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**Research Article**

# 3D QSAR AND MOLECULAR DOCKING STUDIES OF STRUCTURALLY DIVERSE ESTROGEN RECEPTOR LIGANDS

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## ABSTRACT

Hormone-responsive breast cancer is one of leading cause of cancer death world wide in the women community. The female sex hormone estrogen primarily controls the development of female sex characteristics including division of breast cell. This hormone exerts its effects after binding to estrogen receptor (ER), which is nuclear-activated transcription factor. The present study is considered to explore important pharmacophore signals for binding affinity of estrogen ligands using molecular field (CoMFA) and similarly analyses (CoMSIA), substantiated with molecular docking study. Both CoMFA ($R^2$=0.974, *se*=0.240, $Q^2$=0.589, $R^2_{pred}$=0.612) and CoMSIA ($R^2$=0.997, *se*=0.088, $Q^2$=0.703, $R^2_{pred}$=0.624) models suggest that steric and electrostatic factors are crucial for binding affinity. Further, the similarity analysis and docking studies revealed that hydroxyl and alkyl groups are important for formation of potential interactions at the active site cavity of the ER.

**Keywords:** Estrogen, CoMFA, CoMSIA, Molecular docking.

## INTRODUCTION

The estrogen belongs to the sex steroid hormones, secreted by the ovaries and testis with involvement of placenta, adipose tissue, and adrenal glands[1]. Among the several structurally related forms 17*β*-estradiol is found as predominant. Estrogen plays crucial role in female reproductive system and also exerts important effects on nonreproductive targets such as bone, cardiovascular system and neural sites involved in cognition[2]. It is also reported that estrogen influence the brain centers that maintain body temperature, and enable the vaginal lining to stay thick and lubricated[3]. Due to loss of estrogen production after menopause, hot-flushes, vaginal atrophy and sleeping disturbance arise, and also rise of low-density lipoprotein (LDL) that progressively increases the chance of coronary and osteoporosis diseases[1]. The hormone replacement therapy (HRT) in which synthetic estrogens are administered into the body that reduce osteoporotic fractures and improve severe menopausal symptoms[4], but on other hand malevolent aspect of HRT is increasing chance of breast and uterin cancers[5,6]. Presently there are three strategy for treatment of hormone-responsive breast cancer, such as inhibition estrogen from binding to its main target estrogen receptor (ER) using antiestrogen, e.g. tamoxifen[7]; preventing its synthesis using aromatase inhibitor[8]; and down-regulating ER protein level using pure antiestrogen, e.g. fulvesteron[9].

Estrogen mediates its biochemical mechanism in target tissues after binding to intracellular receptor proteins ER[10,11], which is a nuclear ligand-activated transcription factor[12]. ER constituted similar architecture to the other 50-60 members of the steroid/thyroid hormone receptor family[12-14] and comprises six distinct domains A–F. The ligand binding domain (LBD) consisting E/F domain at the carboxy terminal and responsible for ligand binding, receptor dimirization, nuclear translocation and transactivation of target gene expression via activation function – 2 (AF-2)[13,14]. The AF-2 region comprises of 12α-helices, which form a hydrophobic pocket responsible for binding of ligand[15] and fundamental in distinguishing between agonist and antagonist functions[16] of ER. Knowledge of ER has permitted the modeling of estrogenic activity using different chemometric techniques. The structural requirement for binding of steroid to ER is essential both for design of new drug and to evaluate the health risk of chemical of ER affinity[17]. The chemometric drug design (CDD) is widely used to design lead molecules involving two important techniques, ligand-based and structure-based approaches. When the properties of the ligands are analyzed without any information of receptor site is known as ligand-based drug design (LBDD), while the ligands are designed with help of receptor site is called structure-based drug design (SBDD). Researchers are devoted to search potent molecules for treatment of post-menopausal diseases using both LBDD and SBDD approaches. Our group has explored the prime pharmacophore signals for estrogen mediated bioactivities of different groups of structural congeneric compounds through Quantitative Structure Activity Relationships (QSAR) studies[18-21]. Molecular docking and QSAR studies of estrogen ligands are also explored for potent antiestrogens in several studies[22,23]. On the availability of the crystal structure of active site both ligand-based and structure-based studies will be powerful methods to design lead compound. The present work is considered to explore both approaches for a set of structurally diverse compounds[24,25] with respect to binding affinity to ER.

