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# Comparison of ketoralc tromethamine and Cyclophosphamide against the antigenic peptide of ESR1 (Breast cancer) using Insilico techniques.

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**ABSTRACT**

**Background:** To investigate the possible efficacy of NSAIDs (Nonsteroidal Anti-Inflammatory Drugs) against the Estrogen Receptor 1 (ESR1) Antigenic peptide (Model Archive (https://modelarchive.org/doi/10.5452/ma-9z6ga) using insilico procedures. **Objectives:** The primary goal of our current work is to dock the modelled ESR1 peptide (Breast cancr) with an anti-inflammatory drug. Drug docking studies were performed in order to predict the efficacy of *ketoralc tromethamine* against ESR1 peptide. **Materials and methods:** The UniProt database provided the genomic sequence of ESR1-Peptide, which was then docked using the CBDOCK server with *ketoralc tromethamine*, an anti-inflammatory medication currently in use, and *Cyclophosphamide*, a control agent. **Results and discussion:** The current study demonstrates that the reference medication, *Cyclophosphamide*, and *ketoralc tromethamine* interact with ESR1-peptide in an efficient manner. The docking score was used to assess the compound's efficacy against the protein that causes breast cancer. Compared to the control medication *Cyclophosphamide*, *ketoralc tromethamine* exhibits a higher binding affinity. Therefore, when used in conjunction with novel medications to target the anti-cancer activity protein ESR1 in human breast cancer, ketoralc tromethamine may be considered a viable choice. **Conclusion:** This study's conclusion is that anti-cancer medications successfully block ESR1. The results of this study have a substantial influence on the field of current cancer informatics research.

**Keywords:** Estrogen Receptor 1 (ESR1), ketoralc tromethamine, Cyclophosphamide (reference medication), Model Archive, (CBDOCK, and Discovery Studio.

## 1.INTRODUCTION

ESR1 mutations were discovered in breast cancer in 1997 [Zhang QX et al, 1997]. But it wasn't until 2013 that the significance of ESR1 mutations in ET resistance was discovered through the genomic sequencing of metastatic breast cancer (MBC) [4, 5, 6, 7, 8]. Research on patient-derived circulating tumor cell (CTC) lines published shortly after revealed that primary cancer cells with ESR1 mutations are sensitive to ESR1 depletion and rather resistant to endocrine therapy [9]. ESR1 mutations were previously not detectable in The Cancer Genome Atlas because of the sequencing of early, treatment-naïve cancers in this database [10]. On the other hand, ESR1 mutations were present in 4% of tumors in the database with treatment-naïve endometrial cancers. [11].However, ESR1 mutations alone do not fully account for endocrine resistance in MBC. About 50% of cases of endocrine resistance are associated with an ESR1 mutation; other, increasingly identified reasons include ESR1 deletion, amplification, and translocation as well as alterations in the PI3K-AKT-mTORC1, RAS-MAPK, and CDK4/6-RB-E2F pathways [18]. Additionally, ESR1 mutations frequently occur with other concurrent genetic alterations, which together lead to a poorer prognosis globally [19, 20]. Furthermore, ET is increasingly used with other targeted treatments such mTORC1, PI3K, or CDK4/6 inhibition. A common aspect in many situations is that ESR1 mutation alone is insufficient for total resistance, even though this needs to be predicted and examined experimentally.

The frequency of ESR1 mutations in individuals is influenced by the length and conditions of previous endocrine therapy. ESR1 mutations are present in 20–40% of patients who have had aromatase inhibition (AI) for MBC; the frequency varies depending on the locations of the metastatic disease [2, 5, 6, 7, 12, 13, 14]. In contrast, the incidence of ESR1 mutations is less than 1% in ET-naïve MBC [7, 10, 14], 1.5–7% following neo adjuvant AI [16, 17], and only 4–5% in recurrent breast cancer following prior adjuvant AI (including recurrence during adjuvant AI) [12, 14, 15]. Thus, in the instance of spreading HR-positive breast cancer. Computer-Aided Drug Design (CADD) accelerates drug discovery through virtual screening, molecular docking, and predictive modelling. It reduces the time and cost required to find new medicines. In this investigation, we focus on an NSAID (Nonsteroidal Anti-Inflammatory Drug), ketoralc tromethamine, which inhibits the potential antigenic peptide, ESR1 using insilico protocols. *Ketoralc tromethamine* was compared with an existing chemotherapic drug, namely, Cyclophosphamide. From this, we understand how an anti-inflammatory drug can be beneficial in the field of cancer research.

