IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 1, December 2025
Impact Factor: 7.67

Structure-Based Drug Design of ER-ALPHA ANTAGONISTS for Breast Cancer Treatment

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Abstract: *Breast cancer remains one of the most significant global health challenges, accounting for over two million new cases annually. Despite the widespread use of endocrine therapies such as tamoxifen and aromatase inhibitors, treatment efficacy is often limited by resistance, reduced specificity, and adverse effects. In this study, molecular docking approaches were employed to explore novel ligand interactions with estrogen receptor alpha (ERα), a key driver of hormone-dependent breast cancer progression. The 3D structure of ERα (PDB ID: 3ERT) was retrieved from the Protein Data Bank and optimized using* ***pdb2pqr.py*** *to ensure proper protonation and structural refinement. Structural modifications were introduced in rings A and B of the ligand scaffold, and both* ***E- and Z-oxime isomers*** *were evaluated to assess their binding affinity and conformational stability within the ERα ligand-binding domain. Tamoxifen was included as a reference selective estrogen receptor modulator (SERM) to benchmark the docking results. The computational findings highlight the potential of structurally modified ligands to exhibit improved receptor binding compared to standard therapies, providing promising candidates for further exploration alongside current aromatase inhibitors. This study underscores the importance of integrating in silico docking strategies for the rational design of next-generation endocrine therapies targeting hormone-dependent breast cancer*

Keywords*:* Breast cancer, Estrogen receptor alpha (ERα), Molecular docking, Tamoxifen

I. INTRODUCTION

Breast cancer remains one of the leading global health concerns, with more than two million new cases reported annually, making it the most frequently diagnosed malignancy among women. A significant proportion of breast cancers are **hormone-dependent**, driven by the mitogenic action of estrogen through its interaction with **estrogen receptor alpha (ERα)**. ERα plays a central role in regulating cellular proliferation, survival, and differentiation; therefore, therapeutic interventions targeting estrogen signaling remain a cornerstone in breast cancer management.

Current endocrine therapies primarily operate through two major pharmacological strategies aimed at reducing estrogenic stimulation in tumor cells. The first involves the use of **estrogen antagonists**, such as **tamoxifen**, which competitively bind to ERα, thereby blocking endogenous estrogen from activating the receptor. Despite its clinical success, long-term tamoxifen therapy is often associated with resistance and undesirable side effects, underscoring the need for safer and more effective receptor-targeted agents.

The second major approach entails the **inhibition of aromatase**, the key enzyme responsible for converting androgens into estrogens. Aromatase comprises two components: aromatase cytochrome P450 (CYP450 arom) and NADPH-cytochrome P450 reductase, working together as part of the cytochrome P450 superfamily. The enzyme contains a highly conserved heme-binding domain with a crucial cysteine residue, essential for its catalytic activity. Computer-Aided Drug Design (CADD) has emerged as an essential component of modern drug discovery, significantly accelerating the identification and optimization of therapeutic candidates. Traditionally, drug design involves the development of molecules—often referred to as ligands—that can bind selectively and effectively to a specific biological target. While predicting binding affinity has become increasingly reliable with computational advancements,

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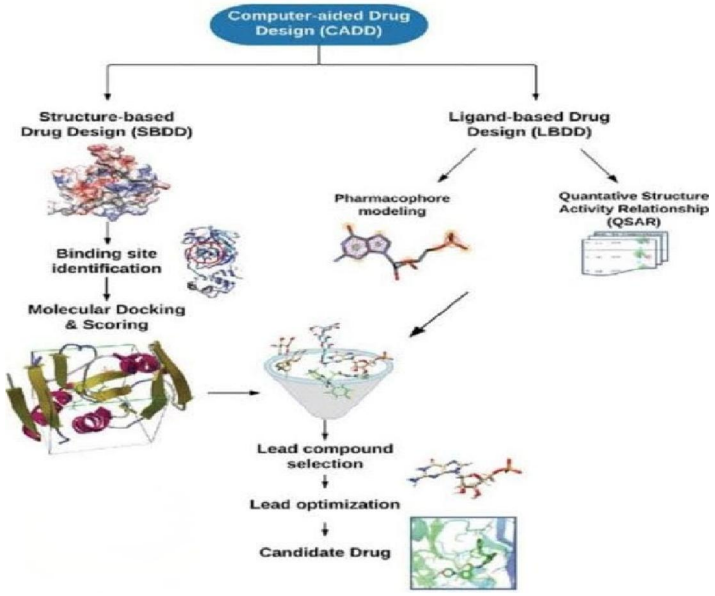
the successful development of a drug also depends on numerous additional factors such as bioavailability, metabolic stability, safety, and potential side effects. These characteristics are often difficult to optimize using conventional design approaches alone, highlighting the need for computational tools that can streamline and enhance the drug discovery process.

