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Machine Learning-Based Virtual Screening and QSAR Analysis of ESR1 Inhibitors for Breast Cancer Treatment

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ABSTRACT
Estrogen receptor alpha (ESR1) is a critical therapeutic target in hormone receptor positive breast cancer, however, endocrine resistance remains a challenge. The aim of this study is to identify potential inhibitors of the oestrogen receptor (ESR1) from bioactivity data from ChEMBL using an integrated computational workflow. A collection of 3130 compounds that have been reported with IC50 values were subjected to pIC50 transformation, PubChem fingerprint encoding, Random Forest QSAR modeling, Lipinski screening, ADMET profiling, molecular docking, and molecular dynamics simulation. The Random Forest model showed acceptable predictive performance, with a test-set R^2 of 0.738 and cross-validated Q^2 values of 0.625 and 0.638. After filtering, 115 candidates were prioritized for docking against ESR1. Docking analysis identified CHEMBL2403358 as the top candidate, exhibiting a binding affinity of 10.0 kcal/mol, which surpassed that of the reference ligand, estradiol. This molecule established key interactions with residues GLU353, ASP351, LEU387, LEU391, and PHE404. MD simulations corroborated the stability of the ESR1–CHEMBL2403358 complex throughout the trajectory. This integrated in silico workflow designates CHEMBL2403358 as a promising ESR1 inhibitor scaffold, warranting further experimental validation for the development of novel therapeutic strategies against endocrine-resistant breast cancer.

Keywords: Breast cancer; ESR1 inhibitors; Molecular docking; Molecular dynamics; QSAR; Virtual screening

Graphical abstract:

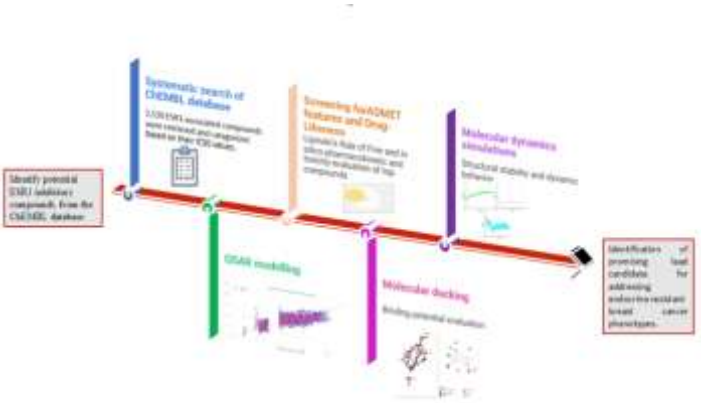


Figure 1. Integrated QSAR, docking, and simulation workflow for ESR1 inhibitor screening

Introduction

Breast cancer remains one of the most common malignancies among women and a major cause of cancer-related mortality worldwide [1,2]. Hormone receptor-positive breast cancer is strongly influenced by estrogen receptor alpha (ESR1), which regulates estrogen-dependent transcriptional signaling and tumor proliferation. ESR1 is therefore a major therapeutic target for endocrine therapies, including selective estrogen receptor modulators and selective estrogen receptor degraders [3-6]. However, acquired resistance to endocrine therapy continues to limit durable clinical response, creating a need for new ESR1-targeting molecules with improved inhibitory potential [7-10].

Computational drug discovery can accelerate early-stage lead identification by combining ligand-based and structure-based approaches. QSAR modelling helps to identify the molecular features associated with activity, while molecular docking, ADMET screening and molecular dynamics simulation can be used to prioritise drug-

like compounds with stable binding to the target. In this study, ChEMBL-derived ESR1 bioactivity data were used to develop a QSAR model based on machine learning and to identify potential ESR1 inhibitors by integrated ADMET filtration, molecular docking and molecular dynamics simulation [11-14].

2. Material and Methods

2.1. Target Protein Identification and Bioactivity Data Retrieval

Bioactivity data of ESR1 were extracted from the ChEMBL database (version 26) with the UniProt ID P03372 and the ChEMBL target ID CHEMBL206. Reported half maximal inhibitory concentration values of small molecules were gathered. To enhance the robustness of the dataset, entries with missing, inconsistent or duplicate IC50 values were removed. The final curated dataset contained 3130 compounds for the downstream QSAR modelling and virtual screening.

