP295ASP296ILE297LEU231LEU234SER235GLU236SER240GLN241ALA244ILE835GLY836GLU837SER838THR841 Hydrogen (6), hydrophobic (5), weak hydrogen (1), pi-pi (1) |
| 6SBO | MET343LEU346THR347LEU349ALA350TRP383LEU384LEU387MET388LEU391PHE404VAL418MET421ILE424PHE425GLY521LEU525MET528ASN532 VAL533 Hydrophobic (18), hydrogen (1) | MET343LEU346THR347 LEU349ALA350ASP351GLU353LEU354TRP383LEU384LEU387PHE404LEU525ASN532 VAL533VAL534PRO535 Hydrogen (4), weak hydrogen (2), hydrophobic (17) | MET343LEU346THR 347LEU349ALA350GLU353TRP383LEU384LEU387 MET388ILE389LEU391ARG394PHE404LEU428LEU 525MET528 VAL533 Hydrogen (4), hydrophobic (17), pi-pi (1), weak hydrogen (1), ionic (1) |
| 4OAR | GLU695 PRO696ASP697 VAL698ILE699GLN725SER728VAL729TRP732LEU758MET 759GLY762TRP765ARG766PHE778ALA779PRO780PHE818LYS822 | GLU276 PRO277PRO278 HIS279GLU305LEU306HIS308MET309VAL338LEU339GLY342TRP345ARG346HIS394TYR397LYS401 Pi-pi (2), weak hydrogen (1), | PRO696ASP697VAL 698ILE699TYR700LEU721GLN725SER728VAL729TRP732SER757LEU758MET 759PHE761GLY762LEU763ARG766PHE778ALA779 |

| | | | |
|---|---|---|---|
| | Hydrophobic (12), pi-pi (2), weak hydrogen (2), ionic (1), hydrogen (4), cation-pi (1) | hydrogen (3), ionic (1), cation-pi (2), hydrophobic (15) | PRO780PHE818 LYS822 Weak hydrogen (2), hydrogen (9) cation-pi (3), hydrophobic (16) |
| 7JHD | MET343LEU345LEU346 THR347LEU349ALA350GLU3 53TRP383LEU384LEU387ME T388LEU391ARG394PHE404 ILE424PHE425LEU428GLY521 LEU525LEU540 Ionic (1), hydrogen (1), hydrophobic (23) | LEU320 GLU323PRO324 PRO325ILE326LEU327GLU3 53LEU354HIS356MET357TR P360ILE386LEU387GLY390T RP393ARG394GLY442PHE44 5VAL446LYS449 Cation-ion(2), pi-pi (1), hydrogen (2), weak hydrogen (3), ionic (1), hydrophobic (18) | MET343LEU345LEU 346THR347LEU349ALA35 0GLU353LEU384LEU387 MET388LEU391ARG394PHE 404VAL418GLY420ME T421ILE424PHE425LEU4 28GLY521HIS524 LEU525 Pi-pi (2), ionic (1), hydrogen (3), weak hydrogen (2), hydrophobic (11) |
| 2J7Z | VAL3 PRO10ARG12LYS27 LEU29ASN30THR31VAL39GL N48LYS24 HIS25LYS27ARG41 ASN46 Hydrophobic (11) | ARG20ALA21VAL23 LYS 43GLU60TYR61LYS64ALA65 Chain B: SER6TYR7ASN30THR31 PRO32 GLN37 Hydrophobic (11), hydrogen (5), weak hydrogen (1) | VAL3 SER6TYR7ARG8 CYS9PRO10LEU29ASN30 THR31ASN33CYS34VAL 23LYS24HIS25ARG41 LYS43 Hydrogen (9), hydrophobic (5), weak hydrogen (1) |

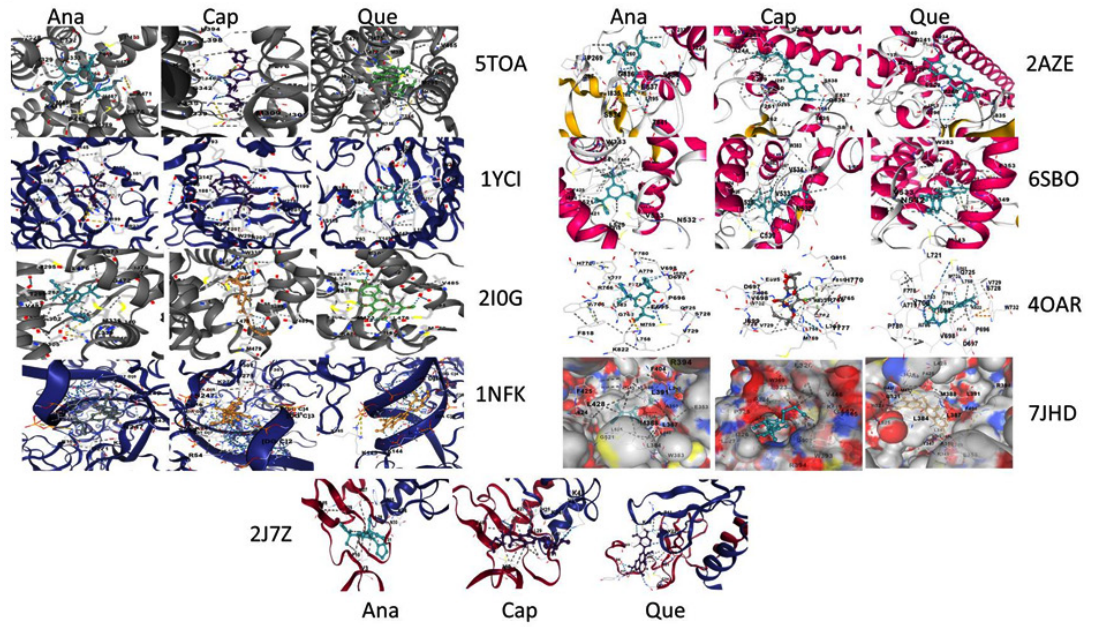



**Fig. 11.** Binding poses of transcription factors in breast cancer cell lines with the ligands

species initiate tumorigenesis, inhibit apoptosis, promote hyper cellular proliferation, and promote angiogenesis. These conditions cause the NFkB pathways to be activated. Although NFkB is required for normal mammary cell morphogenesis, irregular expression has been observed in BC cells[24]. A good idea is to target NFkB to control cell proliferation. The molecules studied were (1NFK), but with a vina score of -9.6, quercetin came out on top. The mitogen-activated protein kinase (MAPK) pathway regulates several processes including tumor development. In conjugation with the MAPK cascade, beta-arrestin proteins target G protein-couple receptors and promote tumor progression[25]. Targeting beta-arrestin is a good choice, and in this study, quercetin effectively targeted (6K3F) beta-arrestins. Estrogen receptors aid in the binding of estrogen, which is required for cell proliferation, and blocking these receptors aids in the supervision of cancer disease. Again quercetin has a strong

affinity for the estrogen receptor (4PP6).

