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# *In Silico Study of Imidazole-Morpholine-1,2,4-Oxadiazole Derivatives as Candidate Breast Cancer Drugs via Molecular Docking Targeting ER-α, ADMET Analysis and Drug-Likeness Assessment*

# Studi in Silico Senyawa Turunan Imidazole-Morpholine-1,2,4-Oxadiazole Sebagai Kandidat Obat Antikanker Payudara Melalui Docking Molekuler Terhadap ER-α, Analisis ADMET dan Drug-likeness

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***ABSTRACT***

*Breast cancer is one of the leading causes of death among women worldwide. One of the causes of breast cancer is the overexpression of estrogen receptor alpha (ER-α). Imidazole-morpholine-1,2,4-oxadiazole derivatives have been reported to exhibit cytotoxic activity against MCF-7 cells, however their interaction with ER-α has not yet been studied. This study aims to evaluate the potential of imidazole-morpholine-1,2,4-oxadiazole derivatives as a candidate anti-breast cancer agent using an in silico approach targeting ER-α through molecular docking, as well as to predict the pharmacokinetic properties and toxicity of the compound using ADMET analysis. Molecular docking was performed using MOE 2019.0102 software with the ER-α receptor (PDB: 3ERT), while ADMET predictions were conducted using pkCSM and swissADME software. The molecular docking results showed that the tested compounds exhibited good binding affinity for the target ER-α receptor, specifically compound 7f, with a binding energy of -7.43 kcal/mol and an RMSD of 1.8 Å. Although compound 7f has a higher binding energy than tamoxifen, molecular docking predicts this compound interacts with the active site residues of the ER-α receptor, specifically with Glu353. Furthermore, the ADMET results indicate that compound 7f meets the criteria for drug candidacy based on Lipinski's rules and ADMET predictions. However, it has drawbacks such as low permeability in Caco-2 cells, as well as being a P-gp substrate and exhibiting positive Ames toxicity and hepatotoxicity. Therefore, further experimental optimization and validation through in vitro or in vivo studies are necessary to improve the drug's distribution and safety before proceeding with further development.*

*Keywords: Molecular docking, breast cancer, imidazole-morpholine-1,2,4-oxadiazole, ADMET, ER-α*

**ABSTRAK**

Kanker payudara adalah salah satu penyebab utama kematian di kalangan wanita di seluruh dunia. Salah satu penyebab kanker payudara adalah ekspresi berlebihan reseptor estrogen alfa (ER-α). Turunan imidazol-morfolin-1,2,4-oksadiazol telah dilaporkan menunjukkan aktivitas sitotoksik terhadap sel MCF-7, namun interaksi mereka dengan ER-α belum dipelajari. Penelitian ini bertujuan untuk mengevaluasi potensi turunan imidazole-morpholine-1,2,4-oxadiazole sebagai kandidat obat anti kanker payudara menggunakan pendekatan in silico yang menargetkan ER-α melalui docking molekuler, serta untuk memprediksi sifat farmakokinetik dan toksisitas senyawa menggunakan analisis ADMET. Docking molekuler dilakukan dengan menggunakan software MOE 2019.0102 dengan reseptor ER-α (PDB: 3ERT), sedangkan prediksi ADMET dilakukan dengan menggunakan software

pkCSM dan swissADME. Hasil docking molekuler menunjukkan bahwa senyawa yang diuji menunjukkan afinitas pengikatan yang baik untuk reseptor ER-α target, khususnya senyawa 7f, dengan energi pengikatan -7,43 kkal/mol dan RMSD 1,8 Å. Meskipun senyawa 7f memiliki energi pengikatan yang lebih tinggi daripada tamoxifen, pemodelan docking molekuler memprediksi bahwa senyawa ini berinteraksi dengan residu situs aktif reseptor ER-α, khususnya dengan Glu353. Selanjutnya, hasil ADMET menunjukkan bahwa senyawa 7f memenuhi kriteria pencalonan obat berdasarkan aturan Lipinski dan prediksi ADMET. Namun, ia memiliki kelemahan seperti permeabilitas rendah dalam sel Caco-2, serta menjadi substrat P-gp dan menunjukkan toksisitas Ames dan hepatotoksisitas positif. Oleh karena itu, optimalisasi dan validasi eksperimental lebih lanjut melalui studi in vitro atau in vivo diperlukan untuk meningkatkan distribusi dan keamanan obat sebelum melanjutkan pengembangan lebih lanjut.