2.2. QSAR modeling

2.2.1 Bioactivity Classification, Normalization and Statistical Validation

The retrieved compounds were classified into three categories based on their IC50 values: Active (IC50 ≤ 100 nM), Inactive (IC50 ≥ 10,000 nM) and Intermediate (100 nM < IC50 < 10,000 nM) (Figure 1). IC50 values were transformed to pIC50 (−log10(IC50)) to improve the distribution of data for modelling purposes, which linearises the logarithmic relation between concentration and potency (15-17). The statistical significance of the selected activity thresholds was validated using the Mann-Whitney U test ($\alpha = 0.05$),(19), ensuring that the active and inactive groups were statistically distinct in their pIC50 distributions. The Mann-Whitney U test confirmed significant differences between active and inactive compounds, supporting the activity-based separation used for QSAR modeling.

2.2.2 Molecular Fingerprinting and Feature Encoding

The descriptors in this research were calculated using PaDEL software. Structural features of the compounds were encoded using PubChem fingerprints (881-bit), (18), which capture substructural patterns as binary vectors. These fingerprints served as input features for machine learning models.

2.2.3 Predictive Model Development and Validation

The dataset was split into training and test subsets using an 80:20 stratified partition. Random Forest regression was implemented in Python and optimized through grid search with 10-fold and 20-fold cross-validation. Model performance was assessed using R^2, Q^2, and RMSE. SVM and XGBoost were also compared, and Random Forest was selected as the final model. Descriptor importance was evaluated using mean decrease in impurity, and the top-ranked features were retained for further analysis (19).

2.3. Screening the selected hit molecules for ADMET features and Drug-Likeness

Drug-likeness screening was performed using Lipinski's Rule of Five, including molecular weight ≤ 500 Da, LogP ≤ 5, hydrogen bond donors ≤ 5, and hydrogen bond acceptors ≤ 10. ADMET-related properties were evaluated for prioritized compounds to assess absorption, distribution, metabolism, excretion, and toxicity profiles before docking.

2.3.1 Lead Optimization

Lead candidates were prioritized using predicted pIC50, Lipinski compliance, ADMET profile, and favorable QSAR-derived structural features. This filtering process yielded 115 compounds for molecular docking against ESR1.

2.4. Molecular Docking

Molecular docking was performed against ESR1 using AutoDock through the PyRx interface. Shortlisted ligands were retrieved in SDF format, energy-minimized using the Universal Force Field, and converted to PDBQT format. The docking grid was centered at 15.4143, −0.3242, and 9.9533, with dimensions of 61.73 × 45.08 × 65.44 Å. Docking was performed with an exhaustiveness of 8 and an energy range of 4 kcal/mol. Estradiol was used as the reference ligand. Protein-ligand interactions were visualized using BIOVIA Discovery Studio Visualizer and PyMOL.

2.5. Molecular dynamics (MD) simulations

The best docked ESR1-ligand complex was subjected to 100 ns molecular dynamics simulation using GROMACS. The AMBER03 force field was used, and the system was solvated in a triclinic TIP3P water box with a 12 Å buffer. Na+ and Cl− ions were added for neutralization and 0.15 M salt concentration (20). Energy minimization was followed by NVT equilibration for 500 ps at 300 K and NPT equilibration for 1 ns at 1 atm. Production simulation was performed for 100 ns with a 2 fs time step. RMSD, RMSF, and radius of gyration were analyzed to assess complex stability.

