doi: 10.30934/kusbed.1347829 **e-ISSN:** 2149-8571

Kocaeli Üniversitesi Sağlık Bilimleri Dergisi

Özgün Araştırma / Original Article

http://dergipark.org.tr/kusbed

LOMITAPIDE AS A POTENTIAL ESTROGEN RECEPTOR INHIBITOR: A COMPUTATIONAL DRUG REPURPOSING STUDY

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Geliş Tarihi / Received: 22.08.2023 **Kabul Tarihi / Accepted:** 18.10.2023 **Yayım Tarihi / Published:** 15.03.2024

Abstract

Objective: Estrogen receptor (ER) inhibitors have significant therapeutic potential for hormone-dependent cancers and related disorders. Tamoxifen, a well-known selective estrogen receptor modulator, has been widely used as adjuvant therapy for estrogen receptor-positive breast cancer. However, tamoxifen may exhibit a tendency to develop resistance with prolonged usage and particularly elevate the risk of uterine cancer. Therefore, there is a need for the discovery and development of new ER modulators or inhibitors. In this study, we identified potential estrogen receptor inhibitors through computational drug repositioning.

Methods: A set of 2048 compounds, encompassing FDA-approved drugs and active metabolites, were subjected to molecular docking, molecular dynamics simulations, and free energy calculations to evaluate their interaction with estrogen receptor α (ERα).

Results: Among the compounds evaluated, conivaptan, atogepant, and lomitapide exhibited the highest affinities for ERα. Lomitapide displayed a superior docking score (-12 kcal/mol) compared to the established ER inhibitor, tamoxifen (-10 kcal/mol). Further investigation using molecular dynamics simulations and free energy calculations disclosed lomitapide's heightened binding affinity of -380.727 kJ/mol, surpassing tamoxifen's binding affinity of -352.029 kJ/mol.

Conclusion: This comprehensive computational exploration underscores lomitapide's potential as a compelling candidate with an envisaged stronger estrogen receptor affinity than the acknowledged standard, tamoxifen. To validate lomitapide's promise as a novel ER inhibitor, essential in vitro and in vivo studies are suggested. These investigations will provide essential insights into lomitapide's reposition in addressing the challenges tied to hormone-dependent cancers and associated maladies.

Keywords: *Estrogen receptor antagonists, drug repositioning, lomitapide, tamoxifen, molecular docking, molecular dynamics simulation.*

Introduction

17β-Estradiol (E2), a primary female sex hormone, plays a pivotal role in the regulation of various physiological processes, including reproductive development, bone metabolism, and cardiovascular function.[1] However, dysregulation of estrogen signaling can lead to the development and progression of hormone-dependent diseases, such as breast cancer and endometrial cancer. The estrogen receptor exists in two isoforms, ERα and ERβ, which are encoded by different genes and exhibit distinct tissue distribution patterns. ERα is predominantly expressed in the mammary gland, uterus, and bone, while ERβ is widely distributed in various tissues, including the prostate, ovary, and brain. Upon binding to estrogen, ER undergoes a conformational change and translocates to the nucleus, where it interacts with specific DNA sequences known as estrogen response elements (EREs) to modulate gene expression.[2]

Estrogen receptor inhibitors, also known as ER antagonists or ER modulators, act by blocking the binding of estrogen to ER or inhibiting ER-mediated transcriptional activity. These inhibitors can be classified into two main categories: selective estrogen receptor modulators (SERMs) and selective estrogen receptor degraders (SERDs). SERMs exert tissue-specific effects by functioning as ER agonists or antagonists in a cell- and tissue-dependent manner. On the other hand, SERDs directly target ER for degradation, thereby preventing its activation and downstream signaling.[3]

Tamoxifen is a selective estrogen receptor modulator (SERM) that has been widely used as an endocrine therapy for hormone receptor-positive breast cancer.[4] As an ER inhibitor, tamoxifen offers several advantages in the treatment of breast cancer. It has demonstrated efficacy in reducing the risk of disease recurrence, improving overall survival rates, and serving as a preventive measure in high-risk individuals.[5,6] Additionally, tamoxifen's oral administration, cost-effectiveness, and long-standing clinical experience make it a widely accessible treatment option. However, tamoxifen also presents certain drawbacks. Its use is associated with potential side effects such as hot flashes, venous thromboembolism, and an increased risk of endometrial cancer. Moreover, a subset of patients may develop resistance to tamoxifen, limiting its effectiveness.[7–9] Therefore, it is necessary to discover new candidate molecules with lower side effects and more effective as an alternative to tamoxifen for ER inhibition. In this study, using computational biological methods, we investigated the potential targets of the estrogen receptor among FDA-group drugs and active metabolites.