In cancer prevention, redox maintenance in cell is critical. In aerobic conditions, ROS (reactive oxygen species) influence lipid, protein and DNA metabolism and function. Changes in DNA and proteins are important in cancer pathophysiology. Oxidoreductases are the enzymes that maintain ROS and neutralize oxidative stress[26].

**Table 17.** Transferase target classes used in the present study; A: Anatrozole, C: Capecitabine; Q; Quercetin

| No. | Protein molecule | RCSB id | Length | Resolution | Vina score of the drugs used |
|---|---|---|---|---|---|
| 1. | Cell division protein kinase 2 | 2BHH | 298 | 2.60 Å | A:-8.8;C: 7.9;Q:-8.9 |
| 2. | Vascular endothelial growth factor A | 4KZN | 104 | 1.71 Å | A:-5.5;C:-5.8;Q:-6.0 |
| 3. | Rho-associated protein kinase 1 | 3TWJ | 410 | 2.90 Å | A:-8.8;C:-7.5;Q:-8.9 |
| 4. | Epidermal growth factor receptor | 2ITX | 327 | 2.98 Å | A:-7.6;C:-7.1;Q:-8 |
| 5. | Peptidyl-prolyl cis-trans isomerase FKBP5 | 4DRH | 144 | 2.30 Å | A:-8.4;C:-8.5;Q:-8.4 |
| 6. | Dual specificity mitogen-activated protein kinase kinase 1 | 1S9J | 341 | 2.40 Å | A:-6.7;C:-7.5;Q:-8.6 |
| 7. | Nicotinamidephosphoribosyltransferase | 2GVG | 491 | 2.20 Å | A:-8.4;C:-8.8;Q:-10.1 |
| 8. | Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit, gamma isoform | 2A5U | 966 | 2.70 Å | A:-9.6;C:-7.8;Q:-9.3 |
| 9. | Mitogen-activated protein kinase 14 | 4FA2 | 383 | 2.00 Å | A:-8.7;C:-7.8;Q:-9.2 |
| 10. | Ephrin type-A receptor 2 | 1MQB | 333 | 2.30 Å | A:-7.6;C:-7.2;Q:-7.5 |
| 11. | epidermal growth factor receptor | 1M17 | 333 | 2.60 Å | A:-7.7;C:-6.7;Q:-8.4 |
| 12. | Vascular endothelial growth factor receptor 2 | 1YWN | 316 | 1.71 Å | A:-7.2;C:-6.9;Q:-7.9 |
| 13. | v-akt murine thymoma viral oncogene homolog 1 (AKT1) | 3MV5 | 342 | 2.47 Å | A:-8.4;C:-8;Q:-8.2 |
| 14. | Phosphatidylinositol-4,5-bisphosphate 3-kinase | 3OAW | 966 | 2.75 Å | A:-9.6;C:-7.6;Q:-8.3 |
| 15. | Inhibitor of nuclear factor kappa-B kinase subunit beta | 4KIK | 677 | 2.83 Å | A:-7.9;C:-7.4;Q:-8.5 |
| 16. | v-akt murine thymoma viral oncogene homolog 1 (AKT1) | 3OCB | 341 | 2.70 Å | A:-8.2;C:-8.1;Q:-8.4 |
| 17. | Epidermal growth factor receptor | 4WKQ | 330 | 1.85 Å | A:-7.2;C:-6.6;Q:-8.3 |
| 18. | Ephrin type-A receptor 4 | 4M4P | 518 | 2.08 Å | A:-6;C:-6.4;Q:-6.7 |
| 19. | RAC-alpha serine/threonine-protein kinase | 3CQW | 342 | 2.00 Å | A:-8.5;C:-7.9;Q:-8.5 |
| 20. | Cell division protein kinase 6 | 3NUP | 307 | 2.60 Å | A:-8.3;C:-6.8;Q:-8.6 |
| 21. | Cyclin-dependent kinase 2 | 1DI8 | 298 | 2.20 Å | A:-9.3;C:-7.9;Q:-10 |
| 22. | cyclin D1-cyclin-dependent kinase 4 (CDK4) (G1/S-Specific cyclin-D1) | 2W96 | 271 | 2.30 Å | A:-7.9,C:-7.4,Q:-9.2 |
| 23. | Cyclin-dependent kinase 6 | 1XO2 | 254 | 2.90 Å | A:-9.2;C:-8;Q:-10.6 |
| 24. | Epidermal growth factor receptor | 2J6M | 327 | 3.10 Å | A:-7.9;C:-7.2;Q:-8.4 |
| 25. | Protein (CDK2 human) | 1BUH | 298 | 2.60 Å | A:-7.7;C:-7.8;Q:-8.3 |
| 26. | Receptor tyrosine-protein kinase erbB-2 | 3PP0 | 338 | 2.25 Å | A:-8.7;C:-9.2;Q:-9.4 |
| 27. | Vascular endothelial growth factor receptor 2 | 2OH4 | 316 | 2.05 Å | A:-7.5;C:-7.4;Q:-9.6 |
| 28. | RAC-alpha serine/threonine-protein kinase | 3O96 | 446 | 2.70 Å | A:-9.9;C:-8.1;Q:-9.7 |
| 29. | RAC-alpha serine/threonine-protein kinase | 3CQU | 342 | 2.20 Å | A:-8;C:-7.9;Q:-9.2 |
| 30. | RAC-alpha serine/threonine-protein kinase | 3OW4 | 341 | 2.60 Å | A:-7.8;C:-7.3;Q:-8.1 |
| 31. | Epidermal growth factor receptor | 5FED | 328 | 2.65 Å | A:-8.2;C:-7;Q:-7.9 |
| 32. | Ephrin a2 (epha2) receptor protein kinase | 5NKA | 306 | 1.38 Å | A:-7;C:-6.6;Q:-7.9 |
| 33. | Glutathione S-transferase P | 2A2R | 210 | 1.40 Å | A:-7.3;C:-7.1;Q:-7.9 |
| 34. | Ribosomal protein S6 kinase alpha-3 | 3G51 | 325 | 1.80 Å | A:-7.8; C:-7.5;Q:-8.3 |
| 35. | Tyrosine-protein kinase JAK2 | 3KRR | 295 | 1.80 Å | A:-7.9;C:-7.5;Q:-9.1 |
| 36. | Cyclin-dependent kinase 1 | 4YC3 | 302 | 2.7 Å | A:-7.6;C:-7.1;Q:-9.5 |
| 37. | EphA2 ligand-binding domain (LBD) | 6NJZ | 187 | 1.90 Å | A:-7.4; C:-7.8; Q:-8.4 |

