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Molecular Docking of Quinoline-1,2,3-Triazole Derivatives as Potential Anti-Breast Cancer Agents Targeting Estrogen Receptor-α

Molecular Docking Turunan Kuinolin-1,2,3-Triazol sebagai Kandidat Agen Antikanker Payudara yang Menargetkan Estrogen Receptor-α

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ABSTRACT

Breast cancer remains one of the leading causes of cancer-related morbidity and mortality among women worldwide. Estrogen Receptor Alpha (ER-α) is a key regulator of ER-positive breast cancer cell proliferation and represents an important target for anticancer drug development. This study evaluated the potential of quinoline-1,2,3-triazole derivatives as ER-α inhibitors using an in silico approach. Fifteen compounds were analyzed through molecular docking against ER-α (PDB ID: 3ERT) using MOE software. Docking validation confirmed the reliability of the protocol with an acceptable RMSD value. All compounds exhibited favorable binding within the active site of ER-α. Among them, compound 5h showed the strongest binding affinity with a docking score of −12.76 kcal/mol, exceeding that of the native ligand. Interaction analysis revealed the involvement of important amino acid residues, including Glu353, Arg394, Leu387, and Met421. ADMET prediction indicated favorable pharmacokinetic properties. These findings suggest that quinoline-1,2,3-triazole derivatives have potential as anti-breast cancer agents targeting ER-α.

Keywords: breast cancer, ER-α, molecular docking, quinoline-1,2,3-triazole, ADMET

ABSTRAK

Kanker payudara merupakan salah satu penyebab utama morbiditas dan mortalitas akibat kanker pada wanita di seluruh dunia. Estrogen Receptor Alpha (ER-α) berperan penting dalam proliferasi sel kanker payudara positif estrogen sehingga menjadi target yang menjanjikan dalam pengembangan obat antikanker. Penelitian ini bertujuan mengevaluasi potensi turunan quinoline-1,2,3-triazole sebagai inhibitor ER-α melalui pendekatan in silico. Sebanyak lima belas senyawa dianalisis menggunakan molecular docking terhadap protein ER-α (PDB ID: 3ERT) dengan perangkat lunak MOE. Validasi docking menunjukkan protokol yang digunakan memiliki tingkat keandalan yang baik berdasarkan nilai RMSD yang memenuhi kriteria. Seluruh senyawa mampu berikatan pada sisi aktif ER-α. Senyawa 5h menunjukkan afinitas pengikatan terbaik dengan nilai docking score sebesar −12,76 kcal/mol, lebih baik dibandingkan ligan native. Analisis interaksi menunjukkan keterlibatan residu penting Glu353, Arg394, Leu387, dan Met421. Prediksi ADMET menunjukkan profil farmakokinetik yang baik. Hasil penelitian ini mengindikasikan bahwa turunan quinoline-1,2,3-triazole berpotensi dikembangkan sebagai agen antikanker payudara yang menargetkan ER-α.

Kata kunci: kanker payudara, ER-α, molecular docking, kuinolin-1,2,3-triazol, ADMET

INTRODUCTION

Breast cancer remains the most frequently diagnosed malignancy and one of the leading causes of cancer-related death among women worldwide, with more than 2.3 million new cases reported globally; in Indonesia, 65,858 cases have been recorded, accounting for 16.6% of the total cancer burden (Brewster et al., 2026; Mar et al., 2023). At the molecular level, breast cancer is a highly heterogeneous disease comprising multiple biological subtypes, among which hormone receptor-positive breast cancer, particularly the estrogen receptor-positive (ER-positive) subtype, is the most prevalent and represents approximately 60% of cases (Lakshmi et al., 2025). The pathogenesis and progression of this subtype are closely associated with estrogen-driven signaling, which regulates tumor cell proliferation, survival, and disease progression. This condition represents an important therapeutic problem because excessive estrogen-mediated signaling can promote the growth and progression of ER-positive breast cancer cells. Accordingly, estrogen receptor alpha (ER-α), as the main mediator of this pathway, has been recognized as a key molecular target in the development of selective and effective therapeutic agents for breast cancer treatment.(Burstein et al., 2025; Khaerina and Amin, 2025).