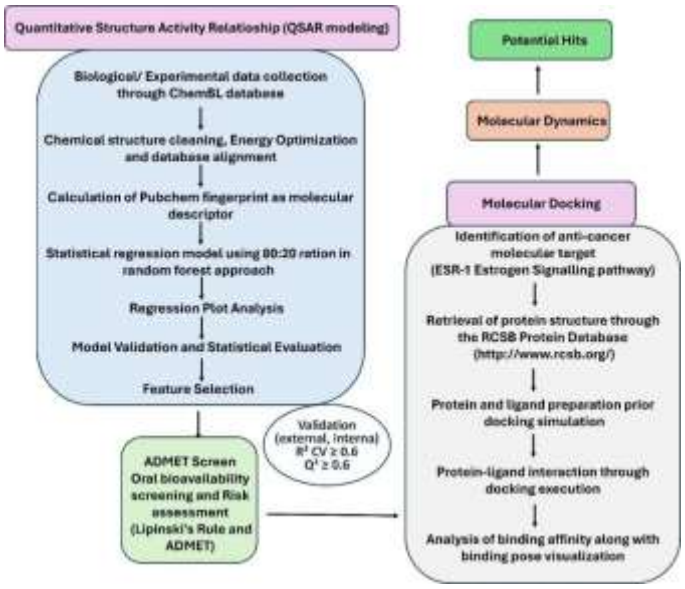


Figure 2. Integrated workflow for virtual screening combining ligand-based (QSAR models) and structure-based (docking) approaches.

3. Results and Discussion

3.1. Dataset Curation and Compound Distribution

The curated dataset contained 3,130 ESR1-associated compounds. Among these, 1,840 compounds were classified as active, 730 as inactive, and 560 as intermediate. The intermediate compounds were excluded to improve class separation, leaving 2,570 compounds for QSAR model development. The resulting modelling data set has thus 2,570 compounds, and the active to inactive ratio is 2.52:1 (**Figure 3**).

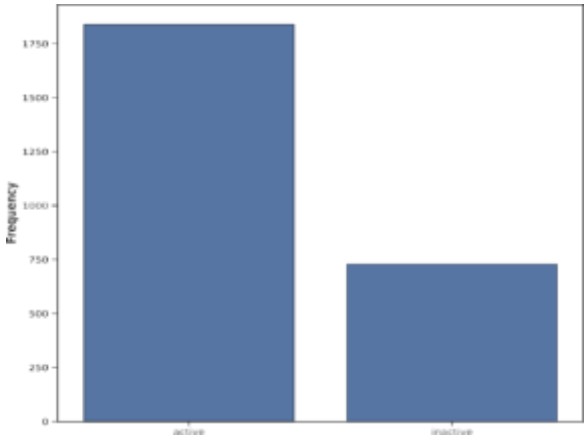


Figure 3. Compound distribution into active and inactive classes.

3.2. QSAR Model Development and Validation

The Random Forest regression model developed using a standard 80:20 train-test split (2,056 training and 514 test compounds), demonstrated robust predictive performance for inhibitors. The model achieved an R^2 value of 0.738 on the independent test set, explaining 73.8% of bioactivity variance, while internal validation through 10-fold and 20-fold cross-validation yielded Q^2 values of 0.625 and 0.638 respectively-confirming stability across different validation protocols (Figure 4). These metrics fall within the well-established acceptability thresholds for QSAR models.

3.3. Identification of Key Molecular Descriptors

The final QSAR model identified five PubChem fingerprint bits that contributed strongly to predicted ESR1 inhibitory activity:

Activity = 6.810 + 0.173 × Bit95 + 0.178 × Bit838 + 0.196 × Bit427 + 0.197 × Bit456 − 0.222 × Bit717.

Bit95, Bit838, Bit427, and Bit456 showed positive effects on predicted activity, whereas Bit717 showed a negative effect. Their structural interpretations are summarised in **Table 1**, and the relative significance of the top bits of the fingerprints is indicated in **Figure 5.** These descriptors indicate that selected heavy-atom, brominated, alkynyl, and phosphoryl features may favor ESR1 inhibitory activity, while chlorinated toluene-like features may reduce predicted potency. Positive coefficients (green bars) indicate structural features that

enhance activity, while negative coefficients (red bars) represent features associated with reduced activity. Bit456 (phosphoryl groups) and Bit838 (brominated moieties) were strongly associated with increased activity, while Bit717 (chlorinated toluene derivatives) had the largest negative impact.