## 2.MATERIALS AND METHODS

**Ligand selection:** The chemical compounds with NSAIDs (Nonsteroidal Anti-Inflammatory Drug properties: ketoralc tromethamine and Cyclophosphamide (control drug) were the focus of molecular docking research. PubChem (https://pubchem.ncbi.nlm.nih.gov/) provided the simplified molecular input line entry system (SMILES) format for the chosen chemical substances [18]. The PDB structure was obtained by submitting the three chemical compounds' canonical SMILES (Simplified Molecular Input Line Entry System) to the Online SMILES Translator (https://cactus.nci.nih.gov/translate/). To conduct pharmacological docking studies, the 3D antigenic Breast cancer peptide was obtained from the PDB-Model archive (https://modelarchive.org/doi/10.5452/ma-9z6ga).

**Molecular drug docking:** One of the most popular insilico drug discovery techniques is molecular docking, which looks at tiny molecules' ideal conformations when they interact with target molecules.

Docking analyses were performed on ESR1 and two chemical molecules. To predict the interaction between receptor and ligand molecules, PDB files for the ligand and receptor 3D structure were uploaded to the CBDOCK website [19] (http://hdock.phys.hust.edu.cn/). Additionally, the CBDOCK analysis provided details about the ligand's and receptor's surface residues. **3D macromolecular visualization:** Two compounds were subjected to molecular drug docking investigations using ESR1, including *Cyclophosphamide* (a control medication) and *ketoralc tromethamine*. Discovery Studio, a molecular visualization program, was used to visualize the compounds' three-dimensional structures.

## 3.RESULTS AND DISCUSSION

To evaluate the binding efficacy, compounds such as the test chemical *ketoralc tromethamine* and the control medication *Cyclophosphamide* were docked with the modelled ESR1 as shown in Table 1. The binding model with the greatest docking score, as shown in Table 1, was chosen from the top 10 binding models generated by the CBDOCK server because it had a higher binding affinity for the receptor. With a docking value of -5.4 *kcal/mol*, the *ketoralc tromethamine* molecule has a higher binding affinity than *Cyclophosphamide* (the control medicine), which have docking scores of -5.4 kcal/mol and -3.3 *kcal/mol*, respectively. The potential energy change that could result from the interaction between the ligand and protein is represented by the score. Therefore, a strong bond is indicated by a very negative score, whereas a weak or missing bond is indicated by a score that is less negative or positive. In this study, *ketoralc tromethamine* and *Cyclophosphamide* (as the control drug) were docked with the modelled Estrogen Receptor 1 (ESR1) Peptide using CBDOCK, an innovative web server for template-based modeling and free docking, as shown in (Table: 1) the drug binding affinities of the ligand and receptor. Following the docking analysis, the molecular visualization program Discovery Studio was used to analyse the three-dimensional (3D) structure of the ligand and receptor, as shown in Figures 2 and 3 for *ketoralc tromethamine* and (ESR1) and Figures 5 and 6 for *Cyclophosphamide* (control drug) and (ESR1). Previous studies have shown the efficacy of the CBDOCK server.

**Table 1: Summary of docking scores of ligand and receptor**

| **Receptor** | **Drug** | **Docking Score** |
|---|---|---|
| Estrogen Receptor (ESR1) | Cyclophosphamide (control drug) | -3.3 *kcal/mol* |
| Estrogen Receptor (ESR1) | *ketoralc tromethamine* | -5.4 *kcal/mol* |

Note: According to the docking score above, ketoralc tromethamine most successfully inhibits the growth of breast cancer protein cells for ESR1. The most successful treatment for Breast cancer is Cyclophosphamide, the control drug.