**Table 18.** Contact amino acids and varieties of bonds between the target and the ligand molecules belong to transferases involved in breast cancer

| PDB | Contact residues and bond pattern | | |
|---|---|---|---|
| | Anastrazole | Capecitabine | Quercetin |
| 2W96 | LEU6CYS8ILE13ARG26VAL27A RG29ALA30LYS33PHE66 HIS68 ASP129 PHE130ALA133 ASN134 Hydrophobic (11), weak hydrogen (1), ionic (1) | ILE12GLY13VAL14GLY15ALA 16TYR17VAL20ALA33LYS35 VAL72PHE93GLU94HIS95VA L96ASP99ARG101ASP140LY S142GLU144ASN145LEU147 ALA157ASP158 Hydrophobic (7), ionic (1), weak hydrogen (3), hydrogen (6) | ILE12GLY15ALA16TYR17VA L20ALA33LYS35HIS95VAL9 6ASP97GLN98ASP99ARG10 1THR102ASP140LYS142GL U144ASN145LEU147 ASP158 Weak hydrogen (7), hydrogen (12), hydrophobic (7), ionic (3) |
| 3TWJ | ILE82 GLY83VAL90 ALA 103MET128VAL137MET153G LU154TYR155MET156ASP160 ASP202ASN203LEU205ALA21 5ASP216PHE368 Hydrophobic (14), weak hydrogen (2), hydrogen (1), ionic (2) | ILE82 GLY83ARG84GLY 85VAL90LEU92ALA103LYS1 05MET128VAL137MET153G LU154TYR155MET156ASP1 60ASP202LEU205ALA215AS P216PHE368 Hydrophobic (20), weak hydrogen (1), hydrogen (1), ionic (1) | ILE82 VAL90 LEU92TYR 102ALA103LYS105VAL137 MET153GLU154TYR155ME T156ASP160VAL162ASP202 LEU205ALA215ASP216 PHE368 Hydrophobic (18), weak hydrogen (2), hydrogen (3), ionic (1) |
| 1BUH | ILE10GLY11GLU12GLY13VAL1 8TYR19ALA1LYS33PHE80GLU 81PHE82LEU83HIS84ASP86GL N131ASN132LEU133LEU134A LA144ASP145 Ionic (3), hydrophobic (15), weak hydrogen (2), hydrogen (1) | ILE10 GLU12GLY13 THR 14VAL18TYR19 ALA31LYS33 PHE80GLU81PHE82LEU83A SP86LYS129GLN131ASN132 LEU134ALA144ASP145THR1 58TYR159GLU162VAL163 Ionic (2), hydrophobic (9), weak hydrogen (4), hydrogen (6) | ILE10GLY11GLU12GLY 13THR14VAL18ALA31LYS33 PHE80GLU81PHE2LEU83HI S84GLN85ASP86ASP127LYS 129GLN131ASN132LEU134 ASP145 Ionic (1), hydrophobic (10), weak hydrogen (3), hydrogen (6) |
| 4YC3 | GLN184ALA185VAL186 TY R223MET224VAL226SER227A SP230ARG231ARG298PRO29 9LEU300PRO301MET326THR 329MET330MET335VAL336P HE338PRO340 ILE343 Hydrogen (7), weak hydrogen (3), hydrophobic (13) | GLU181GLU182GLN184 ALA185VAL186TYR223MET 224VAL226SER227ARG298P RO299LEU300PRO301MET3 35VAL336HIS337PHE338PR O339PRO340 Hydrogen (2), weak hydrogen (6), hydrophobic (8), cation-pi (1) | LEU180GLU181GLU182 GLN184ALA185ARG201TYR 223MET224VAL226SER227 ASP230ARG298PRO299LEU 300PRO301THR329MET33 0ASP332TYR333ASP334ME T335VAL336PHE338 PRO340ILE343 Hydrogen (10), weak hydrogen (3), hydrophobic (14), ionic (1) |
| 4KZN | GLU38 TYR39ARG56GLU 73ASN75SER95PHE96LEU97 Ionic (1), hydrogen, hydrophobic (5),weak hydrogen (2) | CYS57GLY58GLY59CYS60CY S61ASN62ASP63GLU64GLY 65LEU66GLU67 CYS68 VAL69LYS107 Hydrogen (7), hydrophobic (3), weak hydrogen (1) | CYS26GLY59CYS60CYS 61ASN62ASP63 GLU64 LEU66GLU67CYS68CYS104 LYS107 Hydrogen (6), hydrophobic (3), weak hydrogen (2) |
| 1XO2 | ILE19GLY20GLU21GLY22 GLY25VAL27ALA41LEU42LYS4 3GLU61VAL77PHE98GLU99H IS100VAL101GLN103ASP104L YS147GLN149ASN150LEU152 ALA162ASP163 Hydrophobic (13), weak hydrogen (1), hydrogen, ionic (2) | ILE19 GLY20VAL27ALA 41LYS43GLU61VAL77PHE98 GLU99HIS100VAL101ASP102 GLN103ASP104THR107GL N149ASN150LEU152ALA16 2ASP163PHE164 Hydrophobic (13), weak hydrogen (2), hydrogen (6), ionic (2) | ILE19 GLY20VAL27ALA 41LYS43GLU61VAL77PHE9 8GLU99HIS100VAL101ASP10 2GLN103ASP104THR107G LN149ASN150LEU152ALA1 62ASP163PHE164 Hydrophobic (12), weak hydrogen (1), hydrogen (11), ionic (2) |
| 4DHR | TYR57 PHE67 ASP68 HIS71 PHE77 TYR113 PRO120 PHE130SER2035TYR2038PHE 2039LEU2097 THR2098 TRP2101ASP2102TYR2105 Ionic (1), hydrophobic (11),weak hydrogen (2), hydrogen (2), ionic (3) | TYR57ASP68SER70HIS71 PHE77PRO120LEU2031 GLU2032SER2035PHE2039L EU2097THR2098TRP2101AS P2102TYR2104TYR2105 PHE2108 Hydrophobic (17), weak hydrogen (4), hydrogen (5), pi-pi (1), ionic (1) | ASP68HIS71PHE77VAL 78GLN85LEU2031GLU 2032SER2035PHE2039 LEU2097THR2098GLN2099 TRP2101 ASP 2102TYR2104 TYR2105PHE2108 Ionic (2), hydrophobic (8), weak hydrogen (5), hydrogen (4), pi-pi (1) |
| 2ITX | LEU718VAL726ALA743GLU76 2MET766CYS775LEU788THR7 90GLN791LEU792MET793GL Y796CYS797ARG841 ASN842 LEU844THR854ASP855 | ALA702LEU703LEU704MET 766ALA767SER768VAL769A SP770ASN771PRO772ARG7 76LYS852ALA1013ASP1014 TYR1016LEU1017ILE1018 | LEU718GLY719VAL726ALA 743LYS745GLU762MET766 LEU788THR790GLN791LEU 792MET793PRO794PHE79 5GLY796LEU844THR854 |