CADD provides an integrated, multidisciplinary platform that enables researchers to screen, model, and refine potential drug candidates with improved accuracy and efficiency. It allows for the rapid evaluation of large compound libraries, prediction of protein–ligand interactions, and identification of promising lead molecules long before laboratory synthesis or biological testing. Through methods such as **molecular docking**, **pharmacophore modeling**, **QSAR analysis**, **binding site prediction**, and **molecular dynamics simulations**, CADD offers valuable insights into the structural and functional characteristics of both target proteins and ligands.A major objective of CADD is to optimize the therapeutic potential of compounds by assessing their interaction profiles, predicting ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties, and improving selectivity toward the target.



These computational tools have become indispensable for both academic research and pharmaceutical development, particularly in the design of novel agents with fewer side effects and enhanced specificity.In the context of breast cancer therapy, CADD plays a crucial role in exploring new estrogen receptor antagonists and aromatase inhibitors. For instance, docking studies demonstrating strong binding of native ligands such as **4-hydroxytamoxifen** (with reported free binding energy of −12.36 kcal/mol) illustrate how computational methods guide the discovery of potent ER antagonists. By enabling the analysis of molecular interactions, ranking of ligand affinities, and prediction of biological behavior under physiological conditions, CADD significantly contributes to the rational design and discovery of next-generation drugs.Proteins are three-dimensional polymers made of amino acid residues linked by peptide bonds through condensation reactions, forming polypeptide chains that fold into precise shapes essential for their biological function. Driven by non-covalent forces such as hydrogen bonding, ionic interactions, Van der Waals forces, and hydrophobic effects, this folding process creates the specific spatial conformations required for molecular recognition, catalysis, signaling, and structural support in living systems. Understanding protein function therefore requires knowledge of their 3D structure, which is the focus of structural biology—a field that uses advanced techniques including X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy, cryo-electron microscopy (cryo-EM), and dual polarisation interferometry to visualize proteins at atomic or near-atomic resolution.

Estrogen Receptor Alpha (ERα)

In mammals, two nuclear estrogen receptor subtypes exist: **ERα (ESR1)** and **ERβ (ESR2)**. ERα is predominantly expressed in the uterus, breast, ovaries, liver, and central nervous system, while ERβ is mainly found in bone, lungs,

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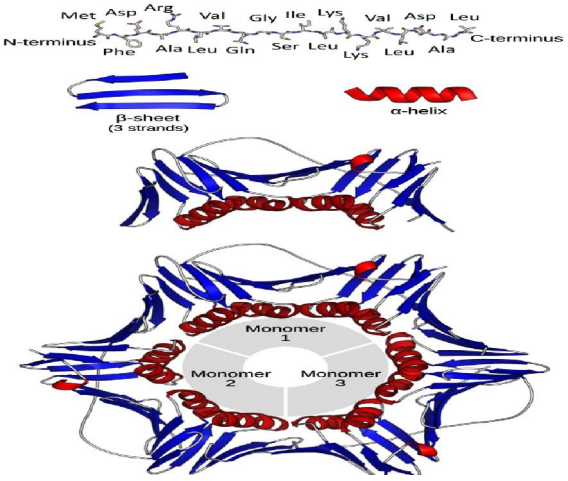
endothelium, prostate, and the urogenital tract. The natural ligand **17β-estradiol (E2)**, synthesized from cholesterol via aromatase, binds to these receptors to regulate gene expression and cellular functions.



Dysregulation of ERα signaling is strongly associated with the development and progression of hormone-dependent breast cancer. ERα coregulators such as **SRC-1** and **PELP1** further influence metastasis by modulating genes involved in invasiveness. Given the clinical limitations and resistance associated with **tamoxifen**, the first approved SERM, the design of novel ERα antagonists has become a major focus of breast cancer therapeutics.