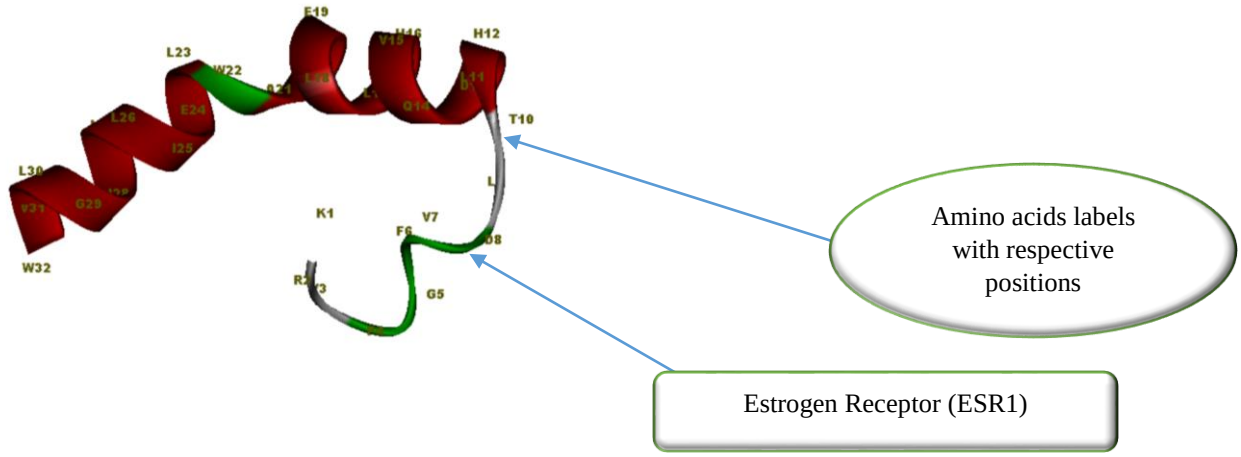


Figure 1: Schematic model view of Estrogen Receptor (ESR1) viewed with visualization tool, Discovery Studio.

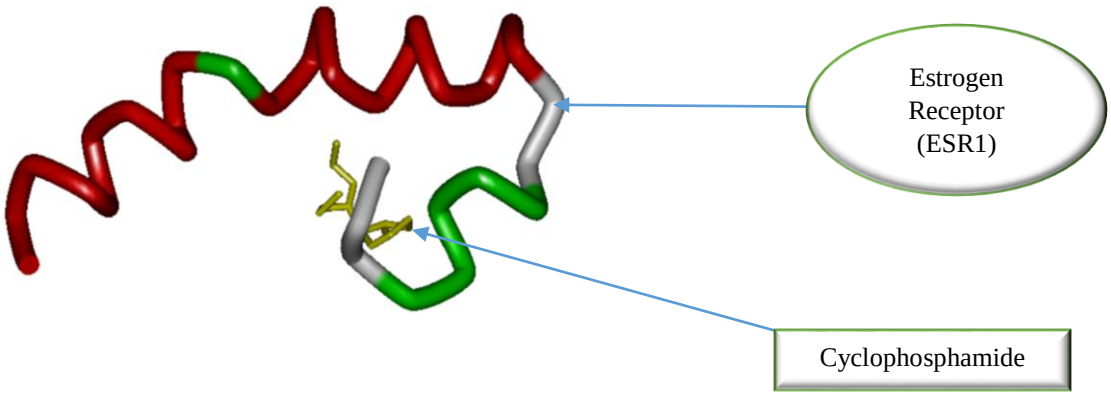


Figure 2: Schematic model view of *Cyclophosphamide* and Estrogen Receptor (ESR1) (3D Complex) viewed with visualization tool, Discovery Studio.