Methods

Homology Modeling and Validation

The human Estrogen Receptor Alpha protein with the code 3ERT (rcsb.org) underwent homology modeling and validation to determine the ideal conformations of the duplicated and missing atom residues Cys381, Ser433, His513, and Met522. The modeling process was utilized by the MODELLER tool implemented in chimera software with the same amino acid sequence [10,11]. Residue duplications within PDB structures have also been eliminated using a MODELLER tool. MODELLER is a comprehensive tool for homology modeling of protein structures, utilizing spatial restraint satisfaction and offering diverse functionalities like loop modeling and structural comparisons.[10]

Molecular Docking

2048 FDA drugs and active metabolites were obtained in three-dimensional conformation from the e-Drug3D database.[12] The POAP tool was preferred for the automation and optimization of the conversion of compounds to pdbqt format for molecular docking calculations.[13] QuickVina 2 software was preferred as the molecular docking algorithm to investigate the binding interaction of 2048 FDA drugs and active metabolites on the human estrogen receptor alpha.[14] During the optimization phase, the weighted rotor search method was used as the ligand conformation generation algorithm.[13] 50 conformations were generated per compound, and the conformation with the lowest energy was selected. During the minimization phase, minimization was performed according to the 2500-step conjugate gradient algorithm by applying the MMFF94 force field. Convergence criteria 1e-6, VDW cut-off distance 6.0 Angstrom, and electrostatic cut-off distance 10 Angstrom were determined. Hydrogen was added. Finally, in the pdbqt file conversion phase, the prepare_ligand4.py script, which is an autodock software script, was used.[15] 3D interactions were visualized with UCSF ChimeraX.[16] 2D plots were visualized with BIOVIA Discovery Studio Visualizer 2021, San Diego: Dassault Systèmes. The RMSD calculations were performed using the DOCKRMSD tool.[17]

Molecular Dynamic Simulations

Using the Autodock Vina software, complexes were formed with the three compounds that demonstrated the best scores for binding to the estrogen receptor: lomitapide, conivaptan, and atogepant. Also, tamoxifen, an estrogen receptor inhibitor, was separately complexed with the estrogen receptor. All complexes were created using ChimeraX software and then converted to PDB format.[16]

The topological data for the resulting compound-protein complex conformations were generated using the ACPYPE tool.[18] The AM1-BCC semi-empirical quantum calculation method was used during production.[19] All molecular dynamics simulations were performed using GROMACS 2021 software with a time step of 2 femtoseconds.[20] The Leap Frog integration method was used, and the TIP3P water model and Amber99SB-ildn force field were chosen.[21]

The system was created under periodic boundary conditions (PBC) in the shape of a rhombic dodecahedron. The size of the system was adjusted to be at least 1.2 nm from the corner of the protein-compound complex, and neutralization was carried out with 0.15 mM NaCl. Energy minimization was performed using the steepest descent algorithm with a maximum of 50,000 steps and an energy cut-off of less than 10.0 kJ/mol.

During the equilibrium phase, NVT and NPT simulations were performed sequentially. The NVT phase ran for 300 ps, while the NPT phase ran for 1000 ps. In the NVT phase, bonds and atoms were constrained, while in the NPT phase only bonds were constrained using the LINCS constraint algorithm.[22] The Berendsen thermostat was used as the temperature coupling algorithm in the NVT phase, and the temperature was set to 310 K.[23]

In the NPT phase, the Berendsen barostat algorithm was used as the pressure coupling algorithm.[23] V-rescale was used as the temperature coupling algorithm. The pressure was set to one atmosphere and the temperature to 310 °K. During the production phase, V-rescale was used as the temperature coupling algorithm, and isothermal compressibility Parrinello-Rahman was used as the pressure coupling Algorithm.[24] The cut-off value for Van Der Waals

interactions was set to 10 Å. All MD simulations were carried out on TÜBİTAK TRUBA clusters.