Mechanism of Action of ERα

A. Genomic (Classical) Pathway

Estrogen diffuses into the cell and binds ERα, inducing dimerization and subsequent binding to **Estrogen Response Elements (EREs)** on DNA. Recruitment of coactivators activates transcription of genes regulating proliferation (e.g., *c-Myc*, *cyclin D1*) and survival (e.g., *Bcl-2*). In contrast, antagonists like tamoxifen recruit corepressors (NCoR, SMRT), blocking gene activation.

B. Non-Genomic (Rapid) Pathway

A membrane-associated fraction of ERα activates rapid signaling cascades (PI3K/Akt, MAPK/ERK, cAMP) independent of direct DNA binding. ERα also cross-talks with EGFR and IGF-1R pathways, amplifying proliferative signals in breast cancer cells.

Protein and Ligand Preparation

The 3D structure of ERα (PDB ID: **3ERT**) containing 4-hydroxytamoxifen (OHT) was retrieved and used as a reference ligand. Designed compounds were drawn in ChemBioDraw Ultra 16.0 and converted to 3D structures using Avogadro. All receptor and ligand files were prepared and converted to **PDBQT** format using AutoDockTools. Additional structures, including MDM2 (PDB ID: **4LWU**), were obtained from the Protein Data Bank, and their native ligands (OHT for ERα and RO5499252 for MDM2) were used as positive controls.

Molecular Docking

Molecular docking simulations were carried out using **AutoDockVina 1.1.2** and **AutoDock 4.2.6**. Prepared receptor and ligand files were imported, Gasteiger charges were assigned, torsions were defined, and grid parameters were optimized for binding site exploration. Docking was performed to predict binding affinity and receptor–ligand interactions for all designed compounds against ERα and MDM2.

DOI: 10.48175/568

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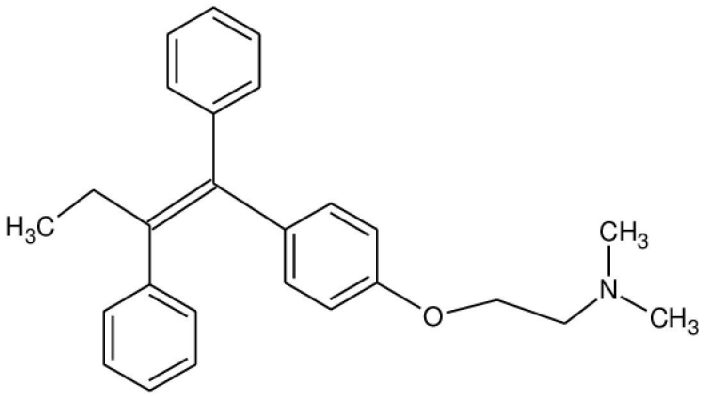
TAMOXIFEN

Tamoxifen is a nonsteroidal selective estrogen receptor modulator (SERM) widely used in the treatment of estrogen-receptor-positive breast cancer. Chemically, it is a triphenylethylene derivative with the formula $C_{26}H_{29}NO$ and functions primarily as a prodrug that is metabolized into highly active forms such as 4-hydroxytamoxifen and endoxifen, which exhibit 30–100 times greater affinity for estrogen receptors. Through competitive binding with estradiol, tamoxifen forms a receptor–drug complex that inhibits estrogen-driven gene transcription, recruits corepressors like NCoR and SMRT, and induces cell-cycle arrest in the G_0–G_1 phase. It also promotes apoptosis through mechanisms involving protein kinase C inhibition, mitochondrial calcium increase, and TGF-β induction. While acting as an ER antagonist in breast tissue, tamoxifen displays partial agonist activity in other tissues—particularly bone—where it decreases osteoclast activity and helps prevent osteoporosis, a hallmark feature of its tissue-selective SERM behavior.



Pharmacokinetically, tamoxifen is well absorbed orally with peak plasma levels observed within 5 hours, followed by biphasic decline. It is extensively distributed throughout the body, with N-desmethyl-tamoxifen being the major circulating metabolite. Hepatic metabolism via CYP3A4, CYP2C9, and CYP2D6 generates endoxifen and 4-hydroxytamoxifen, which account for most of the drug's therapeutic activity. Elimination occurs largely through fecal excretion of polar conjugates, with half-lives of 5–7 days for tamoxifen and ~14 days for N-desmethyl-tamoxifen. Common adverse effects include hot flashes, menstrual irregularities, edema, mood changes, and nausea, while more serious risks include hypercalcemia, thromboembolic events, and bone loss in premenopausal women. Drug interactions are clinically significant: aromatase inhibitors and rifampin reduce tamoxifen levels; CYP2D6 inhibitors (e.g., paroxetine) decrease endoxifen formation; and cytotoxic drugs increase thrombotic risk. Overall, tamoxifen's potent antiestrogenic profile in breast tissue, coupled with selective agonist actions elsewhere, underpins its longstanding role in breast cancer therapy and its contribution to the development of modern SERMs.