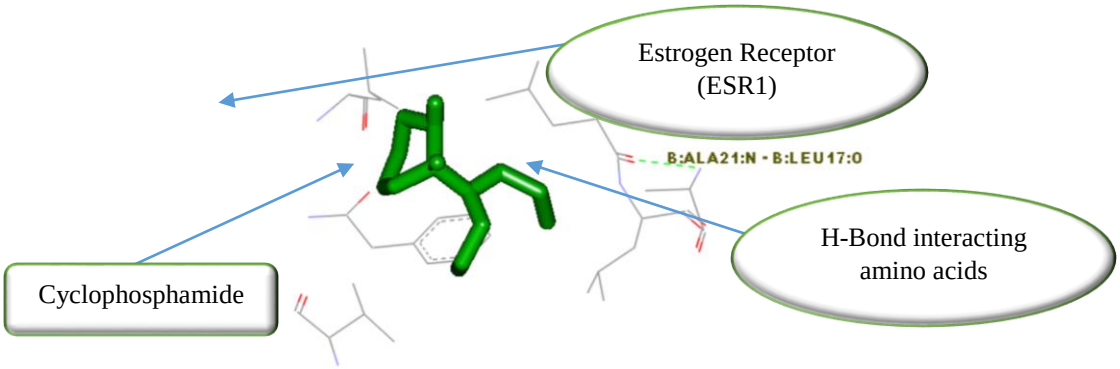


Figure 3: H-Bond interactions model view of *Cyclophosphamide* and Estrogen Receptor (ESR1) viewed with visualization tool, Discovery Studio.

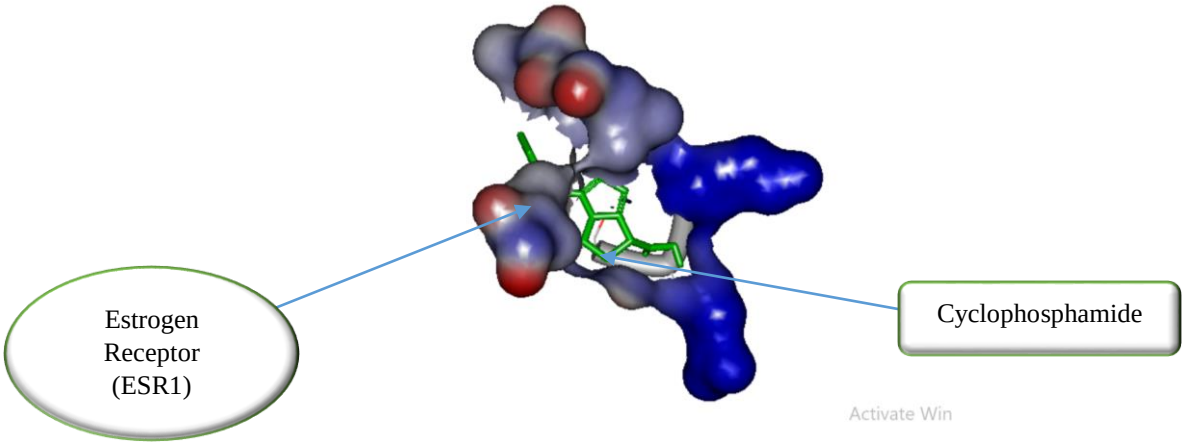


Figure 4: Van der Waals interactions model view of *Cyclophosphamide* and Estrogen Receptor (ESR1) viewed with visualization tool, Discovery Studio.