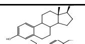
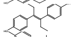
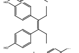
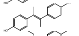
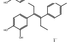
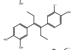
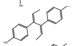
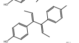
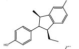
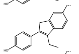
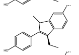
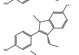
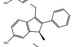
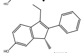
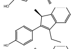
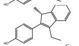
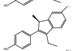
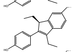
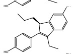
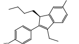
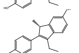
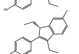
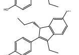
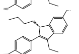
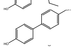
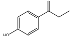
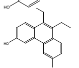
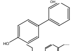
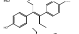
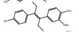
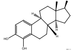
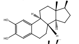
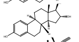
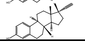
## MATERIALS AND METHODS

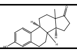
The main objective of the work is to find out correlation between chemical structure with biological activity of the molecules using Partial Least Square (PLS) method and potential interactions between ligand and active site of the receptor molecule. The binding affinity for QSAR study is expressed as $kRBA=\log_{10}(100\text{xRBA})$. The dataset (Table 1) is randomly divided into training set ($n_{tr}$=25) containing most and least active compounds, and test set ($n_{ts}$=10) to validate the derived models in QSAR study. The different control parameters are used to check the superiority of 3D QSAR models are: $R^2$ (correlation coefficient), *se* (standard error of estimate), Cross-validated variance (CVV) $Q^2$ (Leave-One-Out (LOO) cross-validated[26] correlation), *F* (variance ratio) with *df* (degree of freedom), $R^2_{bs}$ (bootstrapped correlation coefficient) and $s_b$ (standard error of bootstrapped correlation). To evaluate the predictive power of the model, $R^2_{pred}$ and $s_p$ (standard error of prediction) of the test set are also estimated. In case of docking study GlideScore[27] and interactions between ligand and receptor are considered for best pose selection.

## 3D QSAR

QSAR is mathematical robust model which attempts to find a statistically significant correlation between chemical structure and biological activity[28]. 3D QSAR is a ligand-based approach which includes Comparative Molecular Field Analysis (CoMFA)[29] and Comparative Molecular Similarity Indices Analysis (CoMSIA)[30], and both analysis techniques reported as effective for understanding of structure-activity relationship, useful to predict the biological activity before synthesis and animal experiment[31], lead optimization and drug-target interaction. In molecular field analysis (CoMFA), steric and electrostatic interaction energies[32] are calculated using Lenad-Jones and Coulombic potentials, and correlated with biological activity of the molecules. In case of CoMSIA study, similarity indices are calculated at regularly placed grid points of the aligned molecules, and additionally hydrogen bond (HB) acceptor and donor along with hydrophobic fields are incorporated[33]. The contour maps of both methods are used to get general insights into the topological features of the binding site.

