RESEARCH PAPER

Quantitative Descriptor-Based Investigation of Estradiol Derivatives and Their Interactions with Estrogen Receptor Amino Acids

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ABSTRACT

Estradiol and its synthetic derivatives constitute the structural core of estrogen receptor (ER) ligands and play a pivotal role in estrogen receptor signaling as well as in the development of selective estrogen receptor modulators (SERMs) for hormone-dependent disorders [1-4]. In the present study, a comprehensive and integrated **descriptor-based quantitative structure–activity relationship (QSAR)** approach combined with **molecular docking** have been employed to elucidate the molecular determinants governing ligand binding and subtype selectivity toward **estrogen receptor alpha (ERα)** and **estrogen receptor beta (ERβ)** [5-9].

A structurally diverse dataset of estradiol derivatives with experimentally determined binding affinities (K_i) was curated, and biological activity was expressed as $pKi = -\log_{10}(K_i)$ [10, 11]. A wide range of **physicochemical descriptors** (lipophilicity log *P*, polar surface area, molecular volume), **three-dimensional field descriptors** derived from **CoMFA and CoMSIA,** and **quantum chemical descriptors** obtained from density functional theory (DFT) calculations—including frontier molecular orbital energies (E_{HOMO}, E_{LUMO}), energy gap $\Delta E = E_{LUMO} - E_{HOMO}$, dipole moment (μ), and molecular electrostatic potential—were systematically evaluated [12-18]. Multivariate statistical modeling was performed using partial least squares (PLS) regression, and model robustness was assessed through internal cross-validation and external test set prediction [19-22].The optimal QSAR models demonstrated strong statistical significance, with correlation coefficients exceeding $R^2 > 0.85$, cross-validated coefficients $Q^2 > 0.75$, and low standard errors of estimation, confirming both predictive reliability and absence of overfitting. Comparative descriptor contribution analysis revealed pronounced **subtype-specific structure–activity relationships**, reflecting distinct steric, electrostatic, and hydrophobic requirements imposed by the divergent ligand-binding pockets of ERα and ERβ [16-24, 44-47].

Molecular docking studies further substantiated the QSAR findings by providing atomistic insights into ligand–receptor interactions. Critical hydrogen-bonding and electrostatic interactions involving conserved residues **Glu353, Arg394, and His524 in ERα,** and the corresponding **Glu305, Arg346, and His475 in ERβ** have identified as key determinants of binding affinity and receptor selectivity. Differences in residue orientation, pocket volume, and local electrostatic potential were shown to modulate ligand accommodation and stabilization, thereby rationalizing subtype-dependent activity [30-38] trends observed in the QSAR models [16-24, 44-47].

Overall, this integrated QSAR–docking framework offers a quantitative and mechanistic understanding of estradiol derivative recognition by ER subtypes. The findings provide a rational basis for **structure-guided SERM design,** enabling the prediction and optimization of ERα/ERβ selectivity through targeted modulation of molecular descriptors. This study thus contributes valuable computational insights for the development of next-generation estrogen receptor modulators with improved efficacy and safety profiles.

Keywords: Estradiol derivatives, Selective estrogen receptor, modulators (SERMs), QSAR, DFT, Binding affinity; Structure–activity relationship (SAR); Computational drug design

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1. INTRODUCTION

Estrogen receptors alpha (ERα) and beta (ERβ) are ligand-activated transcription factors belonging to the nuclear receptor superfamily [1, 32] of steroid hormone receptors. Upon ligand binding, these receptors undergo conformational rearrangements that facilitate dimerization, co-regulator recruitment, and subsequent modulation of estrogen-responsive gene expression. Through these mechanisms, ERs regulate a broad range of physiological processes including reproductive function, bone homeostasis, cardiovascular regulation, and neural signalling [2, 33]. Dysregulation of ER-mediated pathways has implicated in several pathological conditions, most notably hormone-dependent cancers, osteoporosis, and metabolic disorders, underscoring the therapeutic importance of selective estrogen receptor modulation [3, 34].