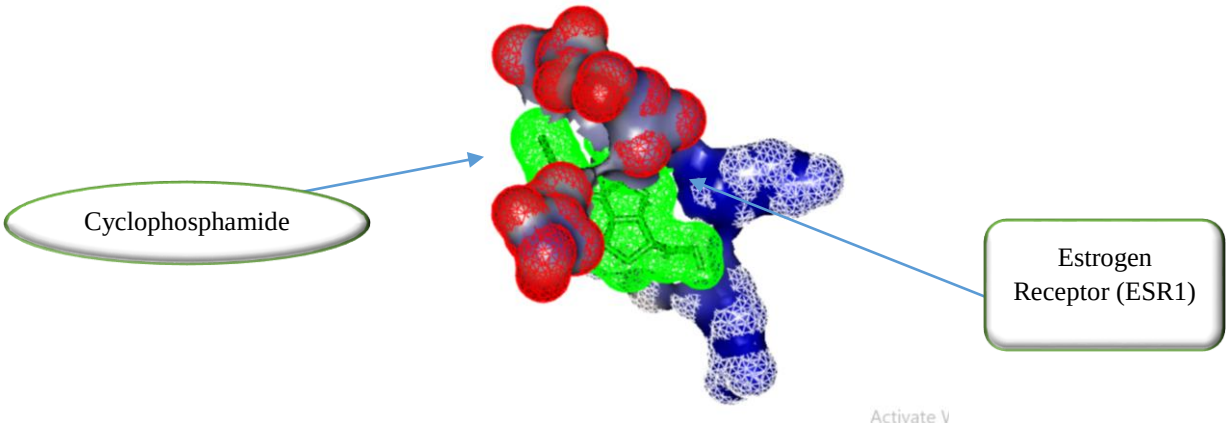

Figure 5: Electrostatics force model view of *Cyclophosphamide* and Estrogen Receptor (ESR1) and Estrogen Receptor (ESR1) viewed with the visualization tool, Discovery Studio.

**Drug and protein complex:** In essence, a drug is a pair of molecular handcuffs sent into the city or a highly specialized, custom-made key. The medication and its matching protein click together. The drug-protein complex is this combination structure. **Electrostatic force drug and receptor:** In electrostatic interaction between a protein and a ligand (often called the electrostatic force between a receptor and a drug) is a strong, non-covalent attraction that happens when a positively charged area on a drug molecule aligns with a negatively charged area on a receptor protein. Picture your receptor protein as a secure electronic door lock and your drug molecule as the corresponding key. Although certain sections of the drug-key must fit the lock's shape, electrostatic forces function like inherent magnets that draw the key toward the keyhole from afar. However, in the molecular realm, if your desired protein features a region of amino acids that carry a negative charge (such as Glu or Asp), an intelligent drug designer will assign a constant positive charge to the drug molecule at the precisely corresponding location. As the medication moves through the congested cellular surroundings, these magnetic forces establish a far-reaching attraction. They insert the drug directly into the binding site and secure it firmly, forming a stable drug-protein complex that either deactivates or activates the target.

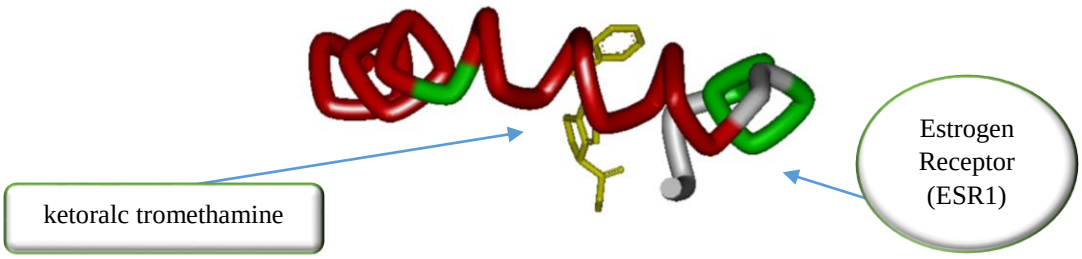


Figure 6: Tube model view of *ketoralc tromethamine* and Estrogen Receptor (ESR1) viewed with the visualization tool Discovery Studio.

According to Sahoo et al., [20] the docking study allows for the assessment, screening, and prediction of the computational electrostatics of the ligand-receptor complex [21]. Mohapatra et al. state that this investigation normally consists of two independent steps [22]. First, ligand conformations are sampled based on the protein's active site. Second, conformations are ranked using a scoring mechanism. According to Dash et al., [23] sampling algorithms should theoretically recreate experimental binding modes, and confirmations should be rated using a scoring mechanism [24]. The dry lab approach offers a significant advantage over in vivo lab studies in terms of resource and time investment, as noted by Sahoo et al. [25] and Pramanik et al., [26]. Nanda et al.,[27] explained that this approach predicts the ligand orientation in a complex formed by the ligand itself with proteins or enzymes. Also, the docked complex's shape and electrostatic interaction quantify the interaction.