Binding Free Energy Calculations

After the molecular docking, free energy calculations were performed using the MM/PBSA method for 100 snapshots taken at intervals of 100 ps during the last 10 ns of a 50 ns MD simulation of complexes formed by Lomitapide, Conivaptan, and Atogepant with the protein, as well as the tamoxifen-protein complex, which acts as an estrogen receptor inhibitor. All calculations were carried out using the g_mmpbsa tool.[25] In the vacuum electrostatic calculation, the dielectric constant of the dissolved substance was set to 2, while the dielectric constant of the solvent was set to 80. The non-polar contribution was estimated using the Solvent Accessible Surface Area (SASA) method.

Results

Molecular Docking

To investigate the molecular interactions between estrogen receptor alpha (ER) and various compounds, 2048 FDA-approved drugs and active metabolites were analyzed using the molecular docking program Autodock Vina. The results showed that over 50 compounds had binding scores lower than -10 kcal/mol, indicating strong binding affinity to the ER. The top three compounds, lomitapide, conivaptan, and atogepant, had particularly strong binding scores of -13.1, -11.7, and -11.2 kcal/mol, respectively. Tamoxifen, a well-known estrogen receptor inhibitor, was also included in the analysis and found to have a binding score of -10 kcal/mol with the ER. Furthermore, a similarity of 1.315 angstroms in RMSD was observed with the experimental crystal structure. A histogram analysis of the binding scores of all 2048 compounds showed that the majority of scores fell between -6.25 and -8.59 kcal/mol (Figure 1). Further analysis revealed that there were 48 compounds with binding scores lower than -10 kcal/mol and 7 compounds with binding scores lower than -11 kcal/mol, suggesting that these compounds may have potential as ER modulators.

According to molecular docking results, lomitapide, conivaptan, and atogepant, as well as tamoxifen, were examined. It was observed that Lomitapide formed a hydrogen bond with His524 on the ER. Additionally, the compound formed halogen bonds with Glu419, Gly420, and Asp351 and established multiple alkyl interactions with residues such as Ala350, Trp383, and Lys529. Conivaptan did not form any hydrogen bonds with the ER, but it did form pi-sigma bonds with Leu346 and Thr347 and a pi-pi stacking interaction with Trp383. Atogepant formed a halogen bond with Asp351 and an amide-pi stacking interaction with Leu346. When the molecular interaction between tamoxifen and the ER was examined, it was found that tamoxifen formed hydrogen bonds with Glu353 and Arg394, as well as an amide-pi stacking interaction with Leu346. Additionally, numerous alkyl and pi-alkyl interactions were detected (Figure 2,3).

Molecular Dynamic Simulations

50 ns molecular dynamics (MD) simulations were performed for the top three compounds selected by the molecular docking method, as well as for tamoxifen, an ER inhibitor. Analysis of the RMSD graphs, which show the conformational stability of the protein and ligand, revealed that, as expected, the ER protein complexed with tamoxifen and the compound were conformationally very stable. The average RMSD deviation for tamoxifen was 1.44 nm, while the closest value was 2.24 nm for conivaptan. The average RMSD values for lomitapide and atogepant were calculated as 3.51 and 4.26 nm, respectively. When the ER protein complexed with the compounds was examined, it was observed that the ER complexed with conivaptan had the least conformational stability with an average RMSD value of 3.8 nm. The ER protein complexed with tamoxifen had the best RMSD value of 2.32 nm, while the RMSD values of the ER proteins complexed with atogepant and lomitapide were calculated as 2.35 and 2.5 nm, respectively (Figure 4).

Binding Free Energy Calculation

Interactions between lomitapide, conivaptan, and atogepant with the ER protein during the 50 ns MD simulation were analyzed using the MM/PBSA method and compared with tamoxifen. It was found that lomitapide had the highest binding affinity, with a value of -380.668 kJ/mol. Tamoxifen, an ER inhibitor, had the second-highest binding affinity with a value of -352.029 kJ/mol. The binding free energies of conivaptan and atogepant to the ER were calculated as -144.724 and -116.168 kJ/mol, respectively (Figure 5).