Table1: Description of PubChem Fingerprints used in QSAR equation

SERIAL NO.	FINGERPRINTS	DESCRIPTIONS	EFFECT ON PREDICTION MODEL
1	Bit95	>= 1 Hg	Positive
2	Bit838	BrC1C(Br)CCCC1	Positive
3	Bit427	C(#C)(-C)	Positive
4	Bit456	P(-O)(=O)	Positive
5	Bit717	Cc1ccc(Cl)cc1	Negative

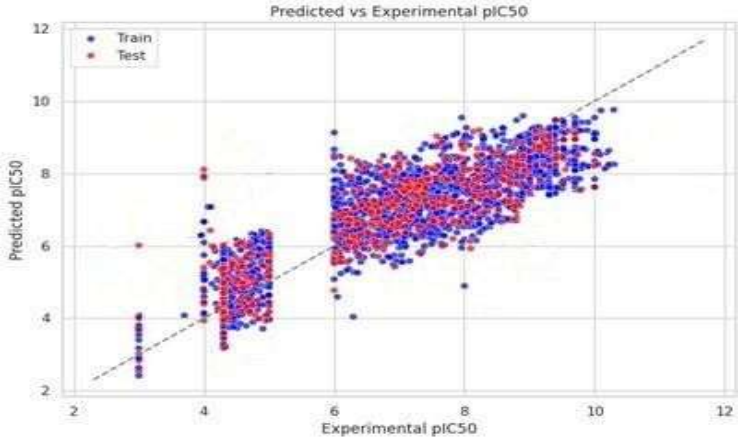


Figure 4. Scatter plot of predicted versus experimental pIC50 values for the training set (blue) and test set (red) using the Random Forest regression

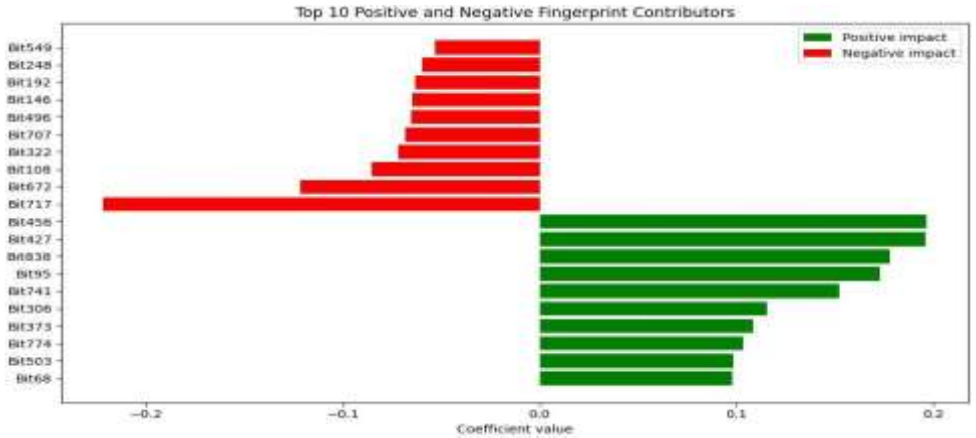


Figure 5. Top 10 PubChem fingerprint bits contributing to predicted biological activity in the final QSAR model.

3.4. ADMET profiling

ADMET analysis of the top 10 prioritized compounds showed generally acceptable pharmacokinetic and toxicity-related profiles. Most candidates showed high predicted human intestinal absorption, acceptable clearance, and low hepatotoxicity risk. CYP450 inhibition risk was limited across the selected molecules, although some compounds showed possible CYP-related interactions. Two compounds showed positive AMES alerts and should be treated cautiously until experimental toxicity validation is performed. The full ADMET and Lipinski profile of the top 10 compounds is provided in Supplementary Table S1.