ER-α was selected as the target protein due to its central role in mediating estrogen signaling through the regulation of gene expression and cellular proliferation, as well as its close association with the growth of ER-positive breast cancer, the most prevalent molecular subtype (Maida et al., 2026). Therefore, inhibition of ER-α is considered a relevant therapeutic strategy for estrogen-dependent breast cancer (Joseph et al., 2021; Kumar et al., 2024). The selection of PDB ID 3ERT is also appropriate, as it represents a crystallographic structure of ER-α that has been widely employed in molecular docking studies(Maida et al., 2026).

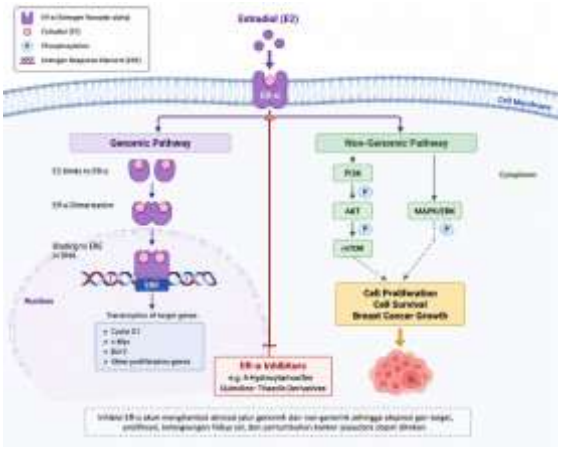

Figure 1. ERα: E2 signaling network and crosstalk with growth factor signaling.

In the classical estrogen signaling pathway, estradiol (E2) binds to ER-α and induces receptor activation, followed by receptor dimerization and translocation into the nucleus. The activated ER-α complex then binds to estrogen response elements (EREs) in DNA and regulates the transcription of estrogen-responsive genes associated with cell proliferation and survival (Nakshatri, 2021). In addition to this genomic pathway, membrane-associated ER-α can also activate non-genomic signaling pathways, including PI3K/AKT/mTOR and MAPK signaling, which further contribute to breast cancer cell growth and survival. In addition, this structure contains a co-crystallized ligand, which can be utilized for docking validation through a redocking procedure to assess the reliability of the applied method (Deka et al., 2025).

Several studies have demonstrated that both quinoline and 1,2,3-triazole possess promising anticancer activity, and quinoline–1,2,3-triazole hybrids have also been reported to exhibit cytotoxic effects against several cancer cell lines (Lavunuri et al., 2024; Sunkara et al., 2024).

ER-α was selected because its ligand-binding pocket accommodates ligands through hydrophobic interactions supported by specific polar and hydrogen-bond interactions. The quinoline–1,2,3-triazole scaffold was considered a rational candidate for ER-α evaluation because the aromatic quinoline moiety may support hydrophobic interactions within the binding pocket, while the nitrogen-rich 1,2,3-triazole moiety may contribute polar interaction sites and influence ligand orientation (Lee and Barron, 2017). However, previous investigations have predominantly focused on other molecular targets, such as EGFR, HER2, VEGFR-2, STK33, and ROCK, whereas the potential of this scaffold toward ER-α remains insufficiently explored (Akter et al., 2022; Lavunuri et al., 2024; Marciniec et al., 2024).

In this study, molecular docking was applied to evaluate the binding affinity and interaction pattern of the investigated compounds toward the target protein. Furthermore, ADMET assessment was carried out to predict the absorption, distribution, metabolism, excretion, and toxicity properties of the compounds, thereby providing an initial evaluation of their potential as drug candidates (Alnuqaydan, 2026; Huang et al., 2026; Ibeyaima et al., 2025).