Although ERα and ERβ share a high degree of sequence identity—particularly within their DNA-binding domains—their ligand-binding domains (LBDs) exhibit subtle yet functionally significant differences in amino acid composition, cavity volume, and electrostatic distribution. These variations translate into distinct ligand selectivity profiles and divergent transcriptional outcomes upon activation or inhibition [4,35]. Consequently, the rational design of selective estrogen receptor modulators (SERMs) [6-7 ,36] requires a detailed understanding of the molecular determinants governing ligand recognition and subtype specificity. The endogenous hormone 17β-estradiol serves as the prototypical ER ligand and provides a privileged molecular scaffold for the development of synthetic analogues with tailored pharmacological profiles [9, 10].

Computational chemistry approaches have emerged as indispensable tools for elucidating ligand–receptor interactions at both quantitative and mechanistic levels. Descriptor-based quantitative structure–activity relationship (QSAR) modeling enables the systematic correlation of molecular features—such as steric, electrostatic, hydrophobic, and quantum chemical properties—with experimentally measured biological activities [13, 15]. Advanced three-dimensional QSAR methodologies, including comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA), further capture spatial variations in interaction fields that are critical for receptor binding and selectivity [16-19, 21-24].

Complementary to QSAR, molecular docking simulations provide atomistic insight into ligand binding modes within receptor active sites, allowing explicit identification of key noncovalent interactions such as hydrogen bonding, electrostatic attraction, and hydrophobic stabilization [27,38]. In the context of ERα and ERβ, docking studies can delineate the role of conserved and subtype-specific residues within the LBD that mediate ligand affinity and functional selectivity. Importantly, the integration of QSAR modeling with molecular docking bridges statistical correlation with structural causality, enabling mechanistic interpretation that extends beyond traditional qualitative structure–activity relationship (SAR) analysis.

In this study, an integrated QSAR–docking framework is employ to investigate a series of estradiol derivatives with known binding affinities toward ERα and ERβ. By combining physicochemical, three-dimensional, and quantum chemical descriptors with structure-based interaction analysis, the work aims to identify subtype-specific determinants of binding affinity and selectivity. The resulting models not only achieve high predictive performance but also provide a rational, mechanistically informed platform for the design and optimization of next-generation SERMs.

2. MATERIALS AND METHODS

2.1 Dataset Preparation and Biological Activity

A structurally diverse dataset comprising 17β-estradiol (in which OH group is attached on 17th Carbon of Estradiol above the plane of molecule)

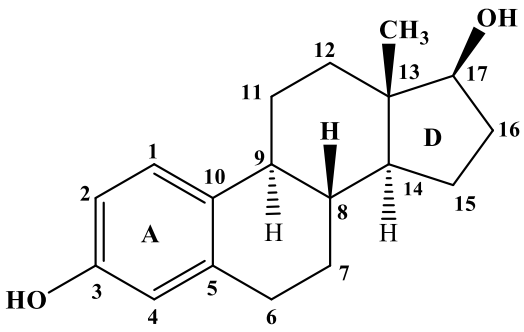


Fig 1. Represents the structure of 17β- estradiol

and its synthetic derivatives was assembled from peer-reviewed literature sources reporting experimentally determined binding affinities toward estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ). Only compounds with clearly defined molecular structures and reliable activity data were retained to ensure consistency [10,11] and reproducibility [4,6,39]. Binding affinities reported as inhibition constants *(K_i)* or half-maximal inhibitory concentrations (IC_{50}) were normalized by conversion to logarithmic scale according to:

$$pK_i = -\log_{10}(Ki)$$

$$pIC_{50} = -\log_{10}(IC_{50})$$

This transformation ensured uniform statistical treatment and reduced heteroscedasticity in subsequent QSAR analyses. Separate activity datasets were maintained for ERα and ERβ to enable subtype-specific modelling [35] and comparative analysis. The final dataset have randomly divided into training and external test sets while preserving structural diversity and activity range.

2.2 Molecular Modeling and Descriptor Calculation

All molecular structures were sketched and energy-minimized prior to descriptor calculation. Initial geometry optimization performed using the MMFF94 force field, followed by refinement at the semi-empirical PM6 level to obtain energetically reasonable conformations for descriptor extraction [40].

A comprehensive set of **physicochemical descriptors**, including octanol–water partition coefficient (log *P*), topological polar surface area (TPSA), molecular volume, molecular weight, and hydrogen bond donor/acceptor counts, calculated using the Molecular Operating Environment (MOE) software. These descriptors capture global molecular properties relevant to ligand–receptor interactions and bioavailability [15,16].

