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In Silico Analysis of Imidazole Derivatives Targeting Estrogen Receptor Alpha (ERα) as Anti-Breast Cancer Candidates

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Abstract. Breast cancer is one of the leading causes of mortality among women worldwide and is frequently associated with the overexpression of Estrogen Receptor alpha (ERα). This study aimed to evaluate the potential of imidazole derivatives as anticancer candidates targeting ERα (PDB ID: 3ERT) using an In Silico approach. Ten imidazole derivatives were analyzed through Lipinski's Rule of Five screening, ADMET prediction, and molecular docking studies, with 4-hydroxytamoxifen employed as the positive control. Lipinski screening indicated that all compounds met the drug-likeness criteria. ADMET prediction revealed that most compounds exhibited good intestinal absorption (HIA > 85%) and adequate Caco-2 permeability, with no predicted hepatotoxicity. Molecular docking results showed that all compounds had RMSD values below 2 Å, indicating stable interactions with the receptor. Among the tested compounds, 1-(2-Phenyl-2-propoxyethyl)-1H-imidazole demonstrated the best binding affinity (-6.3103 kcal/mol) among the imidazole derivatives; however, this value remained lower than that of the positive control, 4-hydroxytamoxifen (-8.6492 kcal/mol), which served as the primary benchmark for binding affinity comparison. Ligand–receptor interactions involved key amino acid residues within the active site of the 3ERT protein. Based on these findings, 1-(2-Phenyl-2-propoxyethyl)-1H-imidazole (compound 9) shows potential as a promising breast anticancer candidate and is recommended for further investigation through In vitro and in vivo experiments are required to verify its biological activity and evaluate its safety profile.

Keywords: *Imidazole, breast cancer, 3ERT, molecular docking, ADMET, in silico.*

Abstrak. Kanker payudara merupakan salah satu penyebab utama kematian pada wanita di seluruh dunia dan sering dikaitkan dengan overekspresi Estrogen Receptor alpha (ERα). Penelitian ini bertujuan untuk mengevaluasi potensi senyawa turunan imidazol sebagai kandidat antikanker yang menargetkan ERα (PDB ID: 3ERT) menggunakan pendekatan in silico. Sebanyak sepuluh senyawa turunan imidazol dianalisis melalui skrining Lipinski's Rule of Five, prediksi ADMET, serta molecular docking, dengan 4-hidroksitamoksifen digunakan sebagai kontrol positif. Hasil skrining Lipinski menunjukkan bahwa seluruh senyawa memenuhi kriteria drug-likeness. Prediksi ADMET menunjukkan bahwa sebagian besar senyawa memiliki absorpsi usus yang baik (HIA > 85%) dan permeabilitas Caco-2 yang memadai, serta tidak menunjukkan potensi hepatotoksisitas. Hasil molecular docking menunjukkan bahwa seluruh senyawa memiliki nilai RMSD di bawah 2 Å, yang mengindikasikan interaksi yang stabil dengan reseptor. Di antara senyawa yang diuji, 1-(2-Phenyl-2-propoxyethyl)-1H-imidazole menunjukkan afinitas ikatan terbaik (−6,3103 kcal/mol) di antara turunan imidazol; namun nilai ini masih lebih rendah dibandingkan kontrol positif 4-hidroksitamoksifen (−8,6492 kcal/mol), yang digunakan sebagai tolok ukur utama dalam perbandingan afinitas ikatan. Interaksi ligan–reseptor melibatkan residu asam amino penting pada sisi aktif protein 3ERT. Berdasarkan hasil tersebut, 1-(2-Phenyl-2-propoxyethyl)-1H-imidazole (senyawa 9) berpotensi sebagai kandidat antikanker payudara yang menjanjikan dan direkomendasikan untuk penelitian lanjutan melalui uji in vitro dan in vivo guna memverifikasi aktivitas biologis serta mengevaluasi profil keamanannya

Kata kunci: *Imidazol, kanker payudara, 3ERT, molecular docking, ADMET, in silico.*