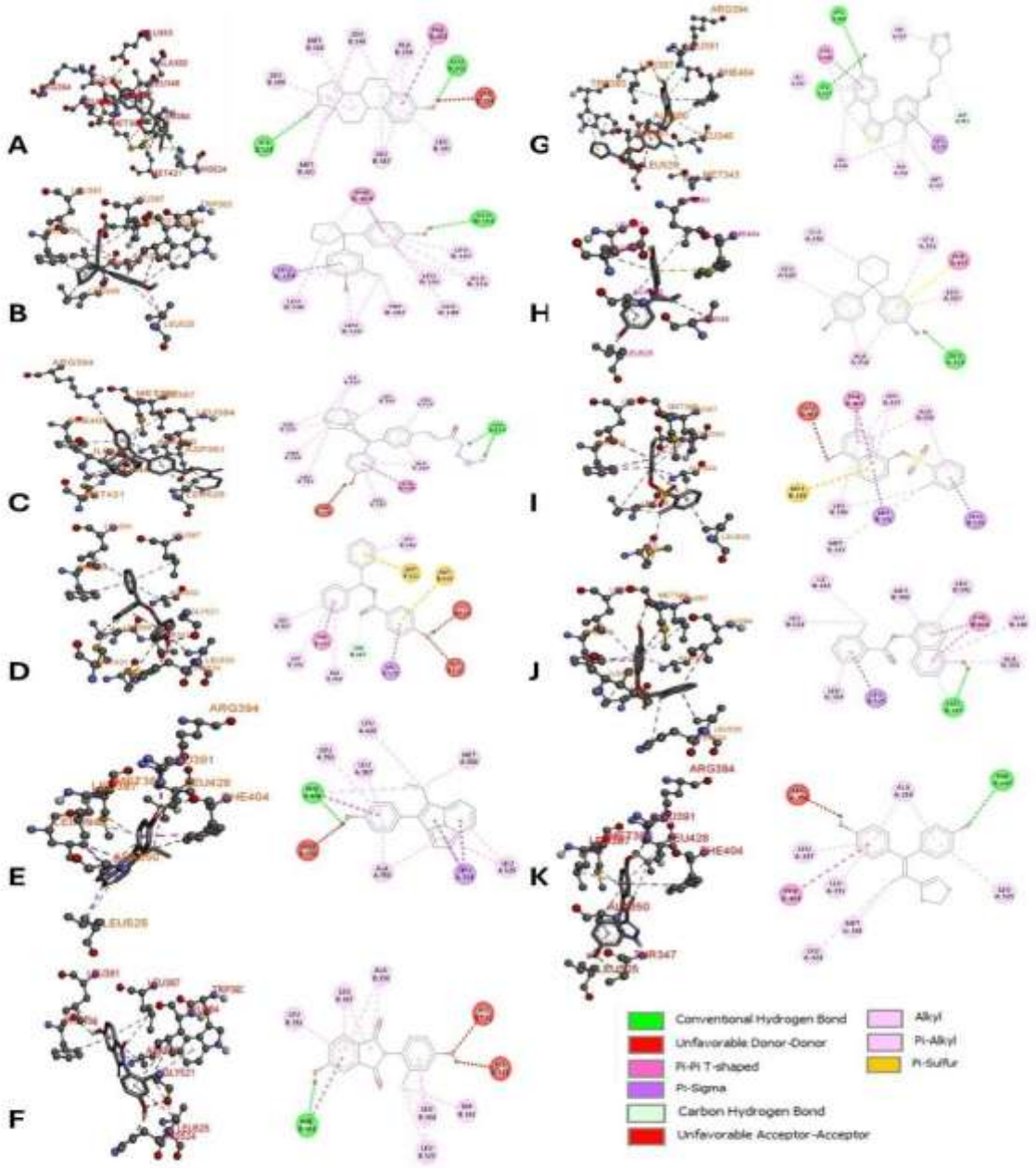
3.5. Molecular docking

Docking scores ranged from −9.5 to −10.0 kcal/mol, outperforming estradiol, which showed −9.2 kcal/mol. CHEMBL2403358 had the strongest affinity at −10.0 kcal/mol and interacted with key ESR1 residues, including PHE404, GLU353, LEU387, ALA350, LEU391, LEU525, and TRP383. CHEMBL4073395 and CHEMBL2071180 followed with scores of −9.9 and −9.8 kcal/mol. Recurrent interactions with ALA350, LEU346, LEU387,

LEU391, PHE404, and LEU525 supported stable binding, leading to the selection of CHEMBL2403358 for molecular dynamics simulation. Molecular docking of the shortlisted compounds against ESR1 (PDB ID: 1A52) revealed consistently strong binding affinities, ranging from −9.5 to −10.0 kcal/mol (**Table 2**; **Figure 6**).

Table 2: Docking Score and Active Site of the top 5 compounds on protein receptor- ESR1 (PDB AD:1A52)

Ligand	Binding affinity	Key interacting residues
Estradiol	−9.2	ALA350, MET388, LEU525, LEU391, PHE404, ARG394
CHEMBL2403358	−10.0	PHE404, GLU353, LEU387, ALA350, LEU391, LEU525, TRP383
CHEMBL4073395	−9.9	ILE424, ASP351, ALA350, PHE404, LEU387, ARG394
CHEMBL2071180	−9.8	LEU346, MET343, HIS524, GLY521, ALA350, PHE404
CHEMBL420017	−9.7	MET388, LEU525, ALA350, ARG394, PHE404, LEU387
CHEMBL4286596	−9.6	TRP383, ASP351, LEU525, MET343, ALA350, PHE404



Panels A–K correspond to the following docked molecules: A, estradiol; B, 2403358; C, 4073395; D, 2071180; E, 420017; F, 242818; G, 4286596; H, 1231453; I, 1441930; J, 1702774; and K, 5082681.