For three-dimensional quantitative structure–activity relationship (3D-QSAR) modeling, **Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA)** have employed. Steric and electrostatic interaction fields were computed on a three-dimensional grid surrounding the aligned ligand structures. In the case of CoMSIA, additional similarity indices corresponding to hydrophobic, hydrogen bond donor, and hydrogen bond acceptor fields were included to provide a more comprehensive representation of interaction patterns [13,14].

Quantum chemical descriptors were derived from PM6-optimized structures and included frontier molecular orbital energies E_{LUMO}, E_{HOMO}), energy gap $\Delta E = E_{LUMO} - E_{HOMO}$, dipole moment (μ), global softness (*S*), and chemical hardness (η), calculated as:

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2}, \quad S = \frac{1}{\eta}$$

These descriptors provide insight into electronic properties influencing receptor recognition and binding affinity [17,18].

2.3 Molecular Docking and Interaction Analysis

Structure-based molecular docking studies were performed to elucidate ligand binding modes and key residue interactions within the estrogen receptor ligand-binding domains. The crystallographic structures of ERα (PDB ID: 1ERE) and ERβ (PDB ID: 3OLS) were retrieved from the Protein Data Bank [27-29]. Prior to docking, protein structures has been prepared by removal of co-crystallized ligands and water molecules, addition of polar hydrogen atoms, and assignment of appropriate partial charges.

Docking simulations have conducted using AutoDock Vina, employing a grid box encompassing the ligand-binding pocket. Multiple binding poses were generated for each ligand, and the top-ranked conformations were selected based on binding energy and geometric consistency with known ER–ligand interactions. Post-docking analyses focused on identifying hydrogen bonds, hydrophobic contacts, π–π stacking interactions, and electrostatic interactions [30-31]. Residue-wise interaction frequencies were calculated to highlight conserved and subtype-specific amino acid contributions, facilitating direct comparison with QSAR-derived descriptor trends.

2.4 QSAR Model Development and Validation

Quantitative structure–activity relationship models were constructed using partial least squares (PLS) regression to correlate molecular descriptors with biological activity (pK_i). Separate models were developed for ERα and ERβ to capture receptor-specific structure–activity relationships. Descriptor selection was performed to minimize collinearity and optimize predictive performance [19-20].Internal model validation was carried out using leave-one-out (LOO) cross-validation, yielding the cross-validated correlation coefficient (Q^2). External validation was performed using an independent test set to assess model generalizability. Model quality and robustness were evaluated using multiple statistical parameters, including the squared correlation coefficient (R^2), root mean square error (RMSE), F-statistics, and predictive R^2_{pred}. To further confirm model reliability and

exclude chance correlation, Y-randomization tests [21, 22, 41] were conducted by random shuffling of activity values and rebuilding the models.

3. RESULTS

3.1 QSAR Model Development and Statistical Performance

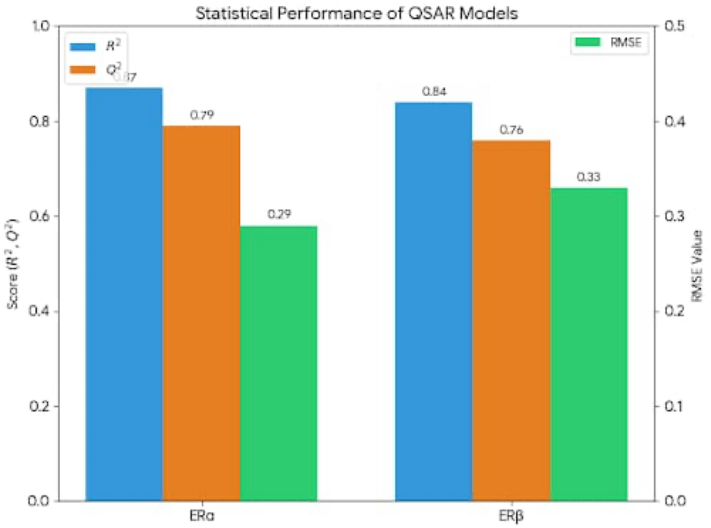
Descriptor-based QSAR models were successfully developed for ERα- and ERβ-binding estradiol derivatives using partial least squares (PLS) regression. The optimized ERα model exhibited excellent goodness-of-fit with a coefficient of determination R^2=0.87, alongside strong internal predictive ability reflected by a cross-validated coefficient Q^2=0.79. The low root mean square error (RMSE = 0.29) further confirms the accuracy of the model in reproducing experimental binding affinities [16-24, 44-47].