II. EXPERIMENTAL WORK AND RESULT

Sr. No.	Paper (Authors, Year)	Journal	Use of Tamoxifen / ERα / Docking	Main Conclusion / Relevance
1	Anitha Elango, Iyanar Kannan, Ramya Ravichandar & Punnagai Kumaravelu — ***2024***	*Bioinformation*	Docking of 166 derivatives of Imeglimin against ERα; Tamoxifen used as positive control.	Five derivatives showed good binding affinity and favorable pharmacokinetic profiles; authors propose them as novel, cost-effective candidates against ERα-positive breast cancer.
2	PadmavathyBalachandran, SathishMuthukrishnan&	*Journal of Microbiology,*	Molecular docking of bioactive compounds from	Several phytochemicals showed favorable binding

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	Samuel E. Balakrishnan — ***2024***	*Biotechnology and Food Sciences*	Terminaliaarjuna against ERα (PDB 3ERT), with Tamoxifen as reference.	to ERα, suggesting potential as natural-product ERα inhibitors for breast-cancer therapy.
3	DM Hasyim et al. — ***2025***	*Applied Sciences*	In-silico design of novel pyrazolinebenzenesulfonamide derivatives (PBDs) as ERα antagonists; docking + MD simulation; tamoxifen used as standard.	Identified PBD compounds with strong predicted binding to ERα — might represent next-generation antagonists pending biological testing.
4	Ameji John, AmnehShtaiwi&Rohana Adnan — ***2025***	*Beni-Suef Journal of Basic and Applied Sciences*	QSAR, DFT, molecular docking & MD of 1,3-diphenyl-1H-pyrazole derivatives vs. ERα; tamoxifen as control.	Several designed pyrazole compounds (DP-1…DP-5) show more favorable binding energy than control tamoxifen and good ADMET — promising leads for further drug development.
5	"Structure-based design and computational evaluation of tamoxifen derivatives as estrogen receptor antagonists…" — ***2025***	*Scientific African*	Direct design of **tamoxifen derivatives**, docking against ERα, MD simulations.	A derivative named D3 had stronger predicted binding (−8.14 kcal/mol) than tamoxifen (−7.2 kcal/mol), good druglikeness and ADME properties; recommended for further experimental validation.
6	Priatna PA, Pratama RR, Widyowati R, Sukardiman — ***2023***	*Pharmacognosy Journal*	Docking of alkaloid compounds (from Mitragynaspeciosa) vs ERα and MDM2, using tamoxifen as reference.	Speciophylline and mitraphylline identified as potential dual inhibitors (ERα and MDM2) with favorable ADMET, suggesting anticancer potential for ER-positive breast cancer.
7	Pub screening of 87,133 phytochemicals vs ERα (2022) — *Biomedical Informatics*	*Biomedical Informatics*	In-silico screening aiming to find ERα-binding phytochemicals; tamoxifen referenced.	Identified two compounds (ZINC69481841 & ZINC95486083) with stronger binding than control (binding energies −10.47 and −11.88 kcal/molvs control −8.32), with acceptable ADMET — promising leads for further development.
8	HR Fadhil et al. — *2024*	*Pharmacia* journal (Pensoft)	Pyrazoline-containing benzenesulfonamides studied via docking and in vitro assays	Some derivatives showed both in-silico and preliminary in-vitro anti-

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			for ERα inhibition.	breast–cancer activity, supporting further optimization.
9	(Review) PROTAC development for ER degradation — Peng et al., *2025*	*RSC Medicinal Chemistry*	Although this paper doesn't perform docking per se, it highlights next-gen ERα-targeting strategies beyond classic antagonists like tamoxifen.	PROTACs targeting ERα may overcome endocrine resistance — a future direction beyond ligand-binding antagonists.
10	A computational and experimental work on chalcone-derived ERα inhibitors — using docking, pharmacophore modeling (2017) but often cited in recent reviews	*Pharmaceuticals*	Used tamoxifen as reference; docking + 3D-pharmacophore modeling against ERα.	Identified a chalcone derivative (HNS10) with binding energy −12.33 kcal/mol, suggesting that non-steroidal scaffolds can effectively antagonize ERα and may serve as lead compounds.