Figure 6. 2D and 3D interaction diagrams of the top ten docked CHEMBL compounds and the reference ligand estradiol within the ESR1 binding pocket.

3.6 MD Simulations

A 100 ns MD simulation of the ESR1-CHEMBL2403358 complex showed stabilized RMSD after initial equilibration, limited binding-site fluctuations in RMSF analysis, and consistent radius of gyration. . The RMSD profile reflected a period of equilibration and then stabilisation, with values steady at 0.6 to 0.8 nm. The results of the root mean square fluctuation (RMSF) analysis showed that there were minor changes in important binding-site residues, whereas the radius of gyration was stable at 2.3-2.4 nm. These results supported the structural stability of the complex and confirmed CHEMBL2403358 as the final computational lead. These findings demonstrate that the complex had structural stability during the simulation (**Figure 7**).

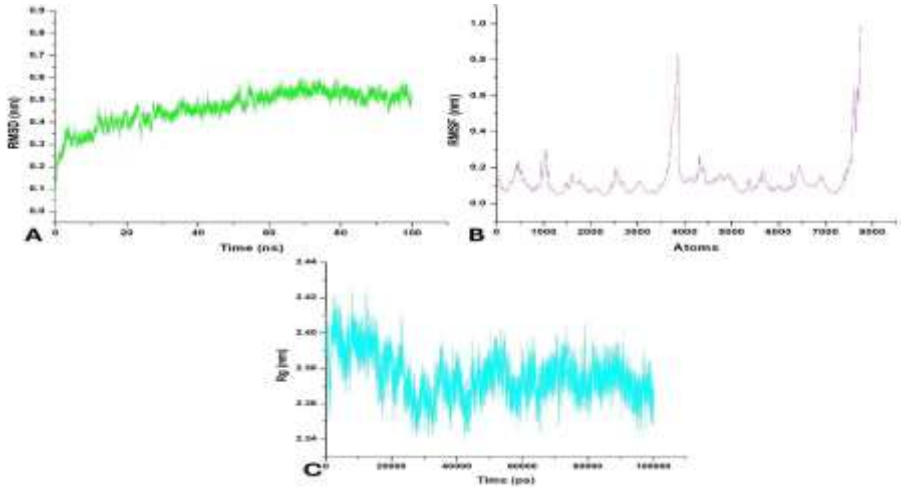


Figure 7: MD simulation results of the ESR1–ligand complexes showing (a) RMSD, (b) RMSF, and (c) Rg over the 100 ns simulation period.

4. Discussion

Here, we demonstrated the utility of an integrated ligand and structure based computational workflow to prioritize potential ESR1 inhibitors. This approach is particularly relevant as ESR1 remains a primary therapeutic target in estrogen-driven breast cancer, yet endocrine resistance continues to limit long-term clinical success. Notably, mutations in the ESR1 ligand-binding domain have emerged as a major factor in resistance to tamoxifen, aromatase inhibitors, and other endocrine agents, necessitating the development of novel therapeutic inhibitors capable of overcoming these resistant phenotypes.

The curated ChEMBL dataset was sufficient for QSAR model development, and the Random Forest model had acceptable predictive ability as suggested by the test set R^2 and the cross validated Q^2. These results suggested that PubChem fingerprint descriptors encoded relevant structural features in relation to ESR1 inhibitory activity. The positive and negative fingerprint contributors identified also indicate that some substructural patterns may contribute to predicted potency and can be used to guide further scaffold optimization. In addition to prediction, interpretable structural insights were also obtained using the model. Fingerprint features that were related to phosphoryl groups, brominated aliphatic motifs, and other hydrophobic fragments had a positive effect on activity, but chlorinated toluene-like features had a negative impact. Mechanistically, these findings are possible due to a balance between polar contacts and hydrophobic enclosures in the ligand-binding domain, which is required to drive ESR1 ligand recognition. The compounds that are able to deliver hydrogen-bond-accepting activity yet retain the right lipophilic complementarity have an increased likelihood of obtaining high-affinity receptor interactions. On the other hand, sterically unfavorable or electronically large aromatic replacements can make both the binding cavity and ligand accommodation poor [21,22].