*Kata kunci: Docking molekuler, kanker payudara, imidazole-morpholine-1,2,4-oxadiazole, ADMET, ER-α*

## INTRODUCTION

Breast cancer is one of the leading causes of death among women worldwide and generally develops in the milk ducts and milk-producing glands (Abdullahi et al., 2023; Suanjaya et al., 2025). According to 2020 data from the World Health Organization (WHO), there were approximately 3 million cases and 685,000 deaths globally. Breast cancer accounts for 23% of all cancer cases and 14% of cancer deaths. The number of cases is projected to rise to 40% by 2040 (Bandgar et al., 2025). The incidence of breast cancer can be influenced by several factors, such as advancing age, heredity, alcohol consumption, and smoking (Siddiqui et al., 2024). In addition to these risk factors, the development of breast cancer is also associated with the expression of estrogen receptor alpha (ER-α), which can influence cell growth, differentiation, and apoptosis (Masand et al., 2024). ER-α is found in Luminal A and Luminal B subtypes of breast cancer and is expressed in more than 70% of breast cancer cases. However, excessive ER-α expression can lead to uncontrolled cell growth, which can result in breast cancer (Liao et al., 2014).

ER-α activation occurs through two signaling pathways, as shown in Figure 1. The first is the genomic pathway, which occurs when E2 binds to the receptor, causing it to dimerize and translocate into the nucleus. It then binds to estrogen-responsive elements (EREs), which play a role in cell proliferation and survival. Second is the non-genomic pathway, which interacts with the cell membrane via G proteins and growth factor receptors, leading to the activation of the PI3K/Akt and Ras-MAPK signaling pathways (François Ferrière et al., 2023). Therefore, inhibiting ER-α activity is one of the effective therapeutic approaches for breast cancer. One drug that has been widely used in the treatment of breast cancer is tamoxifen.

Tamoxifen is a hormonal therapy that acts as an ER-α antagonist and has often been used as a comparator. However, its use can trigger resistance associated with the activation of the PI3K/PTEN/AKT/mTOR and MAPK signaling pathways, as well as ER-α activation, which can

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reduce the therapy's effectiveness (Yao et al., 2020). In addition, tamoxifen also has side effects such as endometrial cancer, blood clots in the lungs and legs, stroke, and cataracts (Asaumi et al., 2026). Therefore, the development of new, more effective drug candidates is needed.

One compound with potential for development as a new drug candidate is an imidazole-morpholine-1,2,4-oxadiazole derivative. Kannekanti et al. (2024) have synthesized this hybrid compound and reported its antiproliferative activity against human breast cancer cell lines, including MCF-7, MDA-MB-231, and MDA-MB-468, as determined by the MTT assay. Additionally, molecular docking studies have been conducted to evaluate the compound's interactions with the target protein EGFR. However, there have been no studies on the interactions of these derivatives with ER-α as a breast cancer target, nor on their pharmacokinetic predictions.

The design of imidazole–morpholine–1,2,4-oxadiazole derivatives is based on the molecular hybridization of three pharmacologically important scaffolds. Imidazole derivatives have been reported to possess diverse biological activities, including anticancer, antimicrobial, antifungal, anti-inflammatory, and antiviral activities. Imidazole compounds are also polar, which allows them to form hydrogen bonds and coordinate chemical bonds with various molecules (Kumar et al., 2026; Lavunuri et al., 2024). Morpholine compounds can increase a compound's binding affinity for receptors (Kannekanti et al., 2024). Meanwhile, 1,2,4-oxadiazole compounds possess bioisosteric equivalence and can contribute to anticancer activity by inhibiting protein kinase enzymes (Lavunuri et al., 2024). Therefore, the imidazole–morpholine–1,2,4-oxadiazole derivatives reported by Kannekanti et al. (2024) were chosen for molecular docking and ADMET prediction to evaluate the predicted binding affinity to ER-α and their pharmacokinetic properties.