Figure 7: H-Bond interactions model view of *ketoralc tromethamine* and Estrogen Receptor (ESR1) viewed with visualization tool, Discovery Studio.

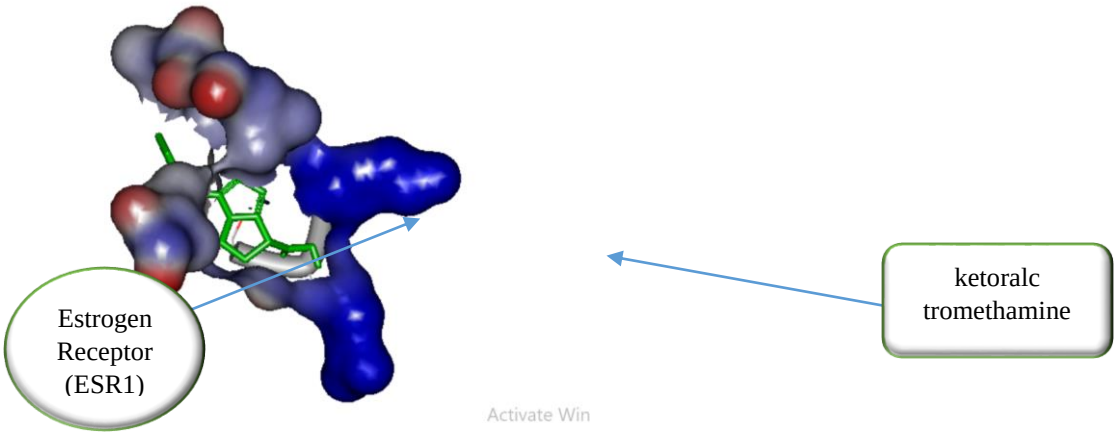


Figure 4: Van der Waals interactions model view of *ketoralc tromethamine* and Estrogen Receptor (ESR1) viewed with visualization tool, Discovery Studio.

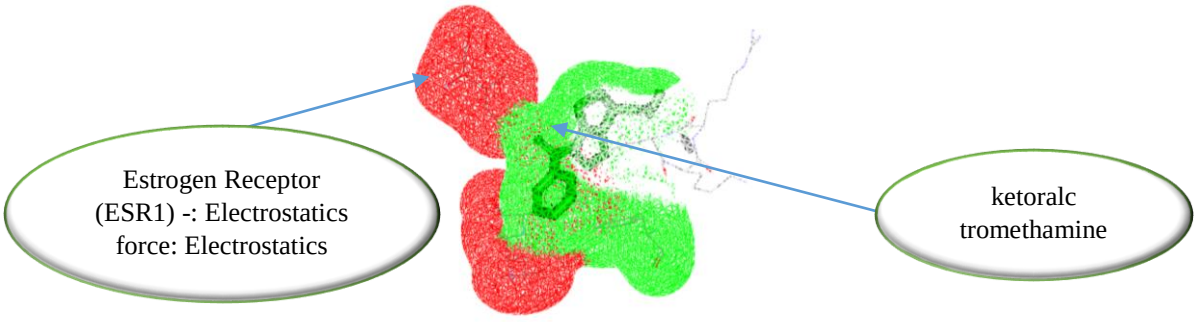


Figure 6: Electrostatics force model view of *ketoralc tromethamine* and Estrogen Receptor (ESR1) and Estrogen Receptor (ESR1) viewed with the visualization tool, Discovery Studio.