**Table 1: Observed and predicted relative binding affinity (RBA) to the receptor of estrogen ligand**

| Comp. No. | Ligand | Smiles | Obs.[1] | Predicted activity (CoMFA) | Predicted activity (CoMSIA) | Glide Score |
|---|---|---|---|---|---|---|
| 1 |  | CC12CCC3C(CCc4cc(ccc43)O)C2CCC1O | 100.000 | 95.280 | 86.696 | -8.420 |
| 2 |  | CC\C(\c1ccc(cc1)O)=C(\CC)/c1ccc(cc1)O | 288.400 | 133.968 | 194.536 | -8.810 |
| 3 |  | CC/C(/c1ccc(cc1)O)=C(\CC)/c1ccc(cc1)O | 0.790 | 0.418* | 0.427* | -5.600 |
| 4 |  | C/C(=C(/C)\c1ccc(cc1)O)/c1ccc(cc1)O | 33.110 | 19.770 | 34.834* | -6.670 |
| 5 |  | CC\C(\c1ccc(cc1)O)=C(\CC)/c1ccc(c(c1)O)O | 100.000 | 99.083 | 104.472 | -11.170 |
| 6 |  | CC\C(\c1ccc(c(c1)O)O)=C(\CC)/c1ccc(c(c1)O)O | 25.120 | 133.968 | 19.454* | -10.250 |
| 7 |  | C/C=C(/c1ccc(cc1)O)\C(=C/C)\c1ccc(cc1)O | 0.300 | 0.308 | 0.299 | -6.240 |
| 8 |  | C\C=C(/c1ccc(cc1)O)\C(=C\C)\c1ccc(cc1)O | 19.950 | 12.647* | 8.913* | -6.230 |
| 9 |  | CCC1C(C(C)c2cc(ccc12)O)c1ccc(cc1)O | 2.000 | 1.069 | 2.158 | -9.730 |
| 10 |  | CCC1=C(Cc2cc(ccc12)O)c1ccc(cc1)O | 13.800 | 15.311 | 10.520 | -9.330 |
| 11 |  | CCC1=C(C(C)c2cc(ccc12)O)c1ccc(cc1)O | 100.000 | 28.119* | 162.555* | -8.780 |
| 12 |  | CCC1=C(C(C)c2cc(ccc12)O)c1ccc(cc1)O | 141.250 | 83.176* | 83.176* | -9.660 |
| 13 |  | CCC1=C([C@@H](C)c2cc(ccc12)O)c1ccccc1 | 1.820 | 1.954* | 1.429* | -9.040 |
| 14 |  | CCC1=C([C@H](C)c2cc(ccc12)O)c1ccccc1 | 0.200 | 0.084* | 0.331 | -9.070 |
| 15 |  | CCC1=C([C@@H](C)c2ccccc12)c1ccc(cc1)O | 5.620 | 4.721* | 6.950 | -8.120 |
| 16 |  | CCC1=C([C@H](C)c2ccccc12)c1ccc(cc1)O | 0.890 | 0.226 | 1.028* | -8.500 |
| 17 |  | CCC1=C([C@@H](C)c2cc(ccc12)O)c1ccc(cc1)O | 288.400 | 326.588 | 304.790 | -8.7100 |
| 18 |  | CC[C@H]1c2cc(ccc2C(=C1c1ccc(cc1)O)CC)O | 295.102 | 230.144 | 301.995 | -10.110 |
| 19 |  | CCC[C@H]1c2cc(ccc2C(=C1c1ccc(cc1)O)CC)O | 22.090 | 208.449 | 182.390 | -12.180 |
| 20 |  | CCCC[C@H]1c2cc(ccc2C(=C1c1ccc(cc1)O)CC)O | 177.803 | 131.220 | 231.740 | -12.410 |
| 21 |  | CCC1=C([C@H](C)c2cc(ccc12)O)c1ccc(cc1)O | 12.880 | 28.119 | 16.255 | -9.530 |
| 22 |  | CC[C@@H]1c2cc(ccc2C(=C1c1ccc(cc1)O)CC)O | 10.960 | 20.464* | 16.218 | -9.850 |
| 23 |  | CCC[C@@H]1c2cc(ccc2C(=C1c1ccc(cc1)O)CC)O | 18.200 | 63.241 | 17.906 | -10.990 |
| 24 |  | CCCC[C@@H]1c2cc(ccc2C(=C1c1ccc(cc1)O)CC)O | 7.940 | 6.442 | 7.691 | -12.120 |
| 25 |  | Oc1ccc(cc1)c1ccc(cc1)O | 0.020 | 0.069 | 0.017 | -7.580 |
| 26 |  | CCC(=O)c1ccc(cc1)O | 0.100 | 0.062 | 0.101 | -5.600 |
| 27 |  | CCc1c(c2ccc(cc2c2cc(ccc12)O)O)CC | 0.160 | 0.147 | 0.169 | -7.010 |
| 28 |  | Oc1ccc(cc1)c1ccccc1 | 0.020 | 0.017 | 0.019 | -12.410 |
| 29 |  | CC\C(=C(\CC)/c1ccc(cc1)O)\c1ccc(cc1)OC | 19.950 | 15.241 | 22.491 | -8.240 |
| 30 |  | CC/C(=C(/CC)\c1ccc(c(c1)OC)O)/c1ccc(cc1)O | 10.000 | 21.727* | 8.670 | -9.650 |
| 31 |  | CC12CCC3C(CCc4c(c(ccc43)O)O)C2CC[C@@H]1O | 52.900 | 42.170 | 60.117* | -10.480 |
| 32 |  | CC12CCC3C(CCc4cc(c(cc43)O)O)C2CC[C@@H]1O | 22.400 | 63.826* | 22.751 | -11.290 |
| 33 |  | CC12CCC3C(CCc4cc(ccc43)O)C2C[C@@H](O)[C@@H]1O | 9.720 | 13.062 | 9.931 | -8.690 |
| 34 |  | CC12CCC3C(CCc4cc(ccc43)O)C2CCC1(O)C#C | 190.000 | 133.045 | 179.473 | -10.250 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 35 |  | CC12CCC3C(CCc4cc(ccc43)O)C2CCC1=O | 7.310 | 8.630 | 6.918 | -8.900 |