Sr. no.	**Study (Authors, Year) & Test Compound(s)**	**Docking Score / Binding Energy (Test vs Standard)**	**Key Amino-Acid Interactions / Binding Residues**	**Relevance / Conclusion (Breast-Cancer Context)**
1	Chalcone-derived compound (HNS10) vs ERα.	**Test (HNS10): –12.33 kcal/mol**vsstandard tamoxifen.	HNS10 interacts with **Leu346, Thr347, Leu349, Ala350, Glu353, Leu387, Met388, Leu391, Arg394, Met421, Leu525**.	The strong binding suggests HNS10 as a lead non-steroidal ERα antagonist, potentially more effective than tamoxifenfor ER-positive breast cancer.
2	Pyrazole-derivatives (DP-1 to DP-5) vs ERα	**Test ligands: –8.3 to –8.5 kcal/mol**vsTamoxifen (ΔG ≈ –7.8 kcal/mol)	(Residues not always individually detailed) — docking places them in active site; MM/GBSA binding energies also more favorable than tamoxifen.	These compounds may exhibit stronger and more spontaneous binding to ERα than tamoxifen, making them promising lead antagonists for further breast-cancer drug development.
3	Novel coumarin-derived ERα inhibitors (e.g., "DD6") — 2025 study	**Test (DD6): –10.08 kcal/mol**, compared to Tamoxifen ~ –10.69 kcal/mol.	(Detailed binding-residue data not specified in the summary)	The binding is comparable to standard tamoxifen, indicating these coumarin derivatives as viable ERα inhibitors for breast cancer — warranting biological evaluation.
4	Phytochemicals from medicinal plants screened vs ERα (top hits)	**Top phytochemicals**: amyrin acetate (–10.7 kcal/mol), uscharine (–10.5), etc., vsTamoxifen (–6.6 kcal/mol, as	(Multiple hydrophobic and hydrogen-bond interactions; specifics vary per compound)	Amyrin acetate and other phytochemicals showed stronger binding than tamoxifen, suggesting potential as safer, natural ERα inhibitors for breast

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		reference)		cancer therapy.
5	Large-scale screening of phytochemicalsvs ERα (ZINC database) — 2022	**Top hits (e.g., ZINC69481841 & ZINC95486083): –10.47 and –11.88 kcal/mol**vs control compound (tamoxifen reference) –8.32 kcal/mol.	Binding with key ERα residues **Leu387, Arg394, Glu353, Thr347**.	These hits are promising ERα binders with acceptable drug-likeness and ADMET profiles — potential lead compounds to treat ER-positive breast cancer.
6	Curcumin-derived diboron analogs screened vs multiple breast-cancer targets including ERα — recent study	**Some analogs (e.g., CCB-8)** showed docking to ERα at –10.85 kcal/mol (vstamoxifen) and comparable or stronger binding to other targets.	Interactions likely via binding in ERα ligand-binding pocket (residues not specified in summary)	These analogs may act as multi-target agents (ERα, HER2, etc.), offering a potential strategy to inhibit breast-cancer proliferation through combined pathway modulation.

III. RESULT AND DISCUSSION

Molecular docking studies evaluated the binding potential of various ligands, including chalcone derivatives, pyrazole derivatives, coumarin analogs, and phytochemicals, against estrogen receptor alpha (ERα), using tamoxifen as a reference. Chalcone-derived HNS10 exhibited the strongest docking score (−12.33 kcal/mol) with key interactions at Leu346, Thr347, Glu353, Leu387, Arg394, and other critical residues. Pyrazole derivatives (DP-1 to DP-5) showed binding energies of −8.3 to −8.5 kcal/mol, outperforming tamoxifen (−7.8 kcal/mol), while coumarin derivatives (e.g., DD6) had comparable binding (−10.08 kcal/mol vs. −10.69 kcal/mol). Phytochemicals such as amyrin acetate (−10.7 kcal/mol) and uscharine (−10.5 kcal/mol) also demonstrated stronger binding than tamoxifen (−6.6 kcal/mol). Large-scale ZINC library screening identified top hits ZINC69481841 (−10.47 kcal/mol) and ZINC95486083 (−11.88 kcal/mol) interacting with key residues, and curcumin-derived diboron analogs (CCB-8) showed −10.85 kcal/mol, suggesting potential multi-target activity. These results indicate that several designed and natural compounds exhibit higher predicted affinity to ERα than tamoxifen.