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INTRODUCTION

Cancer is the second leading cause of death in the world after cardiovascular diseases, contributing approximately 15% to global mortality (Sharfalddin & Hussien, 2021). In general, there are about thirteen major types of cancer. Among women, breast cancer is one of the most common types, mainly due to hormonal stimulation of highly sensitive breast cells and the high levels of estrogen in the female body (Zagouri et al., 2013). Breast cancer ranks as the second most common cancer worldwide (Bae et al., 2018). However, effective and specific therapeutic options for breast cancer are still limited (Bai et al., 2021; P. Sharma et al., 2021), making the development of more effective chemotherapeutic agents with lower toxicity levels very important. Most breast cancers respond to hormonal therapy and express estrogen receptors (ER) and progesterone receptors (PR) (Dandawate et al., 2012). Each year, breast cancer affects about 2.3 million women worldwide and in 2022 it was estimated to cause approximately 670,000 deaths, equivalent to 15% of all cancer-related deaths among women. The incidence of breast cancer continues to increase globally in almost all countries, although its prevalence is higher among women living in industrialized regions. In addition to age and sex, nearly half of breast cancer cases occur in women who do not have specific risk factors (Health, 2023).

Imidazole is a compound that demonstrates a wide range of pharmacological and biological activities. For example, metronidazole and nitroimidazole show bactericidal properties, while vinyl imidazole demonstrates fungicidal activity, and imidazoline exhibits antileishmanial and other antimicrobial activities (Abdullah et al., 2024). The imidazole group is highly effective in binding various proteins in organisms through the limited interactions formed that arise from the unique structural characteristics of the imidazole scaffold, which is distinguished by its electron-rich nature. (Gopalakrishnan et al., 2021). The imidazole ring, commonly found in natural products and pharmaceutical compounds, is one of the most significant nitrogen-containing five-membered heterocyclic frameworks (Zheng et al., 2020).

Imidazole is an important class of heterocyclic compounds that serves as a core structure in various natural products and biological systems (Zhang, 2013). This heterocyclic compound exhibits a wide range of pharmaceutical properties, including antibacterial, antifungal, analgesic, and anticancer activities (P. Sharma et al., 2021). Imidazole, characterized by a dipole moment of 3.6 D, is highly polar and readily soluble in water. This compound is amphoteric, demonstrating the ability to act as both an acid and a base. Its aromatic classification is associated with the presence of a π-electron sextet, consisting of a pair of electrons from the protonated nitrogen and four electrons from the remaining ring atoms (Burungale Swati, 2013). The importance of the imidazole ring arises from its structure containing two nitrogen atoms, one of which can readily coordinate with various metal ions. Numerous studies have reported that imidazole derivatives possessing hydrogen-bond donor groups exhibit cytotoxic activity and potential antiviral properties. (Boryski et al., 1988; D. Sharma et al., 2009). Numerous imidazole complexes have been prepared through reactions with various metals, including new complexes Incorporating an

imidazole ring derived from Schiff base compounds that have been synthesized by many researchers (Desai D G, 2021), as well as coordination polymers employing imidazole derivatives are used to generate imidazole-based polymer complexes (Nath & Baruah, 2013).

Ligands and metal ions are important components in the design of new anticancer drugs and therapies through their interactions with oncogenic viruses (Turel & Kljun, 2011). Imidazole plays an important role as both a complete component and a partial part of binding sites for various transition metal ions (Mukherjee et al., 2004). This study investigates the properties and in silico bioactivity of several metal complexes formed from reactions between imidazole-derived ligands and various transition metals.

Previous research conducted by (Faris et al., 2024) reported that synthesized imidazole derivatives exhibited biological activity and were tested on various cell lines, supported by molecular docking studies to explain the ligand–target interaction mechanisms. However, the study did not specifically focus on candidate selection was not carried out in the context of breast cancer and did not integrate drug-likeness evaluation and ADMET prediction as an early screening strategy. Therefore, this study offers novelty by aiming to rationally evaluate and select simple imidazole derivatives as potential breast anticancer candidates targeting ERα through the integration of molecular docking, Lipinski–Veber rules, and ADMET analysis to identify compounds with favorable binding affinity and pharmacokinetic properties. The selected compounds were chosen as a structurally coherent series of simple imidazole derivatives with systematic variations in substituents, including phenyl, halogen, methoxy, hydroxyl, and alkoxy groups, to enable a focused preliminary structure–activity relationship (SAR) analysis. This approach allows a clearer understanding of how steric, electronic, and lipophilic factors influence ligand–receptor interactions and drug-like properties. The in silico approach is employed as an initial strategy to predict the biological potential of compounds prior to further experimental validation (Gazpersz et al., 2024).