[1]Observed activity[24,25]; *test compounds

To develop robust CoMFA/CoMSIA models, conformer selection and molecular alignment are important factors. The molecules of data set are expected to be aligned against each other to maximize the overlap of the pharmacophores to generate molecular fields correctly[34]. If the crystal structure of target proteins is available then molecular docking is the solution of alignment of molecules for development of 3D QSAR models. It is reported that docking conformers are appropriately aligning the ligands and developing reliable QSAR models[35,36]. As crystal structure of ER are available in RCSB Protein Data Bank[37], combination of molecular docking and 3D QSAR approach would be desired for development of potent ER ligands. Individual molecules of dataset are docked with crystal structure of ER (PDB ID: 3OMO[38]) respectively obtained from Protein Data Bank[37], and best docked conformer of each compound has been considered for 3D QSAR studies. In case of CoMFA, fields are generated using steric ('s') and electrostatic ('e') interactions, and calculated on a regular space grid of 3Å. Values of the field are truncated at 30.0 kcal/mol. Partial atomic charges are calculated by the Gasteiger–Huckel method[39]. In case of CoMSIA, 's', 'e' and hydrophobic ('p') parameters are considered together with hydrogen bond (HB) acceptor ('a') and donor ('d') factors.

### Molecular Docking

In molecular docking method, ligand interacts to the protein or nucleic acid target and provides a conceptual frame work for designing the desired potency and specificity of potential drug leads for a given therapeutic target. Main objective of docking procedures is to identify correct poses of ligands in the binding pocket of a protein and to predict the affinity between the ligand and protein. A number of algorithms[40,41] can be used for docking which include matching ligand and receptor complementary surfaces or the calculation of the ligand-receptor interaction energies. The method validates ligand-receptor interacting ability by the calculation of scoring functions. Docking can be performed by placing rigid molecules or fragments into the protein's active site using different approaches like clique-search[42], geometric hashing[43] or pose clustering[44].