The potential activity of a compound can be predicted using in silico methods, which are more effective and can reduce costs, time, and failures (Agamah et al., 2020; Putri & Azra, 2025; Toni & Azra, 2022). One in silico method used is molecular docking, a technique that simulates the binding of a ligand to a macromolecule such as a protein to evaluate a compound's interaction with its target and analyze its interactions with amino acid residues (Muhammed & Aki-yalcin, 2022). In this study, the induced-fit method was used, in which the protein can adjust the shape of its active site when binding to a ligand, thereby producing a more stable interaction and more accurate prediction of a compound's activity as a drug candidate (Iwaloye et al., 2020).

Therefore, this study aims to evaluate the potential anticancer activity of imidazole-morpholine-1,2,4-oxadiazole derivatives in inhibiting the ER-α receptor (PDB ID: 3ERT) in silico through molecular docking to examine the interactions between the receptor and the active compounds in the search for breast cancer drugs.

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It also aims to predict their pharmacokinetic properties and toxicity.

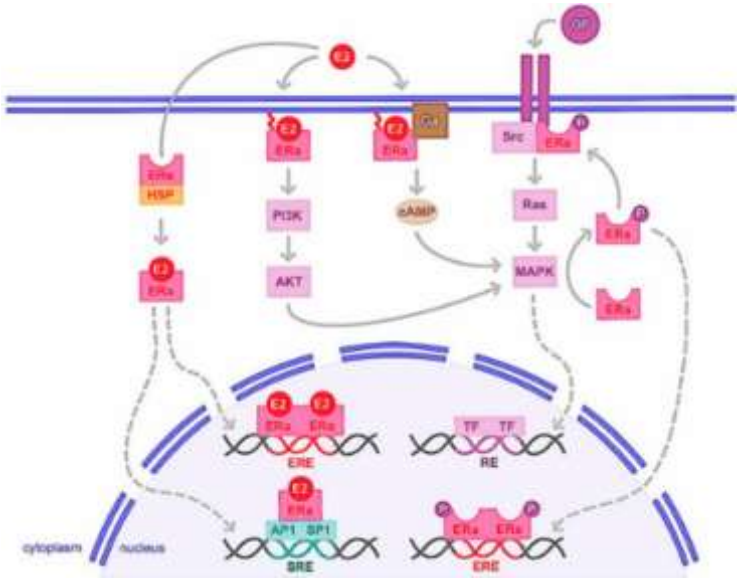


**Figure 1**. The ER-α signaling pathway

## RESEARCH METHODS

### Materials and Methods

### Software and hardware

The tools used in this study included hardware such as a laptop equipped with an Intel® Celeron® N4120 CPU @ 1.10 GHz 4.00 GB (3.82 usable) 238 GB storage. It also included software such as ChemDraw, Molecular Operating Environment (MOE) 2019.0102, Discovery Studio Visualizer 2021 (Biova), pkCSM, and SwissADME. Ligan and Reseptor

### Ligands and Receptor

This study used 15 imidazole–morpholine–1,2,4-oxadiazole derivative compounds that were synthesized and tested against MCF-7 breast cancer cells by Kannekanti et al. (2024), where the selection of compounds is based on the reported $IC_{50}$ values. In addition, the structure of the target receptor ligand (PDB ID: 3ERT) can be downloaded from the Protein Data Bank (http://www.rscb.org/pdb/).

### Protein preparation

The ER-α protein structure (PDB: 3ERT) was obtained from the Protein Data Bank. Protein preparation was performed using Discovery Studio Visualizer 2021 to remove water molecules and co-crystal ligands present in the protein structure. Next, the preparation was continued using MOE 2019.0102 with the CHARM27 force field to obtain the minimum energy and geometry, correct the number of

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hydrogen atoms and partial charges, and determine an RMS gradient of 0.001 kcal/mol/Å. The prepared protein was saved in .pdb format.