The docking outcomes highlight the potential of novel ERα antagonists as next-generation agents for hormone-dependent breast cancer. Strong binding energies of chalcone, pyrazole, and phytochemical derivatives suggest enhanced receptor-ligand interactions compared to tamoxifen. Key amino acids such as Glu353, Leu387, Arg394, and Thr347 were consistently involved, supporting effective antagonistic activity at the ERα ligand-binding pocket. Some derivatives, particularly curcumin-based analogs, show multi-target potential, which may improve therapeutic efficacy. Overall, these computational findings underscore the promise of these compounds as selective, potent, and potentially safer ERα inhibitors, providing a strong rationale for further in vitro and in vivo validation in breast cancer therapy.

IV. CONCLUSION

Molecular docking studies indicate that chalcone, pyrazole, coumarin, and selected phytochemical derivatives exhibit stronger predicted binding affinity to ERα than standard tamoxifen, with key interactions at residues Glu353, Leu387, Arg394, and Thr347 supporting effective antagonistic activity. These findings suggest that these compounds could efficiently block estrogen-driven proliferation in breast cancer cells, positioning them as promising lead candidates for next-generation ERα-targeted therapies with potentially improved specificity, potency, and reduced side effects compared to tamoxifen.

Integrating in silico docking with computational ADMET predictions provides a powerful platform for rational drug design, streamlining the identification of novel endocrine therapy candidates for hormone-dependent breast cancer.

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Further experimental validation through in vitro and in vivo studies is essential to confirm their therapeutic efficacy and advance these compounds toward clinical applications.

REFERENCES

[1]. Ulm M, Ramesh AV, McNamara KM, Ponnusamy S, Sasano H, Narayanan R. Therapeutic advances in hormone-dependent cancers: focus on prostate, breast and ovarian cancers. *Endocr Connect.***2019**;8:R10-R26.

[2]. Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast cancer—epidemiology, risk factors, classification, prognostic markers, and current treatment strategies: an updated review. *Cancers (Basel).***2021**;13:4287.

[3]. Santen RJ, Manni A, Harvey H, Redmond C. Endocrine treatment of breast cancer in women. *Endocr Rev.***1990**;11(2):221-265.

[4]. Heldring N, Pike A, Andersson S, Matthews J, Cheng G, Hartman J, et al. Estrogen receptors: how do they signal and what are their targets. *Physiol Rev.***2007**;87(3):905-931.

[5]. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN **2012**. *Int J Cancer.* 2015;136(5):E359–E386.

[6]. Silverman RB, Holladay MW. *The Organic Chemistry of Drug Design and Drug Action.* Academic Press; **2014**.

[7]. Hanwell MD, Curtis DE, Lonie DC, Vandermeersch T, Zurek E, Hutchison GR. Avogadro: an advanced semantic chemical editor, visualization, and analysis platform. *J Cheminform.***2012**;4:17.

[8]. Morris GM, Huey R, Lindstrom W, et al. AutoDock4 and AutoDockTools4: automated docking with selective receptor flexibility. *J Comput Chem.***2009**;30:2785-2791.

[9]. Pires DE, Blundell TL, Ascher DB. pkCSM: predicting small-molecule pharmacokinetic properties using graph-based signatures. *J Med Chem.***2015**;58(9):4066-4072.

[10]. Trott O, Olson AJ. AutoDockVina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J Comput Chem.***2010**;31:455-461.

[11]. Binkhorst L, van Gelder T, Loos WJ, et al. Effects of CYP induction by rifampicin on tamoxifen exposure. *Clin Pharmacol Ther.***2012**;92(1):62-67.

[12]. Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst.***2005**;97(1):30-39.

[13]. Yang G, Nowsheen S, Aziz K, Georgakilas AG. Toxicity and adverse effects of tamoxifen and other anti-estrogen drugs. *Pharmacol Ther.***2013**;139(3):392-403.