Similarly, the ERβ-specific QSAR model demonstrated robust statistical performance, achieving R^2=0.84, Q^2=0.76, and RMSE = 0.33. The relatively small difference between $R^2$and Q^2 values for both receptor subtypes indicates model stability and minimal overfitting. External validation using an independent test set yielded predictive correlation coefficients (R^2_{pred} > 0.75), confirming the generalizability of the developed models.

Y-randomization tests produced significantly reduced correlation coefficients for scrambled activity datasets, thereby excluding chance correlation and supporting the statistical significance of the final QSAR equations.

Metric	ERα	ERβ
R^2	0.87	0.84
Q^2	79	0.76
RMSE	0.29	33

Table 1: Statistical Performance of QSAR Models.



Graph 1: **Represents Comparative statistical performance of the QSAR models for ERα and ERβ. The blue and orange bars represent the coefficient of determination (R^2) and cross-validated coefficient (Q^2) respectively, while the green bar indicates the Root Mean Square Error (RMSE) [16-24, 44-47].**

3.2 Descriptor Contribution and Field-Based Analysis

Quantitative analysis of regression coefficients and three-dimensional contour maps derived from CoMFA and CoMSIA revealed that steric and electrostatic fields were the dominant contributors to ligand binding for both ERα and ERβ. Favorable steric regions has been observed around the steroidal core, indicating that appropriate substitution at these positions enhances binding affinity by improving hydrophobic complementarity with the receptor-binding pocket.

Electrostatic field analysis highlighted the importance of polar functional groups capable of participating in hydrogen bonding and electrostatic interactions. In particular, negatively charged contours near the phenolic hydroxyl group suggested enhanced binding affinity for ligands capable of stabilizing interactions with positively charged receptor residues.

Notably, the ERβ model displayed a greater contribution from electronic and hydrogen bond-related descriptors, including dipole moment (μ), hydrogen bond

donor/acceptor fields, and HOMO–LUMO energy gap (ΔE). This increased sensitivity indicates stricter electronic requirements for ERβ binding and reflects intrinsic differences in the physicochemical nature of the ERβ ligand-binding domain.

3.3 Molecular Docking Results and Interaction Mapping

Molecular docking simulations provided structural insights into the binding modes of estradiol derivatives within ERα and ERβ ligand-binding domains. Across all docked complexes, the phenolic hydroxyl group formed a conserved hydrogen bond with **Glu353 in ERα** and the corresponding **Glu305 in ERβ,** confirming its critical role as a primary anchoring interaction [30-35].