Research Methods

Materials

The tools employed in this study consisted of a Dell Inspiron 14 3000 Series laptop, *Molecular Operating Environment* (MOE) software for molecular docking analysis, and pkCSM for ADMET property prediction. The materials used comprised the three-dimensional structure of estrogen receptor alpha (ER-α), obtained from the Protein Data Bank under the PDB code 3ERT, along with 15 quinoline–1,2,3-triazole derivatives adopted from the study of (Lavunuri et al., 2024).

Ligand and Protein Preparation

Fifteen quinoline–1,2,3-triazole derivative compounds reported by (Lavunuri et al., 2024) were used as test ligands in this study. were used as test ligands in this study. Their chemical structures were drawn using ChemDraw and imported into Molecular Operating Environment (MOE) version 2019.0102 (ULC, 2019). The ligand structures were saved in MOE database format and prepared sequentially using the Wash function, partial charge calculation, and energy minimization. Energy minimization was performed using the MMFF94x force field until an RMS gradient of 0.001 was achieved (Gammal et al., 2023). The crystal structure of estrogen receptor alpha (ER-α) was retrieved from the Protein Data Bank under PDB ID 3ERT. The receptor was prepared in MOE by removing unnecessary chains, including the native ligand and water molecules, followed by Protonate 3D, partial charge calculation, and energy

minimization using the same force field and RMS gradient criterion. The prepared ligand and receptor structures were subsequently used for molecular docking analysis (Maida et al., 2026).

Redocking

Validation of the docking protocol was performed through a redocking procedure using 4-Hydroxytamoxifen as the co-crystallized ligand in the 3ERT protein structure, retrieved from the Protein Data Bank (https://www.rcsb.org/structure/3ERT). In this step, 4-Hydroxytamoxifen was separated from the binding site and then redocked into the active site using the same docking parameters applied in the main docking simulation. The resulting binding pose was subsequently compared with the original crystallographic conformation to evaluate the reliability of the docking protocol (Zekri et al., 2020).

Molecular Docking

The docking process adhered to the protocol outlined by Amelia et al., (2024). Molecular docking was performed using MOE version 2019.0102 after ligand and receptor preparation, including energy minimization with the MMFF94x force field until an RMS gradient of 0.001 was achieved. The Triangle Matcher algorithm was used for ligand placement, followed by London dG scoring. Up to 2,500,000 candidate poses were generated for each ligand, and the top 100 poses were subjected to forcefield refinement and rescored using London dG. The final pose was selected based on the lowest docking score, binding orientation, and interactions with amino acid residues in the ER-α binding pocket.

ADMET

The ADMET properties of the investigated compounds were predicted using the pkCSM online platform (https://biosig.lab.uq.edu.au/pkcsm/). In this analysis, the SMILES notation of each quinoline–1,2,3-triazole derivative was submitted to the web server to obtain predictions related to absorption, distribution, metabolism, excretion, and toxicity. The predicted results were then used as a preliminary assessment of the pharmacokinetic behavior and safety profile of the compounds as potential drug candidates.

Results and Discussion

Docking method validation was performed through redocking of the native ligand, 4-hydroxytamoxifen, into the active site of estrogen receptor alpha (ER-α) with PDB ID 3ERT. The 3ERT structure is an X-ray crystallographic structure with a resolution of 1.90 Å and is known to be complexed with 4-hydroxytamoxifen, making it suitable as a reference for docking protocol validation. The redocking result showed a docking score (ΔG) of -12.2978 kcal/mol and an RMSD value of 1.7954 Å. The RMSD value, which is below the commonly accepted validation threshold of <2 Å, indicates that the redocked ligand conformation closely resembles the ligand position in the crystal structure. Therefore, the docking protocol used in this study can be considered valid and appropriate for docking the test compounds (Maida et al., 2026).