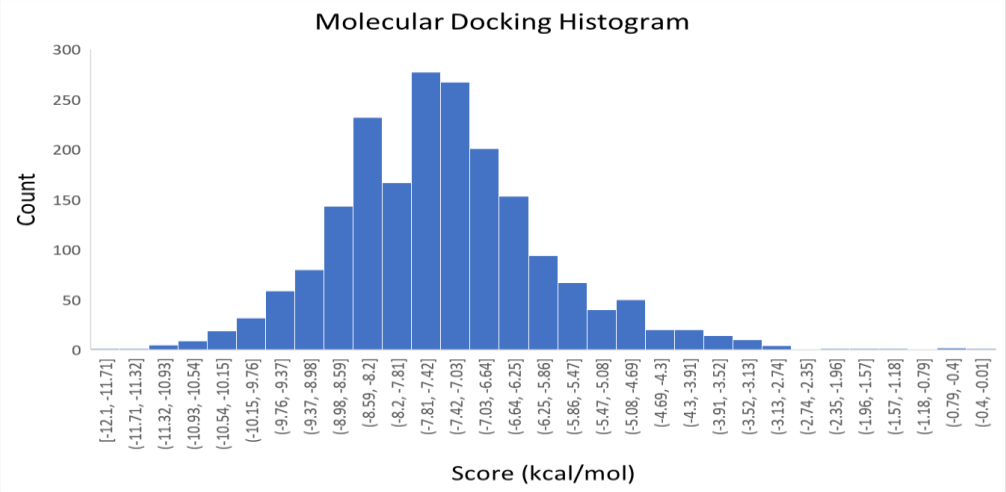

Figure 1. Histograms showing the distribution of binding scores for compounds binding to ER, as evaluated by molecular docking using the Vina program.

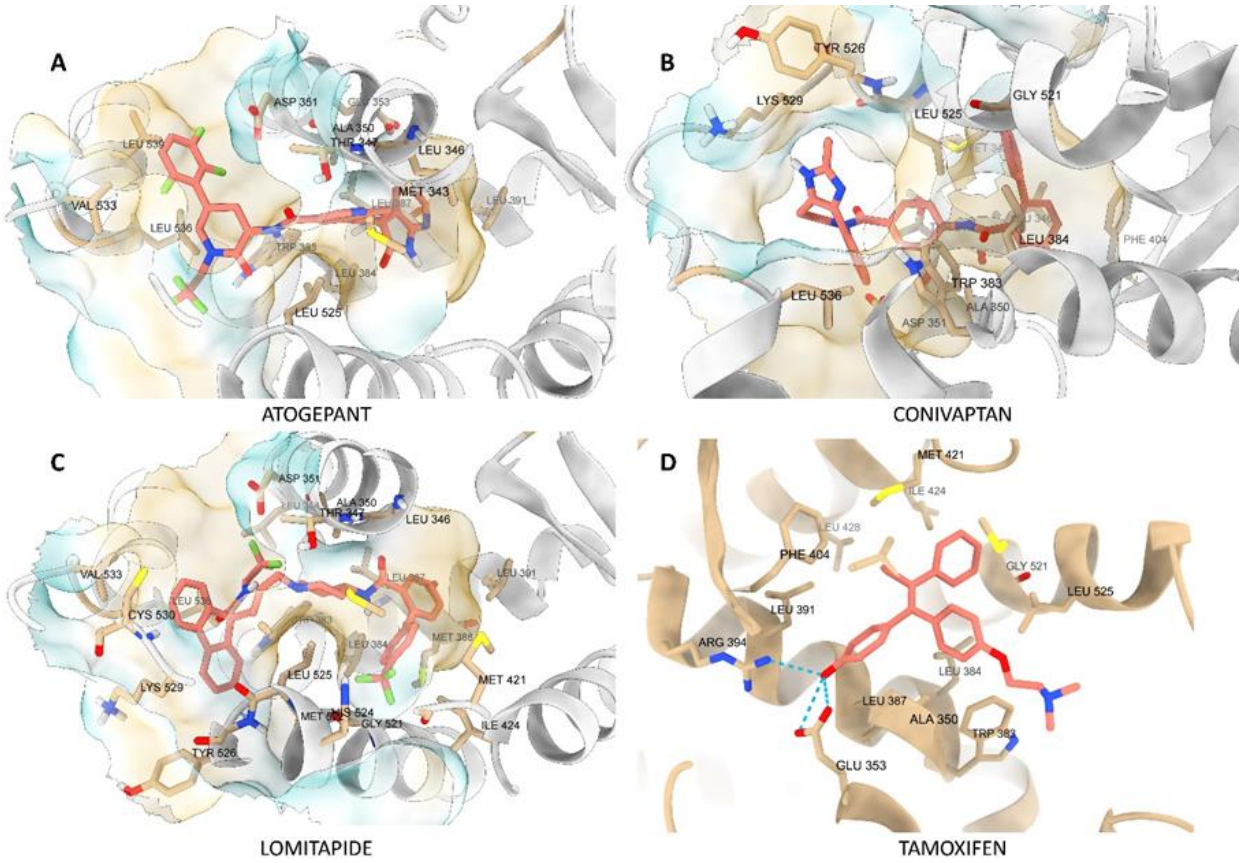

Figure 2. Three-dimensional diagrams illustrating the interactions between the residues of the estrogen receptor and various compounds, as determined through molecular docking studies.