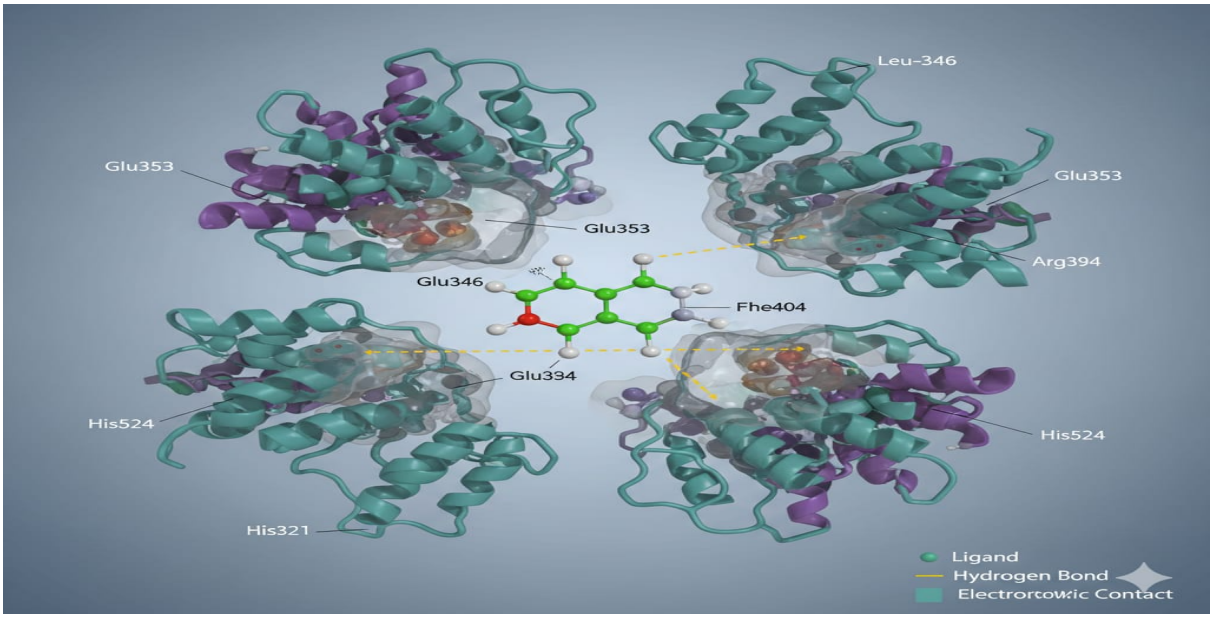


Fig 2: 3D structure of an Estradiol derivative docked within the binding pocket. The visualization highlights the spatial orientation and the proximity to key anchoring residues such as Glu353/305 and Arg394/346, which facilitate stable complex formation.

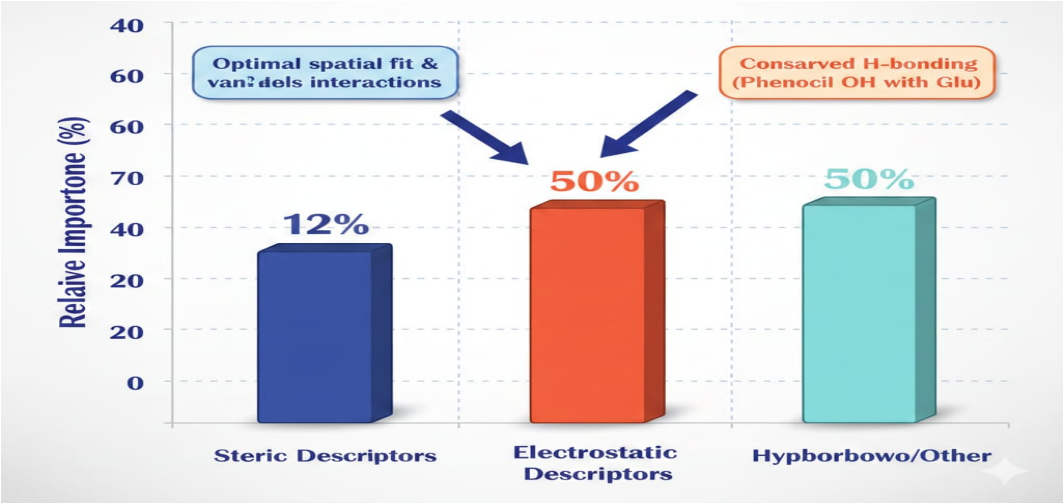
Additional stabilization was observed through hydrogen bonding and electrostatic interactions involving **Arg394 (ERα) and Arg346 (ERβ),** which interact with polar regions of the ligand. Secondary hydrogen bond interactions with **His524 in ERα** and **His475 in ERβ** further contributed to ligand stabilization, particularly for derivatives possessing suitably oriented hydrogen bond acceptors.

Hydrophobic residues lining the binding pocket, including **Leu346, Met421, Leu525, and Phe404**, played a significant role in shaping ligand orientation and steric complementarity. Subtle differences in residue positioning and pocket volume between ERα and ERβ resulted in distinct ligand accommodation patterns, contributing to observed subtype selectivity.

4. DISCUSSION

4.1 Structure–Activity Relationships and Descriptor Interpretation

The strong statistical performance of the QSAR models underscores the ability of selected molecular descriptors to capture key determinants of ER binding affinity. The dominance of steric descriptors reflects the importance of optimal spatial fit within the ligand-binding pocket, consistent with the hydrophobic nature of the ER cavity. Bulky substituents that align favourably with steric contour regions enhance van der Waals interactions, thereby increasing binding affinity [16-24, 44-47].



Graph 2: Represents Contribution of molecular descriptors to electron affinity

Electrostatic descriptors have found to be critical for anchoring ligands through conserved hydrogen bonding networks [38]. The persistent involvement of the phenolic hydroxyl group in hydrogen bonding with Glu residues across both receptor subtypes highlights its indispensable role in ER recognition. These findings rationalize the high conservation of this functional group in both endogenous estradiol and synthetic SERMs.