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| | Ionic (3), hydrophobic (10), weak hydrogen (4), hydrogen (7) | PRO1019 Ionic (1), hydrophobic (5), weak hydrogen (1), hydrogen (6), cation-pi (1) | ASP855 Ionic (1), hydrophobic (8), weak hydrogen (1), hydrogen (6) |
| 2BHH | ILE10 GLY11GLU12VAL18 ALA31LYS33VAL64PHE80GLU 81PHE82LEU83HIS84GLN85A SP86GLN131ASN132LEU134A LA144 ASP145 Ionic (2), hydrophobic (17),weak hydrogen (2), pi-pi (1), ionic (2) | ILE10GLY11VAL18ALA31LYS 33VAL64PHE80GLU81PHE8 2LEU83HIS84GLN85ASP86L YS89GLN131ASN132LEU134 ALA144ASP145 Ionic (1), hydrophobic (20), weak hydrogen (5), hydrogen (5), pi-pi (1) | ILE10GLY11GLU12GLY13TH R14TYR15GLY16VAL18ALA 31LYS33VAL64PHE80GLU8 1ASP127LYS129GLN131AS N132LEU134ALA144 ASP145 Ionic (2), hydrophobic (13), weak hydrogen (1), hydrogen (10) |
| 1S9J | LEU74GLY75ALA76GLY77VAL 82ALA95LYS97MET143GLU14 4HIS145MET146GLY149SER1 50ASP152GLN153SER194ASN 195LEU197CYS207ASP208 Ionic (1), hydrophobic (11), weak hydrogen (3), hydrogen (7) | LEU74GLY75ALA76GLY77AS N78GLY79GLY80VAL82ALA9 5LYS97LEU98ILE99MET143 MET146GLY149SER150ASP 152GLN153SER194ASN195L EU197CYS207ASP208 Ionic (1), hydrophobic (9), weak hydrogen (4), hydrogen (10) | LEU74GLY75ALA76GLY77V AL82ALA95LYS97VAL127M ET143GLU144HIS145MET1 46ASP147GLY149SER150GL N153SER194ASN195LEU19 7ASP208 Ionic (1), hydrophobic (7),weak hydrogen (2), hydrogen (8) |
| 2GVG | ASP192PHE193GLY194ARG19 6GLY197ASP219HIS247ARG3 11ASP313GLY353ASP354GLY 355GLY381SER382GLY383GL Y384ASP16TYR18GLU149ARG 392SER398LYS415LYS423 Ionic (12), cation-pi (1) hydrophobic (5), weak hydrogen (4), hydrogen (7) | ASP16TYR18ARG392ASP393 ASP192PHE193GLY194ARG 196ASP219ARG311ASP313 GLY353ASP354GLY355VAL3 56ASP357SER382GLY383GL Y384GLY385 LYS389 Ionic (4), hydrophobic (6), weak hydrogen (3), hydrogen bonds (9), cation-pi (2) | ASP16TYR18ARG392SER39 8LYS400LYS415HIS191ASP1 92PHE193ARG196ASP219A LA244HIS247ARG311 ASP313 Ionic (4), hydrophobic (3), weak hydrogen bond (4), hydrogen (12), ), pi-pi (2) cation-pi (2) |
| 3MV5 | GLY157LYS158GLY159THR160 PHE161GLY162LYS163VAL164 LYS179LEU181GLU191HIS194 GLU198ASP274LYS276ASP29 2PHE293GLY294LEU295THR5 THR6SER7 Pi-pi (1), ionic (5), hydrophobic (6), weak hydrogen (2), hydrogen (4) | LYS158GLY159PHE161LYS1 79LEU181ILE186GLU191HIS 194THR195GLU198GLU234 ASP274LYS276GLU278ASN2 79ASP292PHE293GLY294LE U295ARG4THR5THR6SER7 Ionic (3), hydrogen (10), hydrophobic (9), weak hydrogen (4) | GLY157LYS158GLY159PHE1 61VAL164GLU191HIS194GL U234ASP274LYS276GLU27 8ASN279THR291ASP292PH E293GLY294LEU295 PHE442ARG4THR5SER7 Ionic (4), hydrophobic (3),hydrogen (12) |
| 1MQB | ILE619GLY620ALA621GLY622 VAL627ALA644LYS646GLU66 MET667ILE676THR692GLU69 3TYR694MET695GLY698ALA6 99ARG743ASN744LEU746SER 756ASP757Ionic (3), hydrophobic (11), hydrogen (5), weak hydrogen (4) | ILE619GLY622GLU623VAL6 27ALA644LYS646GLU663TY R694MET695GLU696GLY69 8ASN744LEU746SER756ASP 757PHE758 Hydrophobic (6), hydrogen (5) weak hydrogen (1) | ILE619GLY622GLU623VAL6 27VAL643ALA644LYS646ILE 676THR692GLU693TYR694 MET695GLU696ASN697GL Y698ALA699ARG743ASN74 4LEU746SER756ASP757Ionic (1), hydrophobic (14), weak hydrogen (3), hydrogen (5), cation-pi (1) |
| 3NUP | ILE19GLY20VAL27ALA41LYS4 3VAL77PHE98GLU99HIS100V AL101GLN103ASP104GLN149 ASN150LEU152ALA162 ASP163 PHE164 Ionic (4) hydrophobic (12), weak hydrogen (2) | ILE19GLY20VAL27LYS29ALA 41LYS43VAL77PHE98GLU99 HIS100VAL101ASP102GLN1 03ASP104THR107GLN149LE U152ALA162 ASP163 Ionic (2), hydrophobic (14), hydrogen (3), weak hydrogen (2) | ILE19VAL27ALA41LYS43VA L77PHE98GLU99HIS100VAL 101ASP102GLN103ASP104 THR107LEU152ALA162ASP 163 Ionic (2), hydrophobic (8), weak hydrogen (1), hydrogen (7) |
| 1M17 | LEU694PHE699VAL702ALA71 9LYS721GLU738MET742CYS7 51LEU764THR766LEU768MET 769GLY772CYS773ARG817LE U820THR830 ASP831 Ionic (4), hydrogen (5), hydrophobic (8), weak hydrogen (3) | LEU694VAL702LYS704ALA7 19LYS721GLU738THR766GL N767LEU768MET769PRO77 0PHE771GLY772CYS773ARG 817LEU820THR830 ASP831 Hydrophobic (7), ionic (2) weak hydrogen (5), hydrogen (5) | LEU694VAL702ALA719ILE7 20LYS721GLU738MET742L EU764ILE765THR766LEU76 8MET769PRO770GLY772CY S773LEU820THR830 ASP831 Ionic (2), hydrophobic (6), weak hydrogen (5), hydrogen (6) |
| 1YWN | LYS866GLU883ILE886LEU887I LE890VAL896VAL897LEU1017 CYS1022ILE1023HIS1024ARG 1025ILE1042CYS1043 ASP1044 | TRP1094TYR1104PRO1105V AL1107PHE1113ARG1116LE U1117THR1121ARG112MET 1123ARG1124ALA1125PRO 1126 ASP1127 | LEU838GLY839VAL846ALA 864LYS866GLU883LEU887 VAL897VAL914GLU915PHE 916CYS917LYS918GLY920L EU1033CYS1043ASP1044 |