MATERIAL AND METHODS

Materials and Instrumentation

The instruments used in this study consisted of hardware in the form of a laptop and software in the form of the Molecular Operating Environment (MOE) 2019.

Procedure

Protein preparation

Preparation of the 3D crystal structure of Estrogen Receptor Alpha (ERα) from the Protein Data Bank (PDB ID: 3ERT) https://www.rcsb.org/structure/3ERT. Protein preparation was carried out using the Quick Prep module implemented in the Molecular Operating Environment (MOE). All co-crystallized molecules, crystallized ligands, and non-essential ions were removed. The Quick Prep workflow automatically adds hydrogen atoms, assigns appropriate protonation states at physiological pH, corrects structural imperfections, and performs energy minimization using the AMBER10 force field, resulting in a stable protein conformation suitable for docking studies.

Ligand preparation

10 isolated imidazole derivative compounds, namely 4,5-diphenyl-1H-imidazole; 2-(1H-imidazol-1-yl)-1-phenylethanone;1-(4-chlorophenyl)-2-(1H-imidazol-1-yl)ethanone; 2-(1H-imidazol-1-yl)-1-(4-methoxyphenyl)ethanone; 2-(1H-imidazol-1-yl)-1-phenylethanol; 1-(4-chlorophenyl)-2-(1H-imidazol-1-yl)ethanol; 2-(1H-imidazol-1-yl)-1-(4-methoxyphenyl)ethanol;1-(2-ethoxy-2-phenylethyl)-1H-imidazole; 1-(2-phenyl-2-propoxyethyl)-1H-imidazole; and 1-(2-(allyloxy)-2-phenylethyl)-1H-imidazole, were selected as test ligands, with 4-hydroxytamoxifen used as the positive control. Ligand structures were collected from the PubChem database https://pubchem.ncbi.nlm.nih.gov as SMILES codes and imported into MOE. Each ligand was converted into a three-dimensional structure, protonated at physiological pH, and energy-minimized using the AMBER10 force field to ensure force-field consistency with the prepared protein.

Interaction analysis

Protein–ligand interaction analysis was performed using BIOVIA Discovery Studio Visualizer. Key interactions, including hydrogen bonds, hydrophobic contacts, π–π stacking, and electrostatic interactions, were identified and visualized. The interaction profiles were correlated with the docking S-score and RMSD values to analyze the stability of ligand binding and its orientation within the active site.

Drug-likeness and ADMET prediction

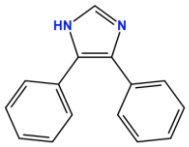
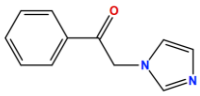
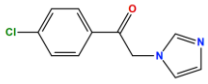
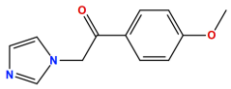
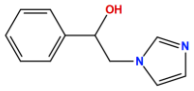
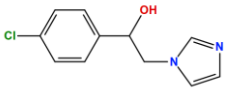
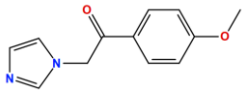
Drug-likeness characteristics were analyzed using SwissADME https://swissadme.ch/index.php based on the Lipinski Rule of Five and Veber rules. Pharmacokinetic and toxicity profiles were predicted using SwissADME, pkCSM, and ADMETlab 2.0, including gastrointestinal absorption, CYP450 enzyme inhibition, bioavailability, hepatotoxicity, and mutagenicity.

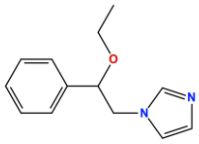
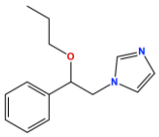
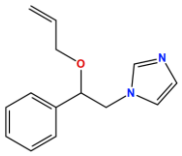
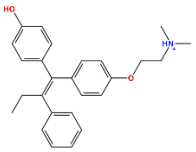
RESULT AND DISCUSSION

Prediction of Lipinski's Rule of Five

The drug-likeness evaluation of imidazole derivatives was performed using the Lipinski Rule of Five and Veber parameters to predict the feasibility of these compounds as oral drug candidates (Zulqurnain et al., 2025). The Lipinski Rule of Five consists of five main criteria, one of which states that compounds with a molecular weight greater than 500 Da tend to have difficulty penetrating cell membranes. In addition, A log P value above 5 indicates a high degree of lipophilicity in the compound, which may result in strong binding to membranes, potentially hindering recognition by target enzymes and increasing the risk of toxicity. The number of hydrogen bond donors and acceptors represents the potential of a compound to form hydrogen bonds. Higher hydrogen-bonding capacity generally requires greater energy during absorption. Lipinski's Rule of Five is widely used to predict the permeability of compounds across cell membranes through passive diffusion and to evaluate their potential drug-likeness (Brito, 2011).