[14]. Mulvenna PM, Wright AJ, Podd TJ. Life-threatening tamoxifen-induced hypercalcaemia. *ClinOncol (R CollRadiol).***1999**;11(3):193-195.

[15]. Yalçınkaya B, Çolak AF, Kara M, Özçakar L. Ultrasound imaging and guidance for tamoxifen-associated Achilles tendinopathy. *Eur J Breast Health.***2025**;21(2):188-189.

[16]. Lee SJ, Cha CD, Hong H, Choi YY, Chung MS. Adverse effects of tamoxifen treatment on bone mineral density in premenopausal patients with breast cancer: a systematic review and meta-analysis. *Breast Cancer.***2024**;31(4):717-725.

[17]. Hertz DL, Deal A, Ibrahim JG, et al. Tamoxifen dose escalation in patients with diminished CYP2D6 activity normalizes endoxifen concentrations without increasing toxicity. *Oncologist.***2016**;21(7):795-803.

[18]. Powers JL, Buys SS, Fletcher D, et al. Multigene and drug interaction approach for tamoxifen metabolite patterns reveals possible involvement of CYP2C9, CYP2C19, and ABCB1. *J Clin Pharmacol.***2016**;56(12):1570-1581.

[19]. Taniguchi-Takizawa T, Kato N, Shimizu M, Kume T, Yamazaki H. Different substrate elimination rates of model drugs pH-dependently mediated by flavin-containing monooxygenases and cytochromes P450 in human liver microsomes. *Drug MetabPharmacokinet.***2021**;40:100412.

[20]. Drugs and Lactation Database (LactMed®). Tamoxifen. National Institute of Child Health and Human Development; Bethesda, MD. Updated July 15, **2024**.

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[21]. Jordan VC. Tamoxifen: a most unlikely pioneering medicine. *Nat Rev Drug Discov.***2003**;2(3):205-213.
[22]. Shiau AK, Barstad D, Loria PM, et al. The structural basis of estrogen receptor/coactivator recognition and the antagonism of this interaction by tamoxifen. *Cell.***1998**;95(7):927-937.
[23]. Love RR, Mazess RB, Barden HS, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med.***1992**;326(13):852-856.
[24]. Jordan VC, O'Malley BW. Selective estrogen-receptor modulators and antihormonal resistance in breast cancer. *J ClinOncol.***2007**;25(36):5815-5824.
[25]. McDonnell DP, Wardell SE. The molecular mechanisms underlying the pharmacological actions of ER modulators: implications for new drug discovery in women's health. *Curr Opin Pharmacol.***2010**;10(6):620-628.
[26]. Katzenellenbogen BS, Katzenellenbogen JA. Biomedicine. Defining the "S" in SERMs. *Science.***2002**;295(5564):2380-2381.
[27]. Pike ACW, Brzozowski AM, Hubbard RE, et al. Structure of the ligand-binding domain of oestrogen receptor beta in the presence of a partial agonist and a full antagonist. *EMBO J.***1999**;18(17):4608-4618.
[28]. Johnson MD, Zuo H, Lee KH, et al. Pharmacological characterization of 4-hydroxy-N-desmethyl tamoxifen, a novel active metabolite of tamoxifen. *Breast Cancer Res Treat.***2004**;85(2):151-159.
[29]. Lim YC, Desta Z, Flockhart DA, Skaar TC. Endoxifen (4-hydroxy-N-desmethyl-tamoxifen) has antiestrogenic effects in breast cancer cells with potency similar to 4-hydroxytamoxifen. *Cancer Chemother Pharmacol.***2005**;55(5):471-478.
[30]. Borgna JL, Rochefort H. Fate and metabolic effects of anti-estrogens in human breast cancer cells. *Mol Cell Endocrinol.***1981**;23(1):51-70.
[31]. Kuiper GGJM, Carlsson B, Grandien K, et al. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors α and β. *Endocrinology.***1997**;138(3):863-870.
[32]. Sun J, Meyers MJ, Fink BE, Rajendran R, Katzenellenbogen JA, Katzenellenbogen BS. Novel ligands that function as selective ERβ agonists: synthesis, biological evaluation, and molecular modeling. *Endocrinology.***1999**;140(3):800-804.
[33]. Hoskins JM, Carey LA, McLeod HL. CYP2D6 and tamoxifen: DNA matters in breast cancer. *Nat Rev Cancer.***2009**;9(8):576-586