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| | Ionic (8), hydrogen (1), hydrophobic (8) | Hydrophobic (7), hydrogen (11), weak hydrogen (4), cation-pi (1) | Ionic (1), hydrophobic (13), weak hydrogen (1), hydrogen (3) |
| 4WKQ | LEU718GLY719VAL726ALA743ILE744LYS745GLU762MET766CYS775THR790LEU792MET793GLY796LEU844THR854<br>Hydrophobic (11), hydrogen (2), ionic (1), weak hydrogen (3) | LEU718GLY719VAL726ALA743ILE744LYS745GLU762MET766LEU788ILE789THR790MET793GLY796ARG841LEU844THR854ASP855<br>Ionic (1), hydrophobic (11), weak hydrogen (5), hydrogen (2) | LEU718GLY719VAL726ALA743LYS745GLU762MET766LEU788THR790GLN791LEU792MET793PRO794PHE795GLY796LEU844THR854ASP855<br>Hydrophobic (6), weak hydrogen (3), hydrogen (6), ionic (2) |
| 2J6M | LEU718PHE723VAL726ALA743LYS745GLU762MET766LEU788THR790GLN791LEU792MET793GLY796 CYS797ARG841ASN842LEU844THR854ASP855<br>Ionic (5), hydrophobic (7), weak hydrogen (1), hydrogen (1) | LEU718VAL726LYS728ALA743LYS745GLU762MET766THR790GLN791LEU792MET793PRO794PHE795GLY796CYS797ASN842LEU844THR854ASP855<br>Ionic (2), hydrogen (5), hydrophobic (10), weak hydrogen (2) | LEU718GLY719VAL726ALA743LYS745GLU762MET766LEU788THR790GLN791LEU792MET793PRO794PHE795GLY796CYS797LEU844THR854ASP855<br>Ionic (2), hydrophobic (8), weak hydrogen (1), hydrogen (7) |
| 1DI8 | ILE10GLY11GLU12GLY13VAL18ALA31LYS33VAL64PHE80GLU81PHE82LEU83HIS84GLN85ASP86GLN131ASN132LEU134ALA144ASP145<br>Ionic (2), hydrogen (2), hydrophobic (19), weak hydrogen (1) | ILE10VAL18ALA31LYS33VAL64PHE80GLU81PHE82LEU83HIS84GLN85ASP86LYS89GLN131ASN132LEU134ALA144ASP145<br>Ionic (1) hydrophobic (15),weak hydrogen (1), hydrogen (3) | ILE10VAL18ALA31LYS33VAL6PHE80GLU81PHE82LEU83HIS84GLN85ASP86GLN131LEU134ALA144ASP145PHE146LEU148<br>Hydrophobic (15), ionic (1), weak hydrogen (2), hydrogen (8) |
| 3KRR | LEU855GLY856LYS857GLY858ASN859GLY861SER862VAL863LYS882GLY935SER936ASP939ARG980ASN981ILE982LEU983GLY993ASP994<br>Hydrogen (3), hydrophobic (10), weak hydrogen bond (2) | LEU855GLY856LYS857GLY858ASN859GLY861SER862VAL863ALA880LYS882GLU930TYR931LEU932GLY935SER936ARG980ASN981LEU983ASP994<br>Hydrophobic (11), ionic (1)weak hydrogen (8), hydrogen (3) | LEU855VAL863ALA880LYS882VAL911MET929GLU930TYR931LEU932PRO933TYR934GLY935SER936ASP939LEU983GLY993ASP994<br>Hydrophobic (8), ionic (1) Weak hydrogen (3), hydrogen (8) |
| 4FA2 | VAL30VAL38ALA51VAL52LYS53ILE84LEU104THR106HIS107LEU108MET109GLY110ALA111ASP112SER154ASN155ALA157LEU167PHE169GLY170LEU171<br>Hydrophobic (14), weak hydrogen (3) | VAL30VAL38ALA51VAL52LYS53GLU71LEU75ILE84LEU104THR106HIS107LEU108MET109GLY110ALA111ASP112ASN115SER154ALA157LEU167ASP168PHE169 LEU171<br>Ionic (1), hydrogen(4), hydrophobic (16), weak hydrogen (3) | VAL30VAL38ALA51VAL52LYS53GLU71LEU75ILE84GLY85LEU86ASP88LEU104VAL105THR106GLY110ALA111SER154ASN155LEU167PHE169GLY170LEU171<br>Hydrophobic (14), ionic (1) weak hydrogen (3), hydrogen (6) |
| 5NKA | ILE619VAL627ALA644LYS646GLU663MET667ILE676ILE690THR692GLU693TYR694MET695GLU696GLY698ALA699ARG743 ASN744 ILE745LEU746SER756ASP757<br>Hydrophobic (8), ionic (1) weak hydrogen (2), hydrogen (1) | ILE619VAL627ALA644ILE645LYS646GLU663ALA664MET667ILE676ILE690ILE691THR692GLU693TYR694MET695GLY698ALA699LEU746SER756ASP757PHE758<br>Hydrophobic (13), hydrogen (6) weak hydrogen bond (1) | ASP708LEU716TRP808MET811THR812TYR813GLU815TRP819PRO837THR838PRO839MET840PHE887 ASP888<br>Hydrophobic (10), hydrogen (8),weak hydrogen (1), pi-pi (1) |
| 3G51 | LEU74GLY75GLN76GLY77SER78GLY80VAL82ALA98LYS100ASP148PHE149LEU150ASP154GLU197ASN198LEU200THR210ASP211LYS216<br>Hydrophobic (11), ionic (2) weak hydrogen bond (1) | LEU74GLY75GLN76GLY77SER78PHE79GLY80VAL82LYS100TYR191ASP193LYS195GLU197ASN198LEU200THR210ASP211PHE212GLY213LEU214LYS216<br>Hydrophobic (9), hydrogen (7), ionic (2), weak hydrogen (5) | LEU74GLY75GLN76GLY77SER78VAL82ALA98LYS100VAL131LEU147ASP148PHE149LEU150ARG151LYS195GLU197ASN198LEU200 THR210<br>Hydrophobic (15), hydrogen(2), weak hydrogen (1) |
| 4KIK | ARG105CYS114GLU214GLY218PHE219ARG220PRO224ASN225PHE424GLN425ARG427LYS428TYR571 ARG575<br>Ionic (2), cation-pi (1) hydrophobic (6), hydrogen (3), weak hydrogen (3) | PHE219VAL244SER246GLU247ASP248LEU249LYS254PHE255SER256SER258LEU259PRO260TYR261GLU408SER409PHE424GLN425LYS428GLN432<br>Ionic (1), hydrophobic (5), weak hydrogen (3), | ARG105LEU108ASN109CYS114CYS115GLU214THR217GLY218PHE219ARG220PRO224ASN225ARG427LYS428VAL429TRP430GLY431GLN432TYR571<br>Ionic (2), hydrophobic (3), weak hydrogen (6), |