Table 1. Lipinski Rule of Five Results

No	Compound Name	Lipinski Ro5				Veber		Bioavailability Score
		H-Donor (<5)	H-Acceptor (<10)	Log P (<5)	Mw (g/mol) (<500)	Rotatable Bonds (≤10)	PSA Å (<140)	
1.	4,5-diphenyl-1H-imidazole 	1	1	1.95	220.27	2	28.68	0.55
2.	2-(1H-Imidazol-1-yl)-1-phenyl ethanone 	0	2	1.59	186.21	3	34.89	0.55
3.	1-(4-Chlorophenyl)-2-(1H-imidazol-1-yl) ethanone 	0	2	1.76	220.65	3	34.89	0.55
4.	2-(1h-imidazol-1-yl)-1-(4-methoxy phenyl) ethanone 	0	3	1.77	216.24	4	44.12	0.55
5.	2-(1H-Imidazol-1-yl)-1-phenylethanol 	1	2	1.68	188.23	3	38.05	0.55
6.	1-(4-Chlorophenyl)-2-(1H-imidazol-1-yl) ethanol 	1	2	1.97	222.67	3	38.05	0.55
7.	2-(1H-Imidazol-1-yl)-1-(4-methoxy phenyl) ethenol 	1	3	2.26	216.24	3	47.28	0.55

8.	1-(2-Ethoxy-2-phenylethyl)-1H-imidazole 	0	2	2.50	216.28	5	27.05	0.55
9.	1-(2-Phenyl-2-propoxyethyl)-1H-imidazole 	0	2	2.66	230.31	6	27.05	0.55
10.	1-(2-(Allyloxy)-2-phenylethyl)-1H-imidazole 	0	2	2.38	228.29	6	27.05	0.55
11.	4-hydroxytamoxifen 	1	3	4.33	387.51	8	32.70	0.55

The results showed that all compounds fulfilled the Lipinski criteria, specifically molecular weight <500 g/mol, number of hydrogen bond donors <5, number of hydrogen bond acceptors within the acceptable limit, and Log P value <5. The molecular weight range of the imidazole derivative compounds was 186.21–230.31 g/mol, whereas 4-hydroxytamoxifen, as the positive control, had a higher molecular weight of 387.51 g/mol, but still remained within the Lipinski limit. The Log P values of all compounds were also within the range of 1.59–3.69, indicating a balance between lipophilic and hydrophilic properties, which supports their ability to be absorbed through biological membranes (Amelia et al., 2025).

In addition, based on the Veber parameters, all compounds have a number of rotatable bonds within the acceptable limit (≤10), ranging from 2–6, as well as low Polar Surface Area (PSA) values of 27.05–47.28 Å², which are far below the maximum limit of 140 Å². These low PSA values indicate that the compounds potentially possess good membrane permeability and can more easily penetrate cells, which is an important aspect for breast cancer drug candidates. Overall, the bioavailability score of 0.55 for all compounds suggests that the tested imidazole derivatives

have good potential for oral bioavailability (Grasianto et al., 2025). Thus, based on the results presented in Table 1, all imidazole derivatives can be categorized as having a supportive drug-likeness profile for development as breast anticancer candidates, particularly for the subsequent stage of ADMET prediction.

ADMET Validation

Active compounds should possess favorable ADME properties and no toxic effects. The compounds were then assessed based on their ADME and toxicity profiles. levels using the SwissADME website. Based on Table 2, the ADME results indicate that all imidazole derivative compounds demonstrate sufficiently good pharmacokinetic profiles to be considered as potential breast anticancer drug candidates. The absorption parameters observed include Caco-2 permeability values and Human Intestinal Absorption (HIA) (Widiyana, 2021).