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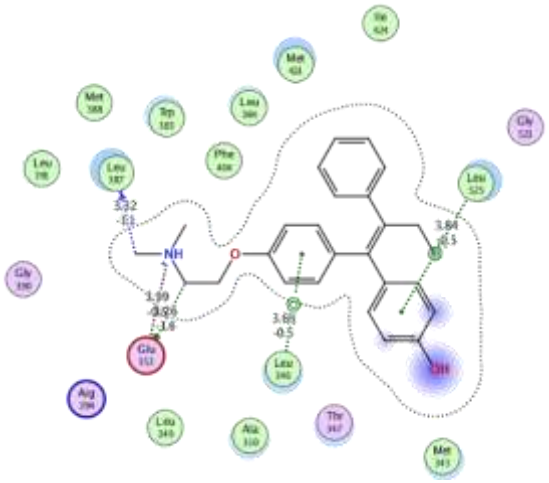

Figure 2 3ERT protein interaction with native ligan

Based on the 2D interaction visualization, 4-hydroxytamoxifen successfully reoccupied the ligand-binding pocket of ER-α after the redocking process. The redocked ligand formed interactions with several amino acid residues, including Glu353, Arg394, Leu346, Thr347, Leu387, Leu391, Met421, Ile424, Gly521, and Leu525. The interaction with Glu353 and Arg394 is particularly important because these residues are commonly involved in ligand recognition and stabilization in the ER-α binding site. Meanwhile, hydrophobic residues such as Leu346, Leu387, Leu391, Met421, Ile424, Gly521, and Leu525 may help stabilize the ligand orientation within the hydrophobic cavity of the receptor. The involvement of residues such as Thr347, Asp351, and Leu346 also supports the relevance of the antagonist binding mode of 4-hydroxytamoxifen in ER-α. In addition, the negative docking score value indicates that the formation of the ligand–receptor complex is energetically favorable. Together with the RMSD value below 2 Å, these results demonstrate that the redocked ligand maintained a binding pose similar to its crystallographic conformation. Therefore, the docking protocol used in this study can be considered valid and applicable for docking the quinoline–1,2,3-triazole derivatives as test compounds (Maida et al., 2026) (Gupta et al., 2026).

The molecular docking study was conducted to evaluate the binding ability of quinoline-fused 1,2,3-triazole derivatives 5a–5o toward Estrogen Receptor-α (ER-α). These compounds were previously reported by Lavunuri et al. as quinoline-linked fused 1,2,3-triazole hybrids synthesized through Cu(I)-catalyzed azide–alkyne cycloaddition followed by intramolecular C–H arylation. In their study, compounds 5a, 5c, 5f, 5g, and 5j were selected as the most active compounds against breast

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cancer cell lines and were further evaluated against EGFR and HER2, not ER-α. Therefore, the present docking study provides a different perspective by evaluating the same compound series against ER-α as a target protein (Lavunuri et al., 2024). Molecular docking is useful for predicting ligand conformation, binding interaction, and affinity toward the receptor active site, while the lowest docking energy is commonly used to select the most favorable binding pose (Zekri et al., 2020).

ER-α was selected because it plays an important role in estrogen-dependent breast cancer, and ER-α antagonists are used to inhibit estrogen-mediated cancer cell proliferation (Maida et al., 2026). In this study, 4-hydroxytamoxifen (4-OHT) was used as the control ligand because it is a well-known ER-α antagonist. Shiau et al. (1998) reported that 4-OHT binds to the ligand-binding domain of ER-α and induces an antagonist conformation by affecting helix 12, thereby blocking coactivator recognition. The control ligand in this study showed a binding energy of −9.5934 kcal/mol and an RMSD value of 0.6671 Å, indicating a stable and acceptable docking.