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| | | hydrogen (4) | hydrogen (10), cation-pi (1) |
| 3OW4 | LEU156GLY157LYS158VAL164 ALA177 LYS179GLU198THR21 MET227GLU228TYR229ALA2 30GLU234ASN279MET281TH R291ASP292 PHE438ARG4Ionic (7), pi-pi (1) hydrophobic (7), weak hydrogen (4), hydrogen(3), cation-pi (1) | LEU156GLY157VAL164ALA1 77LYS179GLU198MET227AL A230GLY233GLU234PHE23 6PHE237ARG241MET281TH R291ASP292TYR437PHE438 ASP439PHE442ARG4 Ionic (2), hydrogen (7) hydrophobic (9), weak hydrogen (1) | LEU156GLY157LYS158VAL1 64ALA177LYS179MET227G LU228ALA230GLU234PHE2 37MET281THR291TYR437P HE438ASP439PHE442ARG4 Ionic (1), hydrophobic (10),weak hydrogen (3), hydrogen (3) |
| 4M4P | ILE336SER337ASN338ASN345 LEU346GLU347LYS397VAL39 8GLU475ARG514ALA519GLY5 20TYR521 Hydrophobic (3), weak hydrogen (1), Ionic (5), pi-pi sticking (1), cation-pi (1) | GLU451THR453TYR455SER4 56ALA458ASP499LYS501GL Y502PRO536SER537ARG53 8ILE539ILE540 Hydrophobic (7), weak hydrogen (5), hydrogen (7), ionic (2) | ARG37SER38GLN40ASP61L YS63ASN64THR65PRO66ILE 67ASP158ILE159GLY160 ASP161 Ionic (2) hydrophobic (2),weak hydrogen (3), hydrogen (9) |
| 6NJZ | TRP43LEU44THR45TYR48TRP 52ASP53LEU54TYR67THR132 LEU44THR45HIS46TYR48THR 132PHE134 Pi-pi (1), hydrophobic (6),weak hydrogen (4), hydrogen (3), ionic (2) | GLY39GLU40LEU41GLY42TR P43LEU44THR45TYR48LEU5 4TYR67TYR48THR132 ASN133MET10 Hydrophobic (7), hydrogen (11) weak hydrogen(1) | TRP43LEU44THR45HIS46TY R48TYR67THR132TRP43LE U44 THR45 TYR48THR132 Pi-pi (1), hydrophobic (8), weak hydrogen (3), hydrogen (5) |
| 2A5U | LEU657HIS658LEU661ARG69 0PHE694PHE698TYR787ASP7 88MET842LEU843LEU845GL N846ARG849PRO866TYR867 GLY868CYS869 ILE870GLU880 Hydrophobic (12), cation-pi (2) weak hydrogen (2), hydrogen (3) | TRP201PRO208TYR210LEU2 11GLN291ARG294HIS295LY S298ASP654LEU657HIS658L EU660ARG690PHE694PHE6 98ARG849GLU852SER853G LU856 Hydrophobic (18), hydrogen (6), ionic (3), cation-pi (1) | MET804PRO810TRP812ILE 831LYS833ASP836LEU838A SP841TYR867ILE879GLU88 0ILE881VAL882LYS883ALA8 85THR886THR887MET953P HE961ILE963ASP964 PHE965 Hydrophobic (18), weak hydrogen (5), hydrogen (4), ionic (2), cation-pi (2) |
| 2J6M | LEU718PHE723VAL726ALA74 3LYS745GLU762MET766LEU7 88THR790GLN791LEU792ME T793GLY796CYS797ARG841A SN842LEU844THR854ASP855 Ionic (5), hydrophobic (7), weak hydrogen (1), hydrogen(1) | LEU718VAL726LYS728ALA7 43LYS745GLU762MET766T HR790GLN791LEU792MET7 93PRO794PHE795GLY796C YS797ASN842LEU844THR85 4ASP855 Ionic (2), hydrophobic (10), weak hydrogen (2), hydrogen (5) | LEU718GLY719VAL726ALA 743LYS745GLU762MET766 LEU788THR790GLN791LEU 792MET793PRO794PHE79 5GLY796CYS797LEU844 THR854ASP855 Ionic (2), hydrophobic (8), weak hydrogen (1), hydrogen (7) |
| 2OH4 | ASP1026ARG1030ASN1031AS P1044PHE1045GLY1046LEU1 047ALA1048ARG1049ASP105 0ILE1051ASP1062ALA1063 ARG1064PRO1066 Ionic (4), hydrophobic (3), weak hydrogen (4), hydrogen (5), cation-pi (1) | ASP1026ARG1030ASN1031 CYS1043ASP1044PHE1045G LY1046LEU1047ALA1048AR G1049ASP1050ILE1051ALA 1063ARG1064LEU1065 PRO1066 Ionic (2), hydrophobic (6), cation-pi (1) weak hydrogen (2), hydrogen (9) | ASP1026ARG1030ASN1031 ASP1044PHE1045GLY1046 ALA1048ARG1049ASP1050I LE1051ARG1064LEU1065 PRO1066 Ionic (1), hydrophobic (15),weak hydrogen (2), hydrogen bonds (8), cation - pi (1) |
| 3CQU | LEU156GLY157LYS158PHE161 VAL164ALA177LYS179GLU19 8THR211MET227GLU228TYR 229ALA230GLY233GLU234GL U278MET281THR291ASP292 PHE438 Ionic (3), hydrophobic (14), weak hydrogen (3), hydrogen (5) | THR160LYS179LEU181ILE18 6LYS189GLU191HIS194THR 195GLU198ASP274ASP292 GLY294LEU295THR6SER7PH E8ALA9GLU10 Ionic (2), hydrophobic (16), weak hydrogen (11), hydrogen (16) | LEU156GLY157LYS158PHE1 61VAL164ALA177LYS179TH R211MET227GLU228TYR22 9ALA230ASN231GLU234GL U278ASN279MET281THR2 91ASP292PHE438PHE442 ARG4 Ionic (2), hydrophobic (13), weak hydrogen (6), hydrogen (9) |
| 5FED | LEU718GLY719VAL726ALA74 3LYS745GLU762MET766CYS7 75LEU788THR790GLN791ME T793GLY796CYS797ARG841A SN842LEU844THR854ASP855 Ionic (1), hydrophobic (9), weak hydrogen (1), hydrogen (3) | LEU718VAL726LYS728ALA7 43LYS745CYS775THR790GL N791LEU792MET793PRO79 4PHE795GLY796CYS797ARG 841ASN842LEU844THR854 Ionic (1), hydrophobic (12), weak hydrogen (3), hydrogen (5) | LEU718GLY719VAL726ALA 743ILE744LYS745GLU762M ET766CYS775LEU788ILE789 THR790LEU792MET793PR O794PHE795GLY796CYS79 7ARG841LEU844THR854 ASP855 Hydrophobic (9), ionic (1) weak hydrogen (5), hydrogen (7) |