Table 2. In Silico ADMET prediction results of imidazole derivative compounds

No	Compound Name	Pharmacokinetic prediction		Metabolism	Excretion		Toxicity	
		Caco-2 (nm/sec)	HIA (%)	CYP3A4	Clearance	Ames	Hepatotoxicity	LD50 (mol/kg)
1.	4,5-diphenyl-1H-imidazole	1.278	85.057	Yes	0.793	Yes	No	2.371
2.	2-(1H-Imidazol-1-yl)-1-phenyl Ethenone	1.793	94.217	Yes	0.973	Yes	No	2.494
3.	1-(4-Chlorophenyl)-2-(1H-imidazol-1-yl) ethenone	1.846	93.268	Yes	0.973	Yes	No	2.507
4.	2-(1H-imidazol-1-yl)-1-(4-methoxy phenyl) ethanone	1.793	94.217	Yes	0.937	Yes	No	2.494
5.	2-(1H-Imidazol-1-yl)-1-phenylethanol	1.793	91.986	Yes	0.977	No	No	2.604
6.	1-(4-Chlorophenyl)-2-(1H-imidazol-1-yl)ethanol	1.538	92.389	No	0.976	Yes	No	3.086
7.	2-(1H-Imidazol-1-yl)-1-(4-methoxy phenyl)ethanol	1.287	92.566	No	0.834	Yes	No	2.789
8.	1-(2-Ethoxy-2-phenylethyl)-1H-imidazole	1.797	92.365	Yes	0.972	Yes	No	2.222
9.	1-(2-Phenyl-2-propoxyethyl)-1H-imidazole	1.803	92.204	Yes	1.023	Yes	No	2.276
10.	1-(2-(Allyloxy)-2-phenylethyl)-1H-imidazole	1.803	92.68	Yes	1.062	Yes	No	2.272
11.	4-hydroxytamoxifen	1.026	93.541	Yes	0.594	Yes	No	2.409

The results show that most compounds have Caco-2 values in the range of 1.278–1.846 nm/sec, indicating good intestinal permeability. In comparison, the positive control, 4-hydroxytamoxifen, exhibited a Caco-2 value of 1.026 nm/sec, indicating moderate

intestinal permeability relative to the tested imidazole derivatives. In addition, the HIA values of all compounds range from 85.057% to 94.217%, indicating a high potential for oral absorption. The highest HIA values were observed for 2-(1H-imidazol-1-yl)-1-phenylethanone and 2-(1H-imidazol-1-yl)-1-(4-methoxyphenyl)ethenone at 94.217%, while the lowest value was found in 4,5-diphenyl-1H-imidazole at 85.057%.

In terms of metabolism, most compounds are predicted to interact with the CYP3A4 enzyme, suggesting that they may undergo hepatic metabolism via this major enzymatic pathway. From a pharmacokinetic perspective, CYP3A4-mediated metabolism plays a crucial role in drug clearance and bioavailability. While this may facilitate elimination and reduce the risk of accumulation, it also raises the potential for drug–drug interactions, as CYP3A4 is involved in the metabolism of many clinically used drugs. Therefore, further studies are required to evaluate the metabolic stability and interaction potential of these compounds in biological systems. However, some compounds such as 1-(4-chlorophenyl)-2-(1H-imidazol-1-yl)ethanol and 2-(1H-imidazol-1-yl)-1-(4-methoxyphenyl) ethanol show a “No” result, indicating that they may have a lower risk of drug–drug interactions through the CYP3A4 pathway (Aslama et al., 2025). The excretion parameter, represented by clearance values, ranges from 0.726 to 1.062, indicating that these compounds have elimination capacities within a reasonable range and do not show a tendency for excessive accumulation in the body.

Docking Validation

In this study, the protein used was 3ERT, which is the crystal structure of the estrogen receptor alpha (ERα) and was used as the molecular target. The 3ERT structure has been widely used in docking studies and drug design due to its good resolution and the availability of a co-crystallized ligand that can serve as a reference for the validation process.