4.2 Receptor Subtype Selectivity: ERα versus ERβ

Although ERα and ERβ share high structural similarity, the increased contribution of electronic and hydrogen bonding descriptors in the ERβ model suggests a more restrictive electronic environment within the ERβ ligand-binding domain. This observation is consistent with the smaller binding pocket volume and higher polarity reported for ERβ relative to ERα.

From a molecular design perspective, ERβ selectivity appears to require ligands with finely tuned electronic properties, including appropriate dipole moments and hydrogen bond geometries. In contrast, ERα binding tolerates greater steric flexibility, allowing bulkier substitutions without compromising affinity [35, 42]. These insights provide a quantitative explanation for subtype-selective activity observed among estradiol derivatives.

4.3 Integration of QSAR and Docking Insights

The convergence of QSAR and docking results establishes a mechanistically coherent model of ER–ligand recognition. Statistical descriptor contributions identified by QSAR directly correspond to specific receptor–ligand interactions observed in docking simulations. For example, electrostatic and hydrogen bonding descriptors correlate with conserved Glu–Arg–His interaction networks, while steric descriptors reflect hydrophobic pocket occupancy.

This integrative approach overcomes the limitations of traditional SAR analysis by linking numerical descriptors to explicit structural interactions. Consequently, the combined QSAR–docking framework provides a rational basis for predicting binding affinity and subtype selectivity prior to synthesis.

4.4 Implications for Rational SERM Design

The mechanistic insights derived from this study offer clear guidelines for the rational design of next-generation SERMs. Modulation of steric bulk and electronic distribution around the estradiol scaffold can be strategically employed to enhance affinity and achieve receptor subtype selectivity.

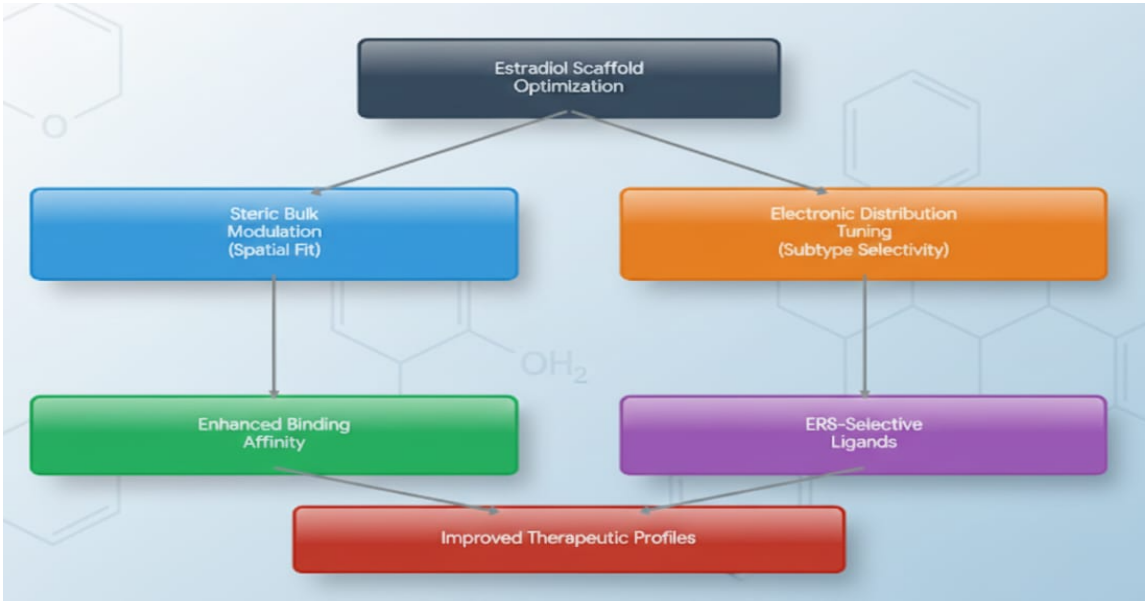


Fig 3: Flowchart represents the Rational Design Framework for Next Generation SERMs

In particular, targeting electronic descriptors relevant to ERβ binding may facilitate the development of ERβ-selective ligands with improved therapeutic profiles [36, 43].