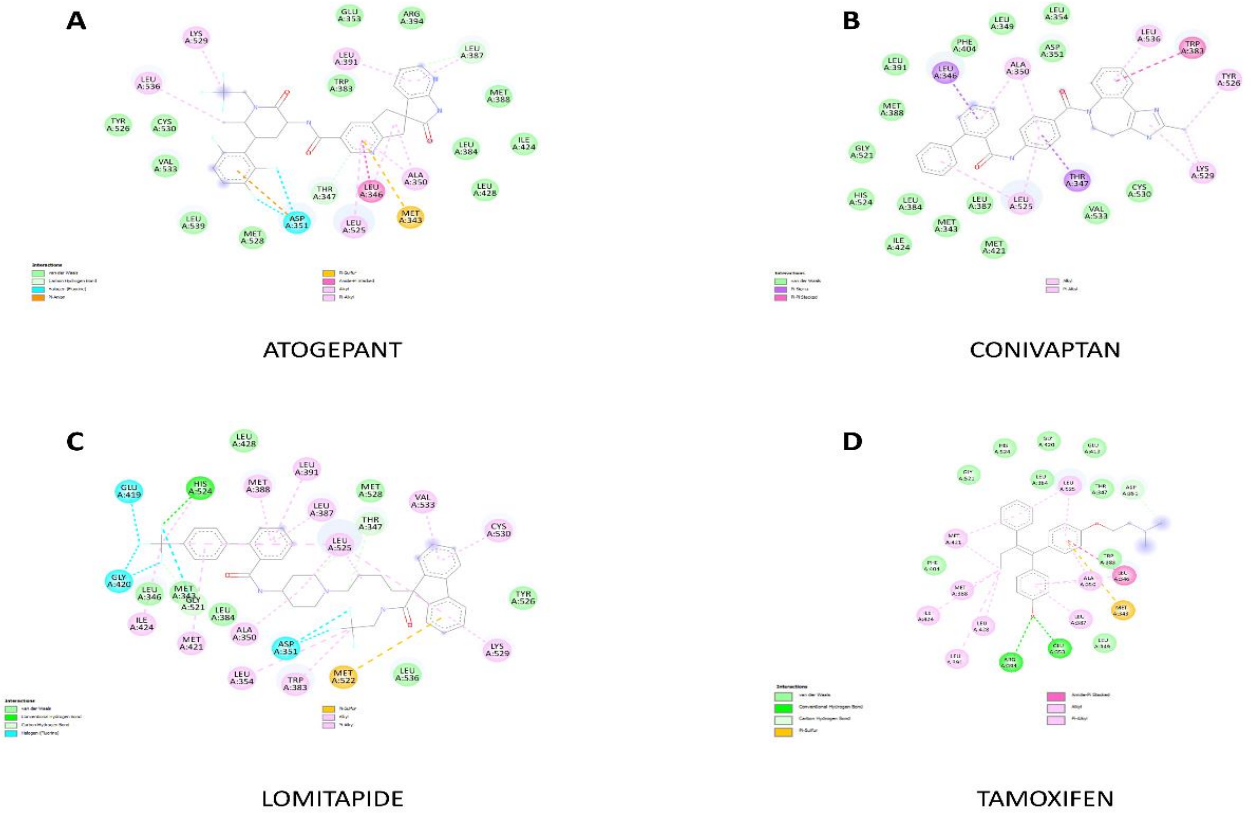

Figure 3. 2D diagrams showing how estrogen receptor residues interact with different compounds calculated via molecular docking studies.