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| 2A2R | TYR7PHE8VAL10GLY12ARG13 GLN51ILE104TYR108ILE203AS N204GLY205ASN206 Hydrophobic (13), pi-pi (1) weak hydrogen (1), hydrogen (4) | ARG13GLN51LEU52PRO53G LN64SER65ASN66ASP94GL U97CYS101ILE104ChainB:A SN66ARG70ASP94GLU97 ASP98 Ionic (2), hydrophobic (6), weak hydrogen (4), hydrogen (9) | ARG74TYR79GLY80LYS81A SP82GLN83ALA86ChainB:G LY73ARG74GLY77LEU78TY R79GLY80LYS81ASP82GLN 83ALA86 Ionic (2), hydrophobic (7), weak hydrogen (2), hydrogen (7) |
| 3OCB | GLY159THR160PHE161GLY16 2LYS163VAL164LYS179LEU18 1ILE186GLU191HIS194THR19 5GLU198PHE225TYR272ASP2 74ASN279ASP292PHE293GLY 294LEU295SER7 Ionic (5), hydrophobic (8), weak hydrogen (3), hydrogen (11), cation-pi (1) | LYS158GLY159PHE161LYS1 79LEU181ILE186GLU191HIS 194THR195GLU198ASP274L YS276GLU278ASN279ASP29 2GLY294ARG4THR5THR6SE R7 Ionic (4), hydrophobic (9), weak hydrogen (3), hydrogen (13) | LEU156GLY157LYS158GLY1 59VAL164ALA177LYS179TH R211MET227GLU228TYR22 9ALA230ASN231GLU234M ET281THR291ASP292PHE4 38PHE442ARG4 Ionic (2), hydrophobic (13), weak hydrogen (1), hydrogen (7) |
| 3O96 | ASN53GLN79TRP80THR81TH R82VAL201SER205LEU210TH R211LEU264LYS268VAL270V AL271TYR272ILE290ASP292 Ionic (1), pi-pi (1), hydrogen (2) hydrophobic (13), weak hydrogen (1), | ASN54GLN79TRP80THR81 THR82VAL83ILE84ARG86LY S179VAL270VAL271TYR272 ARG273ASP274ASP292GLY2 94TYR326 Hydrophobic (11), hydrogen (9) weak hydrogen (3) | ASN54GLN79TRP80SER205 ARG206HIS207LEU210THR 211ALA212TYR263LEU264L YS268VAL270VAL271TYR27 2ARG273ILE290 THR291 ASP292 Hydrophobic (9), pi-pi (1) weak hydrogen (4), hydrogen (9) |
| 3PP0 | LEU726VAL734ALA751ILE752 LYS753SER783LEU796THR79 8GLN799LEU800MET801GLY8 04CYS805ARG849ASN850LEU 852THR862ASP863PHE1004 Ionic (1), hydrophobic (9), hydrogen (3), weak hydrogen (3) | LEU726GLY727SER728GLY7 29VAL734ALA751ILE752L YS753GLU770MET774SER783 LEU785LEU796THR798LEU8 00GLY804CYS805ASP808AR G849ASN850LEU852THR86 2ASP863PHE864 Ionic (1), hydrophobic (12), weak hydrogen (3), hydrogen (5) | LEU726SER728GLY729ALA7 30VAL734ALA751ILE752LYS 753SER783LEU785LEU796V AL797THR798LEU800MET8 01GLY804CYS805ARG849A SN850LEU852THR862 ASP863 Ionic (1), hydrophobic (11), weak hydrogen (3), hydrogen (7) |
| 3OAW | TRP201LEU657HIS658 LEU661ARG690PHE694PHE69 8TYR787ASP788ME842LEU84 5GLN846ARG849PRO86TYR8 67GLY868CYS869ILE870 GLU880 Ionic (1), cation-pi (3), hydrophobic (12), hydrogen (4), weak (3) | SER806LYS807LYS808 ILE831LYS833ASP836ASP84 1TYR867ILE879ASP950ASN 951MET953ILE963ASP964H IS967LEU1090 Pi-pi (2), hydrophobic (11) | ALA889LYS890GLN892GLN 893ASN898THR899PHE902 HIS948ASN949ASP950GLN 1083PHE1084TRP1086PHE 1087LEU1090VAL1091 Pi-pi (3), hydrophobic (10), hydrogen (4) |
| 3CQW | LYS158GLY159THR160PHE16 1GLY162LYS163VAL164LYS17 9LEU181GLU191HIS194GLU1 98ASP274LYS276GLU278ASN 279ASP292PHE293GLY294LE U295ARG4THR5THR6SER7 Ionic (5), weak (3), hydrophobic (6), hydrogen (7) | LYS158GLY159PHE161GLY1 62LYS179LEU181ILE186GLU 191HIS194THR195GLU198A SP274LYS276GLU278ASN27 9ASP292GLY294LEU295THR 312ARG4THR5THR6 SER7 Hydrophobic (12), hydrogen (18), ionic (5), weak (4) | LEU156GLY157LYS158GLY1 59VAL164ALA177LYS179TH R211MET227GLU228TYR22 9ALA230ASN231GLU234GL U278ASN279MET281THR2 91ASP292PHE438PHE442 ARG4 Weak (3), hydrophobic (11), ionic (2) |