**Van der Waals interaction between drug and receptor:** Van der Waals forces are mild, short-range electrostatic attractions that happen when two neutral atoms' electron clouds approach one another. This creates transient dipoles that gently pull the atoms together. Van der Waals forces can be likened to molecular Velcro if electrostatic interactions are similar to strong magnets. Imagine a key (the medication molecule) and a high-security lock (the receptor protein). The key must precisely match the interior geometry of the lock in order to turn it, however the magnets (electrostatic forces) can attract the key to the lock from a distance. Van der Waals forces start to matter at this point. Every atom is surrounded by a swarm of moving electrons. The electron clouds of two atoms automatically adjust to one another when they are very close to one another without creating a chemical bond or having a permanent charge. There is a brief, minor attraction as one side briefly becomes slightly positive and the other slightly negative.

**Mechanisms of drug docking:** Endocrine resistance in MBC is only partially explained by ESR1 mutations alone. An ESR1 mutation is linked to about 50% of endocrine resistance instances; other causes, which are becoming better recognized, include changes in the PI3K-AKT-mTORC1, RAS-MAPK, and CDK4/6-RB-E2F pathways as well as ESR1 deletion, amplification, and translocation [26]. Furthermore, ESR1 mutations typically coexist with many contemporaneous genetic changes, which collectively result in a worse prognosis worldwide [27, 28].

The binding kinetics of the common anti-inflammatory medication ketoralc tromethamine and the Estrogen Receptor (ESR1) inhibitor cyclophosphamide, which served as a reference control molecule, were evaluated in this study using virtual screening and molecular docking simulations. The tromethamine salt of ketorolac, a synthetic pyrrolizine carboxylic acid derivative with analgesic, antipyretic, and anti-inflammatory effects, is called ketorolac tromethamine. Both COX-1 and COX-2 are inhibited by ketorolac tromethamine, a non-selective inhibitor of the cyclooxygenases (COX). By inhibiting COX-2, which is undetectable in most tissues but up-regulated at the inflammation sites, this agent prevents the conversion of arachidonic acid to prostaglandins at the inflammation site. It demonstrated a competitive docking score of -5.4 kcal/mol. Ketoralc tromethamine's constant interaction properties point to a strong steric compatibility with the hydrophobic and electrostatic residues in the functional domain of the target protein. The amino acids that interact with the H-Bond against the ESR1 modeled peptide are (LYS:1, ARG:2, PHE:6, VAL:3).

Phosphorodiamide Cyclophosphamide is 1, 3, 2-oxazaphosphinan-2-amine 2-oxide with two 2-chloroethyl groups added to the amino nitrogen atom. Alkylating, antineoplastic, xenobiotic, immunosuppressive, antirheumatic, carcinogenic, environmental pollutant, and drug allergen are some of its functions. As a reference standard in this context, *Cyclophosphamide* achieved a moderate docking affinity of -5.3 kcal/mol. All three ligand complexes had a well-conserved binding pocket, according to an analysis of the molecular dynamics and electrostatic interaction summaries. For every control medication, essential amino acid residues like ALA: 21 and LEU: 17 were consistently engaged in the structural binding network. These specific hydrophobic, neutral, and hydrophilic amino acid positions are consistently recruited, highlighting their significance as crucial hotspots for accurate structural stabilization. These substances appear to bind to the essential functional regions of the modelled Estrogen Receptor (ESR1) transporter, according to the combined thermodynamic data. The docking studies clearly elucidate that *ketoralc tromethamine* is found at the binding site of the membrane regions [29, 30].

## 4. CONCLUSION

One of the most prevalent malignancies affecting women is breast cancer. It occurs when breast cancer cells proliferate and develop into tumors. The entire findings make it abundantly evident that the medications (*ketoralc tromethamine* and *Cyclophosphamide*, the control drug) may inhibit the hydrophobic parts of the unique anticipated structure of the Estrogen receptor 1 (ESR1) of Breast cancer. The Model Archive has received the docking data and the modelled structures. We infer from this study that the anti-inflammatory (NSAID) medication *ketoralc tromethamine* effectively binds to the Estrogen receptor (ESR1). The findings of this investigation are crucial to the field of contemporary cancer informatics research.

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## 6. CONFLICT OF INTEREST

No conflicts of interest are disclosed by the writers.

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