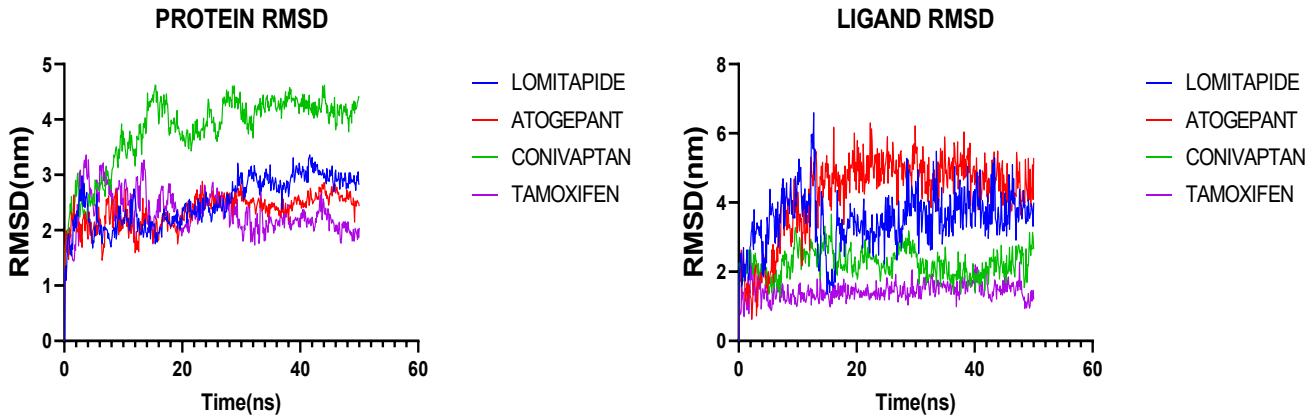

Figure 4. The root mean square deviation (RMSD) values for both the proteins and ligands

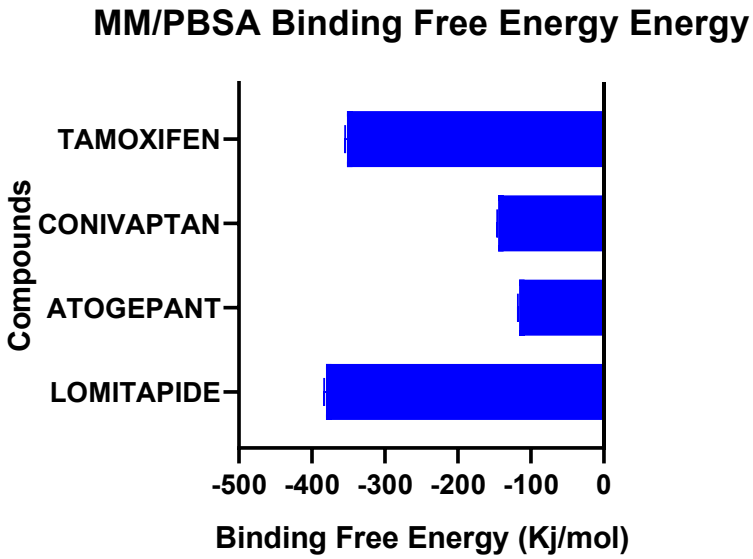

Figure 5. Binding free energies between the estrogen receptor (ER) and selected compounds are determined by the MM/PBSA approach during the final 10 ns of executed molecular dynamics (MD)

Discussion

The advancement and utilization of estrogen receptor inhibitors have brought about a revolutionary shift in the treatment of hormone-driven illnesses, particularly in breast cancer. Tamoxifen, a renowned selective estrogen receptor modulator (SERM), has gained extensive usage as an adjuvant therapy for estrogen receptor-positive breast cancer, showcasing substantial reductions in both disease recurrence and mortality rates.[3] Nonetheless, its usage can result in various side effects. The predominant adverse effects of tamoxifen encompass hot flashes, vaginal dryness, menstrual irregularities, nausea, and fatigue. Additionally, prolonged tamoxifen usage may elevate the risk of endometrial cancer in certain women.[26] The primary concern with tamoxifen is its potential to induce drug resistance.[27] Consequently, the development of novel estrogen receptor inhibitors as alternatives to tamoxifen becomes crucial.

In this study, molecular docking and molecular dynamics (MD) simulations revealed that three compounds-lomitapide, conivaptan, and atogepant-exhibited higher binding affinities to ERα. Lomitapide demonstrated a superior docking score of -12 kcal/mol in comparison to the established ER inhibitor Tamoxifen, which scored -10 kcal/mol. Furthermore, lomitapide displayed a stronger binding affinity of -380.727 kJ/mol, contrasting with tamoxifen's affinity of -352.029 kJ/mol.