The ADMET and Lipinski screening steps allowed a filtration of the set of active compounds towards candidates with better drug-like profiles. Such filtering was important because high predicted activity does not guarantee suitability for further development. The ADMET scores also enhance the translational applicability of the shortlisted candidates. The majority of the best compounds showed high predicted intestinal absorption, minimal blood-brain barrier permeability, low CYP450 risk of inhibition, and acceptable toxicity levels. This type of profile is beneficial when agents are to be used chronically in breast cancer, where oral bioavailability, controlled metabolism, and minimal levels of off-target toxicity are essential factors.

The docking results further validated the prioritization process as the selected compounds showed improved estimated binding affinities over estradiol. CHEMBL2403358 had the highest docking score among them and interacted with key residues in the ESR1 binding site such as PHE404, GLU353, LEU387, ALA350, LEU391 and LEU525. These residues are highly conserved elements of the canonical estrogen receptor binding pocket and

are necessary for receptor recognition, hydrophobic stabilization, and ligand orientation [23]. Of special interest is the observed interaction of GLU353, which is a key interaction site with endogenous estrogen and therapeutic modulators. Similarly, the presence of interactions between ASP351, ARG394, TRP383, HIS524, and GLY521 in a few of the best compounds indicates that these ligands can utilize both the canonical and extended receptor sub-pocket [24]. It can be very applicable to the case of endocrine resistance, as resistant ESR1 mutants like Y537S and D538G stabilize the receptor in an active conformation and change ligand responsiveness. The compounds with the potential to interact with other auxiliary regions of the receptor could better occupy or disrupt these altered conformational states These interactions confirm its compatibility with the ESR1 ligand binding pocket and justify its selection for molecular dynamics simulation.[25]

Molecular dynamics studies also confirmed the stability of the ESR1-CHEMBL2403358 complex. The RMSD was stabilized, the binding-site fluctuations were limited, and the radius of gyration was consistent, indicating the complex was structurally stable during the entire 100 ns simulation time. The combined QSAR, ADMET, docking and MD results indicate that CHEMBL2403358 is a promising computational lead. However, the study remains limited by its in-silico design. Experimental validation through enzyme inhibition assays, receptor-binding studies, and cellular activity testing is required to confirm the predicted ESR1 inhibitory potential and pharmacological relevance of the selected compound [26].

5. Conclusion

This study presents an integrated computational platform designed to identify novel ESR1 inhibitors for the treatment of HR+ breast cancer. A systematic workflow was implemented using a dataset of 3,130 compounds, encompassing Lipinski's Rule of Five filtering, QSAR modelling, ADMET profiling, molecular docking, and MD simulations. The Random Forest-based QSAR model demonstrated good predictive performance, with an R^2 of 0.738 and cross-validation values (Q^2) of 0.625 and 0.638, identifying five critical molecular descriptors influencing biological activity. Among the 1,587 active compounds satisfying Ro5 criteria, 115 were predicted to possess activity, with the top 10 candidates demonstrating favourable ADMET profiles. CHEMBL2403358 emerged as the top-ranking ligand, exhibiting a binding affinity of kcal/mol and establishing stable interactions with key amino acid residues. Structural stability of the ESR1–CHEMBL2403358 complex was further corroborated by 100 ns MD simulations, as evidenced by stable RMSD and RMSF trajectories. These findings validate potential drug-like ESR1 inhibitors that could mitigate endocrine resistance, establish this integrated computational approach as a robust strategy for early-stage drug discovery, and identify CHEMBL2403358 as a promising lead scaffold for addressing endocrine-resistant breast cancer phenotypes.

Declarations

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Conflicts of interest/Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval: Not applicable. (This study did not involve human participants, animal experiments, or biological samples.)

Data availability: The data supporting the findings of this study are available within the article and its supplementary materials. The curated dataset was derived from the public domain ChEMBL database.

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