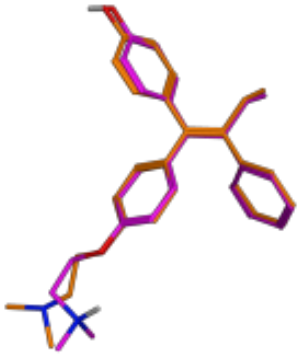


Figure 1. Visualization of the native ligand (orange) and re-docked ligand (purple) validation results

Docking validation is generally performed through a re-docking process by removing the ligand from the crystal structure and then docking the ligand back into the active pocket of the protein using the same parameters applied to the test compounds. The In silico approach using molecular docking is widely used to predict the interaction between bioactive compounds and target proteins, thereby assisting in the discovery of new drug candidates (Gaspersz et al., 2022). In this method, a docking validation step is performed to ensure the accuracy of the docking protocol, which is evaluated based on the Root Mean Square Deviation (RMSD) value between the ligand position obtained from re-docking and the ligand position in the original crystal structure.

Molecular Docking Result Analysis

Molecular docking analysis results are presented in Table 3. Binding affinity serves as

an indicator to evaluate the interaction between the compounds and the target protein. The results show that the binding affinity values range from −5.2776 to −6.3103 kcal/mol, whereas the positive control, 4-hydroxytamoxifen, exhibits the lowest affinity value (−8.6492 kcal/mol). More negative affinity values indicate stronger binding interactions. (Ferreira et al., 2015). Based on the docking results obtained, all compounds show RMSD values below 2 Å, indicating that they possess valid docking poses and are acceptable for further analysis.

Table 3. Molecular docking results of bioactive compounds from imidazole derivatives

No	Imidazole Derivative Compounds	Binding Affinity (kcal/ mol)	RMSD (Å)	Ligand Interactions	Bond distance (Å)	Type of bond
1.	4,5-diphenyl-1H-imidazole	-5.8581	1.2122	MET421 LEU346 THR347 ILE424	4.46 4.27 4.40 4.00	H-donor pi-H pi-H pi-H
2.	2-(1H-Imidazol-1-yl)-1-phenyl Ethanone	-5.2776	0.6968	MET343	3.92	H-donor
3.	1-(4-Chlorophenyl)-2-(1H-imidazol-1-yl)ethanone	-5.5727	0.8216	LEU391	3.97	pi-H
4.	2-(1H-imidazol-1-yl)-1-(4-methoxy phenyl)ethanone	-5.8379	1.3047	PHE404	4.59	pi-H
5.	2-(1H-Imidazol-1-yl)-1-phenylethanol	-5.3486	1.1348	THR347	4.50	pi-H
6.	1-(4-Chlorophenyl)-2-(1H-imidazol-1-yl) ethanol	-5.6140	0.9386	GLU353 MET357	2.81 3.34	H-donor H-acceptor
7.	2-(1H-Imidazol-1-yl)-1-(4-methoxy phenyl) ethenol	-5.8625	0.8793	LEU387	4.20	pi-H
8.	1-(2-Ethoxy-2-phenylethyl)-1H-imidazole	-5.8708	0.9860	THR347	4.11	pi-H
9.	1-(2-Phenyl-2-propoxyethyl)-1H-imidazole	-6.3103	1.1166	THR347	4.49	pi-H
10.	1-(2-(Allyloxy)-2-phenylethyl)-1H-imidazole	-6.1110	0.8343	LEU387	3.71	pi-H
11.	4-hydroxytamoxifen	-8.6492	1.5595	GLU 353 ASP 351 ASP 351 ASP 351 ILE 424	3.62 3.03 4.12 3.42 4.01	H-donor H-donor H-donor Ionic pi-H

Based on the docking scores, the imidazole derivative compounds show variations in binding affinity. The compound 4,5-diphenyl-1H-imidazole has an S score of −5.8581 with an

RMSD of 1.2122 Å. This result indicates that the presence of two phenyl rings in the structure can enhance hydrophobic interactions and allow the formation of π–π stacking interactions, which are important components in stabilizing the ligand–receptor complex, especially in target proteins that possess active pockets with nonpolar characteristics (Lionta et al., 2014). Therefore, this compound can be considered a fairly promising initial candidate compared to compounds that contain simpler substituents.

Imidazole-based compounds containing a carbonyl (ethanone) group, such as 2-(1H-imidazol-1-yl)-1-phenylethanone (S −5.2776) and 1-(4-chlorophenyl)-2-(1H-imidazol-1-yl) ethanone (S −5.5727), show slightly lower binding affinity compared to other compounds.