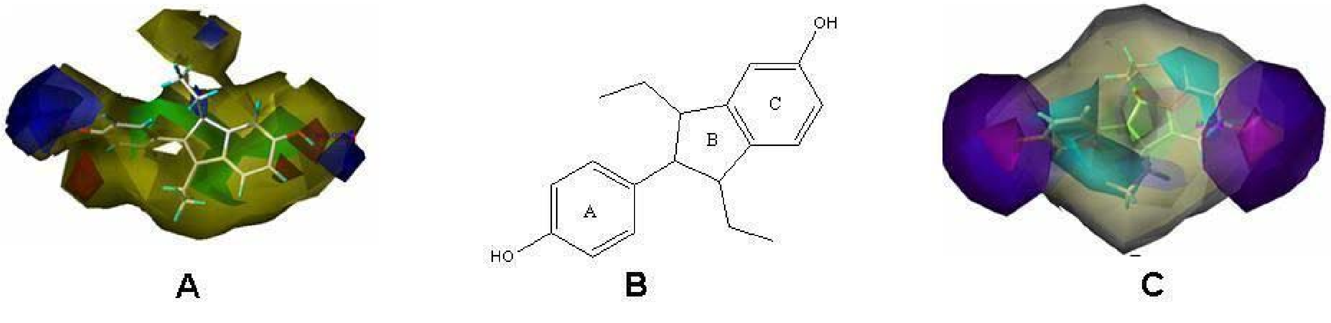
Molecular docking of the data set is performed to understand detailed binding modes of ligands to ER. In the present study, the Grid-Based Ligand Docking with Energetics (Glide) algorithm that approximates a systematic search of positions, orientations, and conformations of the ligand in the receptor binding site using a series of hierarchical filters[27,45,46] are used. The grid represents the shape and properties of the receptor by several different sets of fields, computed prior to docking and provides progressively more accurate scoring of the ligand pose. The binding site is defined by a rectangular box which keeps the mass centre of the ligand within the box. Conformers are generated through an exhaustive search of the torsional minima, and the conformers followed by clustered in a combinatorial fashion. After that each cluster, characterized by a common conformation of the "core" and an exhaustive set of "rotamer group" conformations, is docked as a single object in the first stage[27]. Narrows the search space and reduces the number of poses due to searching with a rough positioning and scoring phase and retain only hundreds. Further the selected poses are minimized on pre-computed OPLS-AA van der Waals and electrostatic grids for the receptor[47]. Finally about 5-10 lowest-energy poses obtained are subjected to a Monte Carlo procedure in which nearby torsional minima are examined, and the orientation of peripheral groups of the ligand is refined[47]. The score of the minimized poses is rescored using the GlideScore function along with force field-based components and additional terms accounting for solvation and repulsive interactions. The best pose considered using a model energy score (Emodel) that combines the energy grid score, GlideScore, and the internal strain of the ligand[27].

## RESULTS AND DISCUSSION

### 3D QSAR

### CoMFA

The best model ($R^2$=0.974, *se*=0.240, $Q^2$=0.589, $R^2_{pred}$=0.612) for field analysis is obtained with contribution of 's' (42.60%) and 'e' (57.40%) factors (Fig. 1A). The statistical results are depicted in Table 2. The regions of green contour suggest that substituents imparting steric influence in these positions might improve the biological activity, while the yellow region indicates that an increased steric influence is unfavorable for the binding affinity. Two phenyl ('A' and 'C' in Fig. 1B) and one acyclic ('B') rings are sterically favorable for the binding interactions at the active site cavity, whereas rest of the surface areas are sterically unfavorable regions. Vicinity to the hydroxyl groups attached to the rings 'A' and 'C' (Fig. 1B), and alkyl group attached to the ring 'B' impart the electronic charges are favorable for electrostatic interactions with the receptor. The observed vs. predicted activity is depicted in Fig. 2. Good predicted correlation value ($R^2_{pred}$=0.612) of the test compounds confirms the suitability of the model selection.



Steric: Green favorable, yellow unfavorable

Electrostatic: Blue favorable, red unfavorable

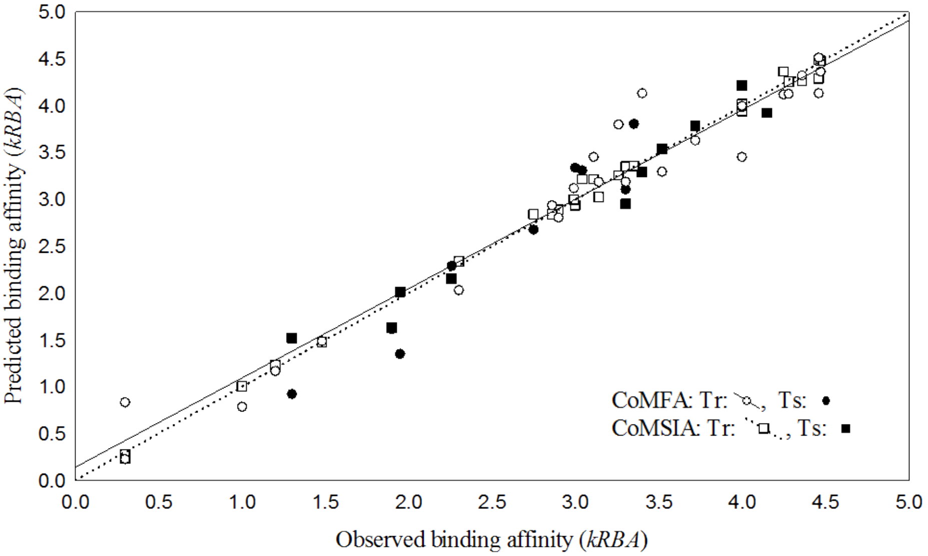
Hydrophobic: Cyan favorable, White unfavorable