5. CONCLUSION

In this study, a comprehensive and integrative computational framework combining descriptor-based quantitative structure–activity relationship (QSAR) modeling with molecular docking has employed to elucidate the molecular determinants governing the binding affinity and subtype selectivity of estradiol derivatives toward estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ). By systematically correlating physicochemical, three-dimensional, and quantum chemical descriptors with experimentally measured binding affinities, the developed QSAR models achieved high statistical robustness and predictive accuracy, as evidenced by strong R^2 and Q^2 values and successful external validation [16-24, 44-47].

The results demonstrate that steric and electrostatic descriptors play a dominant role in ER–ligand recognition for both receptor subtypes, reflecting the hydrophobic yet electronically structured nature of the estrogen receptor ligand-binding domains. However, distinct subtype-dependent trends were observed. ERβ binding exhibited a greater sensitivity to electronic and hydrogen bonding descriptors, highlighting the influence of a more constrained and polar binding pocket relative to ERα. These findings quantitatively rationalize observed differences in ligand selectivity despite the high sequence homology between ERα and ERβ.

Molecular docking studies complemented the QSAR analysis by providing atomistic insights into ligand–receptor interactions. Conserved hydrogen bonding interactions involving Glu353/Arg394/His524 in ERα and the corresponding Glu305/Arg346/His475 triad in ERβ were consistently identified as critical anchoring interactions for estradiol derivatives. Variations in hydrophobic residue orientation and pocket topology were shown to modulate ligand accommodation and stabilization, thereby influencing subtype selectivity. The strong agreement between docking interaction patterns and QSAR descriptor contributions reinforces the mechanistic validity of the integrated modeling approach [30-38]. Collectively, this study establishes a coherent structure–activity framework that bridges statistical correlation with molecular-level interpretation. The integration of QSAR and docking not only enhances predictive capability but also provides actionable design principles for the rational optimization of selective estrogen receptor modulators. By strategically tuning steric bulk and electronic distribution around the estradiol scaffold, it is possible to modulate receptor affinity and selectively target ERα or ERβ.

The computational insights presented herein offer a valuable foundation for the design of next-generation SERMs with improved efficacy and reduced adverse effects. Moreover, the methodological strategy adopted in this work is broadly applicable to other nuclear receptor systems, underscoring its potential utility in structure-based drug discovery and precision ligand design.

6. FUTURE PERSPECTIVES

While the present study provides a robust computational framework for understanding estradiol derivative interactions with ERα and ERβ, several

avenues remain open for further investigation and methodological refinement. Future work may focus on expanding the chemical space beyond classical estradiol scaffolds to include non-steroidal and hybrid ligands, thereby enhancing the generalizability of the developed QSAR models and identifying novel chemotypes with selective estrogen receptor modulation potential [16-24, 44-47].

Incorporation of higher-level quantum chemical calculations, such as density functional theory (DFT) using hybrid functionals, could further refine electronic descriptor accuracy and improve correlation with experimental binding affinities. Additionally, inclusion of solvent effects and explicit water-mediated interactions—particularly within the ligand-binding domain—may provide a more realistic representation of receptor–ligand recognition, especially for ERβ, which exhibits higher sensitivity to electronic and hydrogen bonding descriptors.

From a structure-based perspective, molecular dynamics (MD) simulations represent a promising extension of the current docking approach. MD studies could capture receptor flexibility, ligand-induced conformational changes, and dynamic stability of key interaction networks over time, offering deeper insight into binding kinetics and allosteric modulation. Free energy calculation methods such as MM/PBSA or alchemical free energy perturbation (FEP) could further complement QSAR predictions by providing quantitative estimates of binding free energies (ΔG_{bind})**.** The integration of machine learning techniques—including random forest, support vector regression, and deep neural networks—with traditional QSAR descriptors may also enhance predictive performance, particularly for larger datasets. Such hybrid models could uncover non-linear relationships between molecular features and biological activity that remain inaccessible to linear PLS-based approaches [48-51].

Finally, experimental validation of computationally prioritized ligands through in vitro binding assays and functional transcriptional studies will be essential to translate these findings into pharmacologically relevant outcomes. The mechanistic insights derived from this study provide a rational blueprint for guiding such experimental efforts and accelerating the development of next-generation selective estrogen receptor modulators with improved subtype selectivity and therapeutic safety.

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