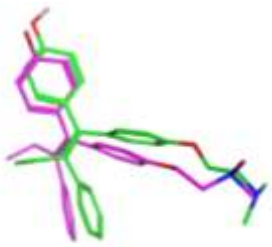

Figure 3. Superimposition of the co-crystallized 4-hydroxytamoxifen (green) and re-docked 4-hydroxytamoxifen (magenta) in the ER-α ligand-binding pocket.

The superimposition image shows that the co-crystallized 4-hydroxytamoxifen (green) and re-docked 4-hydroxytamoxifen (magenta) occupied largely the same spatial region. In docking validation, close overlap between the crystallographic and re-docked ligand poses indicates that the docking procedure can reproduce the experimental binding mode. The central scaffold and side-chain orientation showed close overlap, whereas slight deviations were observed at the terminal aromatic rings and flexible side-chain regions. Overall, both ligand poses displayed a similar orientation within the ER-α binding pocket (Shivanika et al., 2020).

Table 1. Molecular Docking Results of Quinoline-1,2,3-Triazole as Inhibitors of Breast Cancer

No.	Compound	Docking Score (kcal/mol)	RMSD (Å)	Molecular interactions
1	5a	-10.2331	0.9200	Glu 419 (H-donor)
2	5b	-10.5297	1.4086	Leu 387 (pi-H); Leu 387 (pi-H); Leu 387 (pi-H)
3	5c	-9.9026	1.6331	Leu 387 (pi-H); Leu 387 (pi-H); Leu 387 (pi-H)
4	5d	-10.2337	1.3047	Gly 521 (H-donor)
5	5e	-9.2351	1.8142	Leu 387 (pi-H); Leu 387 (pi-H); Leu 387 (pi-H)
6	5f	-9.6248	1.5114	His 524 (H-acceptor); His 524 (H-pi)
7	5g	-9.6470	1.0820	Met 343 (pi-H)
8	5h	-11.1210	0.9625	Glu 353 (H-donor); Leu 346 (H-acceptor); Ala 350 (pi-H)
9	5i	-9.7605	1.1202	His 524 (H-acceptor); Leu 387 (pi-H); Leu 387 (pi-H); Leu 387 (pi-H)
10	5j	-10.0856	1.3587	Leu 387 (pi-H); Leu 387 (pi-H); Leu 387 (pi-H)
11	5k	-10.3806	0.8611	Glu 323 (H-donor)
12	5l	-10.5216	1.4822	Met 421 (H-donor); Met 343 (H-donor)
13	5m	-9.7266	1.2219	Leu 346 (pi-H); Gly 420 (pi-H); Gly 521 (pi-H)
14	5n	-10.820	0.9638	Leu 346 (pi-H)
15	5o	-10.6613	1.9240	Leu 346 (pi-H); Leu 387 (pi-H)
16	4-Hydroxytamoxifen (control)	-9.5934	0.6671	Glu 353 (H-donor); Leu 387 (pi-H)

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Based on the docking results shown in Table 1, the quinoline-fused 1,2,3-triazole derivatives exhibited varied docking scores toward ER-α, ranging from −9.2351 to −11.1210 kcal/mol. Within the applied docking protocol, more negative docking scores were interpreted as more favorable predicted binding poses rather than experimentally determined binding free energies. Compared with the control ligand, several derivatives showed more negative docking scores, indicating relatively more favorable predicted interactions within the ER-α binding pocket.

Among the fifteen tested compounds, 5h, 5n, 5o, 5b, and 5l showed the most favorable docking scores, with values of −11.1210, −10.8208, −10.6613, −10.5297, and −10.5216 kcal/mol, respectively. These compounds were subsequently prioritized for further analysis of their predicted molecular interactions with ER-α residues.

The superior docking performance of compound 5h may be associated with the presence of the bromine atom at the para position of the phenyl ring. Bromine is a bulky and highly polarizable substituent that can enhance hydrophobic and van der Waals interactions within the receptor binding pocket. In the ER-α binding site, compound 5h interacted with Glu353, Leu346, and Ala350 through H-donor, H-acceptor, and π-H interactions. The interaction with Glu353 is particularly important because this residue is known to contribute to ligand recognition and binding stabilization in ER-α.