Chemoresistance is linked to Prostaglandin G/H synthase 2 and is linked to injury, proliferation, and inflammation [27,28]. The Cytochrome P450 1A1/ A2 (CYP1A1/A2) enzyme metabolizes both xenobiotics and endogenous substrates. These enzymes are involved in the activation of pro-carcinogens (estradiol and polycyclic aromatic hydrocarbons)[29].

The targeted proteins (3LN1, 6DWN and 2HI4) bound to quercetin with a highest vina score than the other two drugs. The alpha enzyme, DNA topoisomerase II, changes the topology of DNA during transcription. The enzyme primarily catalyzes the temporary breaking (transient) and rejoining of the two duplex DNA strands, there by altering the topology[30]. With the highest vina score of the three drug molecules, Quercetin targeted this enzyme. Matrix metalloproteinase-9 degrades extracellular matrix proteins, and surface plasma proteins, allowing them to be released to the cell

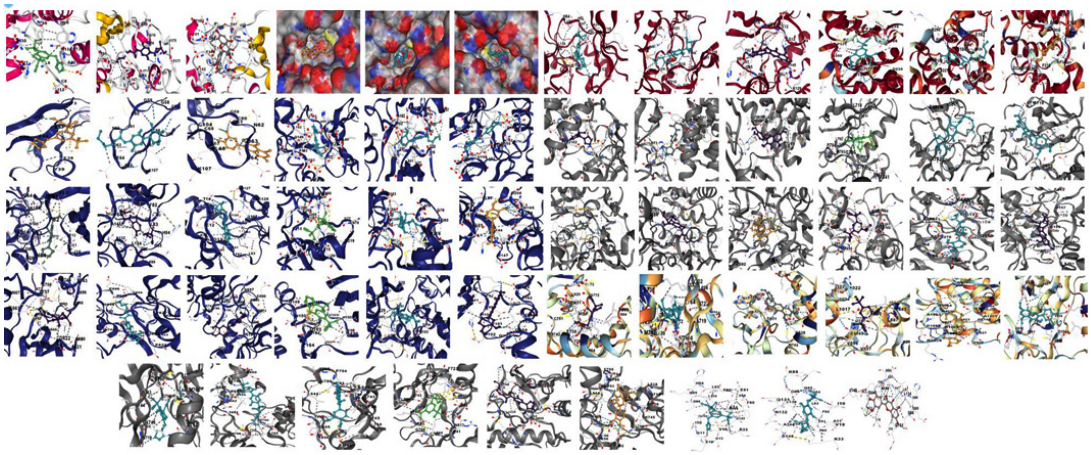

**Fig. 12a.** Binding patterns of breast cancer transferases with drugs

**Fig. 12b.** Binding patterns of breast cancer transferases with drugs

surface. It plays a wide range of roles in invasion, angiogenesis, and metastasis. Targeting MMP-9 is the best option, and present work highlighted that quercetin was the best at it. Myeloid cell leukemia-1, a close relative of B-cell lymphoma 2, promotes survival and invasion of cancer cells, making it an important chemotherapeutic target. The highest vina score of (-8.5) was achieved by quercetin.

The study concluded that cancer metabolism is largely reliant on amino acids, which are aided by the TCA cycle. Amino acid derivatives promote cancer cell progression and improve cells' ability to metastasize. Amino acid catabolism (metabolic intermediates) influences the survival and growth of cancer cells. Targeting the enzymes with the amino acids such as leucine, valine, and glutamine (TCA cycle fuel); asparagine, glycine, and glutamine (nucleotide biosynthesis); serine, methionine, glycine (methionine-folate cycle); glutathione, cysteine, and glycine (to maintain redox balance); methionine, serine, and glycine (DNA and histone methylation) reduces the cancer cell proliferation and tumor burden[31]. More vina score correlates with more hydrogen and hydrophobic interactions.

## CONCLUSION

It confirms that, out of the three drugs tested, the natural compound quercetin establishes the most effective in targeting and controlling

the BC cells, in line with our *in vitro* work[10]. When BC cell lines were fed with quercetin, anastrozole, and capecitabine, both independently and in combination, a decrease in cell viability and increase in apoptosis percentage at low doses of Quercetin[10] was noted. Because quercetin is chemoprotective and radioprotective to healthy/ normal cells, it can be used during cancer treatment.

## ACKNOWLEDGEMENT

Author is grateful to the Academy, Sri Devaraj Urs Acadmy of Higher Education and Research for providing the facility to carry out this docking study. Author is mentioning her gratitude to Dr. Prashanthi K., Assistant Professor, Department of Biotechnology, M.S. Ramaiah University of Applied Sciences, Bengaluru.

**Conflict of Interest**

None.

**Funding Source**

No funds are available.

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