Acceptor: Magenta favorable, purple unfavorable

**Fig. 1: Mapped features of CoMFA (A) and CoMSIA (C) studies fitted with most active compound (B) of the dataset**

**Table 2: Statistical results of 3D QSAR study of estrogen receptor ligands.**

| **Parameters** | **CoMFA** | **CoMSIA** |
|---|---|---|
| $n_{tr}$ | 25 | 25 |
| Components | 5 | 7 |
| $R^2$ | 0.974 | 0.997 |
| *se* | 0.240 | 0.088 |
| *F(df)* | 112.906<br>(6,18) | 705.654<br>(7,17) |
| Contributions (%) | | |
| *s* | 0.426 | 0.133 |
| *e* | 0.574 | 0.396 |
| *p* | - | 0.249 |
| *a* | - | 0.221 |
| $Q^2$ | 0.589 | 0.703 |
| $R^2_{bs}$ | 0.989 | 0.999 |
| $s_{bs}$ | 0.169 | 0.050 |
| $R^2_{pred}$ | 0.612 | 0.624 |
| $s_p$ | 0.321 | 0.389 |



CoMFA: Tr: $n$=25, $R^2$=0.974, $se$=0.240, $Q^2$=0.589

Ts: $n$=10, $R^2_{pred}$=0.612, $s_p$=0.321

CoMSIA: Tr: $n$=25, $R^2$=0.997, $se$=0.088, $Q^2$=0.703

Ts: $n$=10, $R^2_{pred}$=0.624, $s_p$=0.389

**Fig. 2: Observed vs. predicted binding affinity of estrogen receptor ligands as per CoMFA and CoMSIA studies.**

### CoMSIA

The best model ($R^2$=0.997, *se*=0.088, $Q^2$=0.703, $R^2_{pred}$=0.624) for similarity study is obtained with combined contribution of 's' (13.30%), 'e' (39.60%), 'p' (24.90%) and HB 'a' (22.10%) factors (Fig. 1C). Phenyl rings 'A' and 'C' impart steric and hydrophobic properties of the molecule and favorable for formation of steric and hydrophobic interactions of the receptor site, but rest of the surface areas show unfavorable for both steric and hydrophobic properties. Due to increase of electron density surrounding the phenyl rings ('A' and 'C') show favorable for electrostatic interactions, but hydroxyl groups attached to same and alkyl group attached to the cyclopentane ring ('B') have negative influence for electrostatic factor. Hydroxyl groups attached to the phenyl rings are behaved as HB acceptors suggesting hydrogen bond interactions with amino acid residues at the active site. The observed vs. predicted activity is delineated in Fig. 2. Good correlation value ($R^2_{pred}$=0.624) of the test compounds proves robustness of the CoMSIA Model.

### Molecular Docking

Molecular docking is performed to visualize the potential interactions between ligand and catalytic residues of ER (PDB ID: 3OMO[38]). The docking result is characterized on the basis of GlideScore (Table 1) and interactions observed at the active site cavity. The docked pose of most active compound (Comp. **18**) is depicted in Fig. 3. Theoretically more negatively scoring compounds are better binders, and it is observed that all compounds in the data set docked at the active site with high negative score.