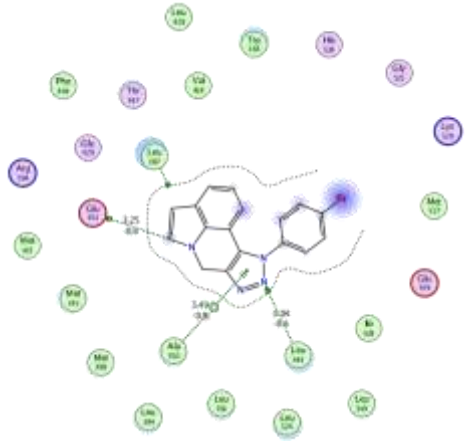

Figure 4. 3ERT protein interaction with 5h

Luo et al., (2017) reported that the hydrogen bond interaction between the 4-OH group of OHT and Glu353/Arg394 plays an important role in stabilizing the binding mode of ligands in ER-α. Therefore, the ability of compound 5h to interact with Glu353 suggests that this compound may occupy a relevant region of the ER-α ligand-binding pocket.

In addition to the interaction with Glu353, the contact of compound 5h with Leu346 and Ala350 may also contribute to its binding stability. These residues are located in the hydrophobic region of the ER-α binding pocket, and the aromatic quinoline–triazole framework of compound 5h, together with its 4-bromophenyl group, may support stronger hydrophobic fitting within this region. The combination of an

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extended aromatic system and a hydrophobic brominated substituent could improve ligand orientation and increase surface contact with the receptor. This structural feature may explain why compound 5h showed better binding energy than other derivatives and the control ligan.

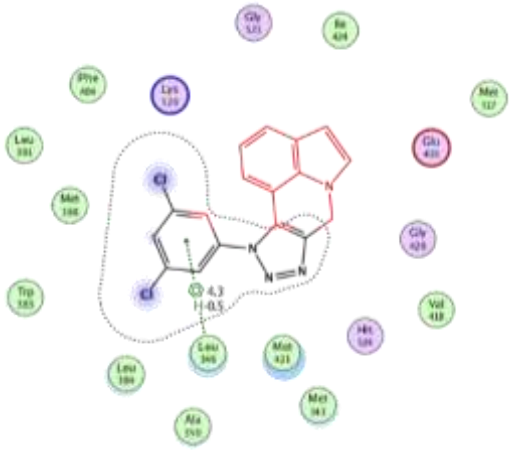

Figure 5. 3ERT protein interaction with 5n

Compound 5n ranked second based on its docking score and showed predicted interactions with key residues in the ER-α binding pocket. Its interaction with Leu346 suggests that hydrophobic interaction contributed to ligand stabilization in the ER-α binding pocket. Compound 5o also showed favorable binding energy and interacted with Leu346 and Leu387; however, indicating that its docking pose should be interpreted more carefully. Compound 5b interacted repeatedly with Leu387, suggesting that its stability was mainly supported by hydrophobic π-H interactions. Meanwhile, compound 5l formed H-donor interactions with Met421 and Met343, which may help maintain ligand orientation in the binding pocket.

The difference between the present findings and those reported by Lavunuri et al. (2024) may be attributed to the different molecular targets evaluated, in which the compounds previously showing the best activity against breast cancer cell lines and EGFR/HER2 were not identical to the compounds with the strongest predicted binding affinity toward ER-α in the present study. This indicates that the biological potential of quinoline-fused 1,2,3-triazole derivatives may depend on the specific target protein, binding pocket characteristics, and the type of interactions formed between the ligand and receptor. In ER-α, important residues such as Glu353 play a key role in ligand recognition and binding stabilization; therefore, compounds that are able to interact with this residue may show a more relevant binding profile toward this receptor. Although several derivatives, including 5n, 5o, 5b, and 5l, exhibited favorable docking scores, their interactions were mostly dominated by hydrophobic contacts or involved residues less specific than Glu353. Among the fifteen tested compounds, compound 5h showed the best overall docking profile because it had the lowest binding energy, and an interaction with the key residue Glu353. Therefore, compound 5h can be considered the most promising ER-α

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binding candidate among the quinoline-fused 1,2,3-triazole derivatives evaluated in this study.