However, compared to diphenyl imidazole, compounds containing halogen substituents often enhance hydrophobic interactions and can form halogen bonding, which contributes to the stability of ligand–protein binding (Ferreira et al., 2015). In addition, the derivative with a methoxy substituent, 2-(1H-imidazol-1-yl)-1-(4-methoxy phenyl) ethanone, shows a relatively good score (S −5.8379), which is likely influenced by the ability of the methoxy group to form polar interactions and improve ligand orientation within the active pocket.

The conversion of the carbonyl group to a hydroxyl group in ethanol derivatives such as 2-(1H-imidazol-1-yl)-1-phenylethanol (S −5.3486) and 1-(4-chlorophenyl)-2-(1H-imidazol-1-yl) ethanol (S −5.6140) shows relatively similar or slightly better binding affinity compared to their carbonyl derivatives. The hydroxyl group can act as both a hydrogen bond donor and acceptor, thereby potentially enhancing the stability of the complex. This explains why the differences in docking scores within this group are not very significant.

Compounds bearing larger alkoxy substituents exhibited more prominent docking results. The compound 1-(2-phenyl-2-propoxyethyl)-1H-imidazole showed the best docking score among the tested derivatives (S = −6.3103) with an RMSD of 1.1166 Å. This compound was followed by 1-(2-(allyloxy)-2-phenylethyl)-1H-imidazole (S = −6.1110) and 1-(2-ethoxy-2-phenylethyl)-1H-imidazole (S = −5.8708). This trend indicates that the introduction of longer alkoxy chains increases the lipophilicity of the ligand, thereby strengthening van der Waals interactions and improving the ligand's ability to optimally occupy the active pocket. Increased lipophilicity is often associated with enhanced binding affinity in docking studies, particularly when the target protein contains a relatively large hydrophobic binding region (Lionta et al., 2014).

Therefore, compounds 9 can be considered the most promising candidates for further investigation. Notably, Compound 9 (1-(2-Phenyl-2-propoxyethyl)-1H-imidazole) exhibited a higher binding affinity despite lacking the second phenyl ring present in Compound 1. This observation indicates that the propoxyethyl side chain plays a significant role in enhancing ligand–receptor interactions. The presence of this moiety increases conformational flexibility and lipophilicity, enabling the ligand to better adapt within the hydrophobic binding pocket of ERα and strengthen van der Waals interactions (Lee & Barron, 2017). Furthermore, the extended alkoxy chain facilitates deeper penetration into the ligand-binding domain, resulting in a more favorable spatial orientation and more effective interactions with key residues such as THR347

and surrounding hydrophobic amino acids. These findings are consistent with previous studies demonstrating that alkyl or alkoxy substituents in imidazole derivatives can enhance binding affinity by improving hydrophobic interactions and conformational adaptability within the active site of target proteins. Therefore, the superior performance of Compound 9 can be attributed not only to aromatic interactions but also to the significant contribution of its flexible propoxyethyl side chain in stabilizing the ligand–receptor complex.

As a positive control, 4-hydroxytamoxifen exhibited the most negative docking score (−8.6492 kcal/mol) with an RMSD of 1.5595 Å, indicating the strongest binding affinity among all tested compounds. This finding is consistent with its well-established role as a selective estrogen receptor modulator (SERM) targeting ERα in breast cancer therapy. The strong binding affinity of 4-hydroxytamoxifen can be attributed to its ability to form multiple stabilizing interactions within the active site, including hydrogen bonding, ionic interactions, and hydrophobic contacts with key amino acid residues. Such interaction patterns are known to enhance ligand–receptor stability and are characteristic of effective ERα-targeted anticancer agents (Du et al., 2025). Based on these data, 1-(2-phenyl-2-propoxyethyl)-1H-imidazole and 1-(2-(allyloxy)-2-phenylethyl)-1H-imidazole represent the most promising candidates among the tested compounds for further development as breast anticancer candidates, particularly through subsequent studies such as ADMET prediction.

CONCLUSION

Based on an in silico approach integrating molecular docking, Lipinski–Veber screening, and ADMET prediction against the ERα (PDB ID: 3ERT) protein, all imidazole derivatives demonstrated supportive drug-likeness characteristics and pharmacokinetic profiles as potential oral drug candidates. The docking results showed stable interactions (RMSD < 2 Å), with Compound 9 exhibiting the strongest binding affinity among the tested compounds. Therefore, Compound 9 can be considered the most promising breast anticancer candidate and warrants further validation through in vitro and in vivo studies to confirm its biological activity and safety profile.

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