From Table 1, it is illustrated that comps. **20** and **28** have highest negative score -12.410 followed by comp. **24** (-12.120) and comp. **19** (-12.180). Comps. **3** and **25** each give lowest negative score -5.600 followed by comp. **8** (-6.230) and comp. **7** (-6.240). The most active compound (comp. **18**) gives GlideScore of -10.110 and least active compounds (compds. **25** and **28**) generate -7.580 and -12.410 respectively.

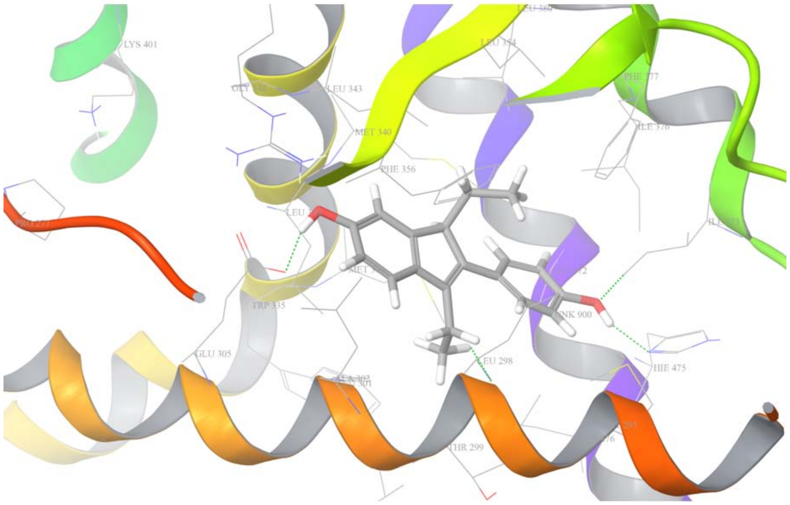


**Fig. 3: Molecular docking interactions at the binding site ER with most active compound (Comp. 18)**

The docked pose of comp. **18** (Fig. 3) explain that polar Trp335 and His475, and non-polar Leu298 and Ile373 are catalytic residues at the active site revealed as crucial for binding interactions. Presence of electronegative hydroxyl group attached to ring ‘A’ interacts with His475 and Ile373 by forming potential hydrogen bonding, whereas hydroxyl group attached to ring ‘C’ is formed HB interaction with Trp335. The bulky alkyl group attached to ring ‘B’ generates the hydrophobic core also found crucial for interaction with non-polar residue Leu298.

The docking study also correlates the functionality developed in 3D QSAR and space modeling[48] studies. The rings ‘A’ and ‘C’ found as sterically and electrostatically favorable in CoMFA study, additionally ring ‘B’ revealed as important for steric interaction. Similarly rings ‘A’ and ‘C’ are important for steric, hydrophobic and electrostatic interactions in CoMSIA study. Moreover hydroxyl groups attached to the phenyl rings ‘A’ and ‘C’ act as HB acceptors for interaction with active site cavity for both CoMSIA and space modeling[48] studies. Bulky alkyl group attached to ring ‘B’ imports hydrophobicity also depicted in pharmacophore study[48]. Observations in both 3D QSAR and space modeling studies are substantiated by the HB interactions between hydroxyl group attached to rings ‘A’ and ‘C’ with Trp335 and, Ile373 and His475 respectively, whereas hydrophobic interaction portrayed between alkyl group attached at ring ‘B’ and Leu298.

## CONCLUSION

In the present work, CoMFA and CoMSIA approaches of 3D QSAR and molecular docking studies are adopted to rationalize the ER binding affinity and molecular interactions of structurally diverse estrogen receptor ligands. The 3D QSAR studies revealed that steric and electrostatic features are prime factors for binding affinity. Both field and similarity analyses models show good predictive ability to test compounds. The contour maps show good compatibility with the receptor properties and explain the crucial regions for steric, electrostatic, hydrophobic and HB interaction with the receptor site. The significant GlideScore supports that molecules of the data set are successfully interacted with right conformation. The docked poses illustrate that hydroxyl and alkyl groups present in the molecular system are important for binding interaction.

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