ADMET Analysis

ADMET analysis was performed to evaluate the pharmacokinetic and toxicity profiles of the quinoline-fused 1,2,3-triazole derivatives. This evaluation is important because drug candidates should not only show good biological activity, but also possess acceptable absorption, metabolism, excretion, and safety profiles. Therefore, the selected parameters in this study, including Caco-2 permeability, P-glycoprotein substrate, CYP3A4 substrate, total clearance, AMES toxicity, hepatotoxicity, and hERG I/II inhibition, were used because they represent key ADMET endpoints related to intestinal permeability, drug transport, metabolism, elimination, mutagenicity, liver toxicity, and cardiotoxicity (Guan and Yang, 2018).

Based on Table 2, the quinoline-fused 1,2,3-triazole derivatives generally showed favorable pharmacokinetic profiles. All compounds exhibited positive Caco-2 permeability values, suggesting good predicted intestinal permeability. In addition, none of the compounds were predicted as P-glycoprotein substrates, indicating a lower possibility of P-gp-mediated efflux. However, all compounds were predicted as CYP3A4 substrates, suggesting that they may be metabolized through CYP3A4-dependent pathways. Total clearance values varied among the compounds, with 5h showing the lowest clearance value, followed by 5o and 5g. Overall, compounds 5g and 5h showed relatively more balanced pharmacokinetic profiles due to their good Caco-2 permeability, non-P-glycoprotein substrate status, and low total clearance values (Guan and Yang, 2018).

Table 2. Predicted ADME properties of compounds 5a–5o

Compound	Caco-2 permeability	P-gp substrate	CYP3A4 substrate	Total clearance
5a	1.314	No	Yes	0.442
5b	1.291	No	Yes	0.669
5c	1.599	No	Yes	0.429
5d	1.589	No	Yes	0.428
5e	1.653	No	Yes	0.356
5f	1.734	No	Yes	0.650
5g	1.606	No	Yes	0.333
5h	1.605	No	Yes	0.312
5i	1.347	No	Yes	0.467

Compound	Caco-2 permeability	P-gp substrate	CYP3A4 substrate	Total clearance
5j	1.188	No	Yes	0.440
5k	1.732	No	Yes	0.392
5l	1.344	No	Yes	0.471
5m	1.148	No	Yes	0.445
5n	1.604	No	Yes	0.366
5o	1.329	No	Yes	0.323

Based on Table 3, all quinoline-fused 1,2,3-triazole derivatives showed toxicity alerts, as all compounds were predicted to be AMES toxic and hepatotoxic. AMES toxicity indicates potential mutagenic risk, while hepatotoxicity suggests possible liver toxicity, both of which are important safety endpoints in early drug candidate evaluation. The importance of toxicity prediction in ADMET analysis is supported by Pires et al., who stated that pharmacokinetic and toxicity properties are crucial factors in determining whether a compound can be further developed as a therapeutic candidate (Pires et al., 2015).