Lomitapide has emerged as a promising pharmaceutical agent in the management of hypercholesterolemia, especially among patients with homozygous familial hypercholesterolemia (HoFH).[28] Through the inhibition of LDL cholesterol synthesis, lomitapide assists in lowering LDL levels in the bloodstream. Moreover, several studies have demonstrated the anticancer effects of lomitapide.[29–31] Lee et al. demonstrated that lomitapide induces autophagic cancer cell death by inhibiting mTOR.[30] Similarly, Zuo et al. demonstrated AMPK/beclin-mediated autophagic cell death induced by lomitapide in colorectal cancer cells.[32] TilakVijay et al. demonstrated that lomitapide exhibits high ER inhibition with an approximate value of 775 kJ/mol, which supports our findings.[33]

Conivaptan is primarily used as a drug for treating hyponatremia, a condition characterized by low levels of sodium in the blood. It belongs to a class of medications

known as vasopressin receptor antagonists.[34] Conivaptan is also employed for the prevention and treatment of hyponatremia in cancer patients.[35] However, there are no studies in the literature addressing the interaction between conivaptan and the estrogen receptor.

Exploring the interaction between Conivaptan and the estrogen receptor may provide valuable insights into its mechanisms of action and offer novel therapeutic perspectives. Future studies focused on elucidating the specific nature and implications of this interaction could potentially lead to the development of innovative treatments or combination therapies.

Furthermore, the observed binding affinities emphasize the importance of understanding conivaptan's broader pharmacological profile, particularly as a potential modulator of hormone-driven pathways.[36,37] These results underscore the need for comprehensive investigations to explore the clinical significance of conivaptan's affinity for the estrogen receptor, potentially paving the way for new treatment strategies or repurposing opportunities. In our study, conivaptan exhibits a notable affinity for the estrogen receptor, potentially implicating its role beyond the treatment of hyponatremia. While conivaptan's vasopressin receptor antagonist properties are well-established, our study sheds light on its potential interactions with the estrogen receptor, which, to our knowledge, have not been previously explored.

Atogepant is a novel small-molecule calcitonin gene-related peptide (CGRP) receptor antagonist used for treating migraines in adults.[38] CGRP is a neurotransmitter that plays a significant role in triggering and sustaining migraine attacks. Atogepant aims to block the effects of this chemical by binding to CGRP receptors. However, no studies have investigated the anticancer activity of atogepant as a new drug. In a phase 1 study, it was determined that the daily use of 60 mg of atogepant with oral contraceptives did not affect the pharmacokinetics of estrogen.[39] In our study, both the binding free energy and RMSD values of atogepant have been demonstrated to be significantly lower compared to tamoxifen. Consequently, it could be inferred that atogepant is not a strong candidate as a potential ER inhibitor.

In this study, three compounds - lomitapide, conivaptan, and atogepant - have demonstrated higher binding affinities to the estrogen receptor than tamoxifen. These compounds could be used as alternative estrogen receptor inhibitors due to the side effects and drug resistance associated with tamoxifen. In particular, lomitapide and conivaptan are novel compounds in this context. Lomitapide is a medication used in the treatment of hypercholesterolemia and has also shown anticancer effects against various cancer types.[31,40] Conivaptan, on the other hand, is used to treat hyponatremia, and its interaction with the estrogen receptor has not been previously investigated.[41]

Limitations of this study include the lack of experimental validation, the lack of elucidation of molecular mechanisms and clinical significance, and the omission of other compounds interacting with the estrogen receptor. Future directions for this study may involve in vitro and in vivo testing of these compounds, assessment of target tissue selectivity, investigation of pharmacokinetic and pharmacodynamic profiles, evaluation of toxicity and safety profiles, and exploration of the effectiveness of combination therapies.

Conclusion

Our study may shed light on the potential of lomitapide as an alternative candidate for ER inhibition in comparison to tamoxifen. The significantly higher binding affinities observed in our molecular docking and MD simulations suggest that lomitapide warrants further exploration as a potential ER modulator. However, for these findings to be translated into meaningful therapeutic strategies, it should be supported by comprehensive *in vitro* and *in vivo* investigations.

Conflict of Interest

The authors declare that they have no conflicting interests.

Financial Disclosure/Funding

The authors declared that no financial support was received for this paper

Author Contributions

ZD; Conceptualization, Methodology, Writing; FD; Conceptualization, Interpretation, Literature review and Writing

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