Table 3. Predicted toxicity properties of compounds 5a–5o

Compound	AMES toxicity	Hepatotoxicity	hERG I inhibitor	hERG II inhibitor
5a	Yes	Yes	No	No
5b	Yes	Yes	No	No
5c	Yes	Yes	No	No
5d	Yes	Yes	No	No
5e	Yes	Yes	No	No
5f	Yes	Yes	No	No
5g	Yes	Yes	No	No
5h	Yes	Yes	No	No
5i	Yes	Yes	No	No
5j	Yes	Yes	No	No
5k	Yes	Yes	No	No
5l	Yes	Yes	No	No
5m	Yes	Yes	No	Yes

Compound	AMES toxicity	Hepatotoxicity	hERG I inhibitor	hERG II inhibitor
5n	Yes	Yes	No	No
5o	Yes	Yes	No	Yes

In terms of cardiotoxicity, all compounds were predicted as non-inhibitors of hERG I, while most compounds were also non-inhibitors of hERG II, except compounds 5m and 5o. This indicates that 5m and 5o may have a higher cardiotoxicity concern compared with the other derivatives. The hERG parameter is important because ADMET-score evaluation includes hERG inhibition as one of the toxicity endpoints, together with AMES and other safety-related parameters (Guan and Yang, 2018). Similar ADMET-based breast cancer studies also include hERG risk and permeability-related parameters to assess the pharmacokinetic suitability and safety of anticancer candidates (Devaraji et al., 2026).

Based on the cardiotoxicity prediction, compounds 5a–5l and 5n showed a relatively better cardiac safety profile than compounds 5m and 5o because they were not predicted to inhibit either hERG I or hERG II. This finding is important when the toxicity results are compared with the docking data. Compound 5o was included among the five best compounds based on binding energy toward ER-α, but the presence of a hERG II inhibition alert may reduce its priority as a safe candidate. In contrast, compound 5h showed a more favorable overall profile because it had the lowest binding energy, acceptable RMSD value, interaction with the important residue Glu353, and no predicted hERG inhibition alert. Thus, among the top-ranked docking compounds, 5h appears to be more promising than 5o from both binding affinity and predicted cardiotoxicity perspectives.

The toxicity profile of these derivatives still requires careful consideration. Although most compounds showed no predicted hERG inhibition, none of the derivatives can be considered fully safe because all compounds were predicted to be AMES toxic and hepatotoxic. AMES toxicity indicates a possible mutagenic risk, while hepatotoxicity suggests potential liver toxicity, both of which are important limitations in early drug candidate evaluation. Therefore, further structural optimization is needed to reduce these toxicity risks, especially mutagenicity and liver toxicity, before the compounds can be proposed as safer anti-breast cancer candidates. Experimental toxicity validation is also required to confirm the

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computational prediction results. This is consistent with previous anti-breast cancer ADMET studies, which combine pharmacokinetic and toxicological prediction with experimental validation to strengthen selection (Pascal et al., 2025).

CONCLUSION

This study demonstrated that quinoline–1,2,3-triazole derivatives have potential interactions with estrogen receptor alpha (ER-α), which is an important molecular target in estrogen-dependent breast cancer. The docking protocol was considered valid based on the redocking result of 4-hydroxytamoxifen, which produced an RMSD value below 2 Å, indicating that the method was reliable for evaluating the binding affinity of the test compounds. Among the fifteen derivatives evaluated, compounds 5h, 5n, 5o, 5b, and 5l showed stronger predicted binding affinities than the control ligand. Compound 5h was identified as the most promising candidate because it exhibited the lowest binding energy, an acceptable RMSD value, and an interaction with Glu353, an important residue in the ER-α ligand-binding pocket.

The ADMET prediction results showed that the quinoline–1,2,3-triazole derivatives generally possessed favorable permeability and were not predicted as P-glycoprotein substrates, suggesting good predicted absorption potential. However, safety-related limitations were also observed, as all compounds showed AMES toxicity and hepatotoxicity alerts, while compounds 5m and 5o were additionally predicted to inhibit hERG II. Therefore, although compound 5h showed the best overall profile based on docking results and no predicted hERG inhibition risk, further structural optimization is required to reduce its predicted toxicity. Experimental validation, including in vitro biological activity and toxicity assays, is also necessary to confirm its potential as an ER-α-targeted anti-breast cancer candidate.

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