### Ligand Preparation

Ligand preparation was carried out by designing fifteen imidazole–morpholine–1,2,4-oxadiazole derivatives using ChemDraw version 8.0. The resulting ligand structures were then prepared using software MOE version 2019.0102 through a process of geometric optimization and energy minimization using the MMFF94x force field with an RMS gradient value of 0.001 kcal/mol/Å. The optimized ligand structures were subsequently saved in .mdb format and used for the molecular docking process.

### Re-Docking

Validation of the docking method was performed using a re-docking approach between the native ligand and the previously prepared 3ERT target protein. The method was validated to evaluate the accuracy of the docking procedure by comparing the conformations of the ligands obtained from re-docking with those of the original crystal ligand, as well as the correspondence of amino acid residues and the types of interactions formed.

### Molecular Docking

The molecular docking process was performed using MOE 2019.0102 software with the induced-fit approach. The docking parameters were set to generate 100 conformations, and the 10 best poses were then selected based on the binding affinity and RMSD values obtained. Visualization of the interactions between the ligand and the receptor was performed using BIOVA Discovery Studio Visualizer 2021 to analyze the types of interactions formed at the active site of the target protein.

### Determination of pharmacokinetic properties and drug-drug interactions

Pharmacokinetic and toxicity predictions for compounds can be performed using SwissADME and pkCSM. Pharmacokinetic evaluations were selected based on Lipinski's Rule of Five parameters, while toxicity predictions and other ADMET parameters were analyzed using pkCSM. (http://www.swissadme.ch/index.php)(https://biosig.lab.uq.edu.au/pkcsm/).

## RESULTS AND DISCUSSION

### Re-docking

Re-docking is a validation method used to assess the feasibility and accuracy of a docking method by examining the interaction between a protein and its native ligand. The results of the re-docking are compared with the ligand's pose in the receptor's crystal structure to assess their similarity. They are then evaluated based on the Root Mean Square Deviation (RMSD) value.

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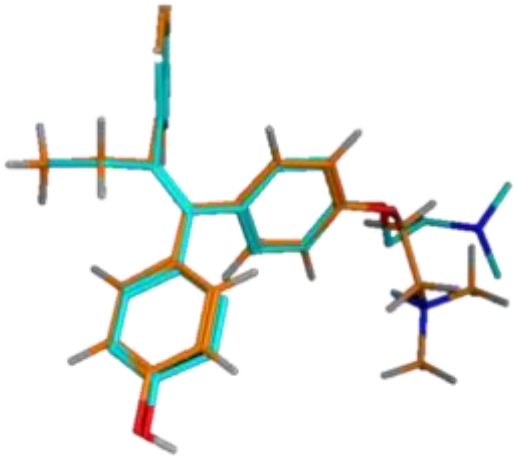

**Figure 2.** Overlay of the native ligand (blue) and the re-docked ligand (orange).

Based on the re-docking results for the 3ERT receptor in Table 1, it can be concluded that the method used is valid because the resulting RMSD is approximately 1.8596 Å. An RMSD value ≤ 2 Å indicates that the docking method used has good validity and accuracy (Asaumi et al., 2026). Furthermore, the results of the interactions between the re-docked ligand and the receptor show similarities in amino acid residues compared to the crystal complex prior to re-docking. In the re-docked ligand, there are two hydrogen bonds between Arg394 and Glu353. Based on the crystal structure of 3ERT, the amino acid residues Arg394 and Glu353 are key residues in the binding pocket that play a role in ligand-receptor binding to ER-α (Shiau et al., 1998). The similarity in the bound residues between the two (Arg394 and Glu353) indicates that the re-docking pose can maintain the most important interactions at the receptor's active site. Therefore, the method used has been validated and can be applied to bioactive imidazole-morpholine-1,2,4-oxadiazole derivatives. The visualization of the interaction between the original ligand from re-docking and the residues in the ER-α active pocket is shown in Figure 3.

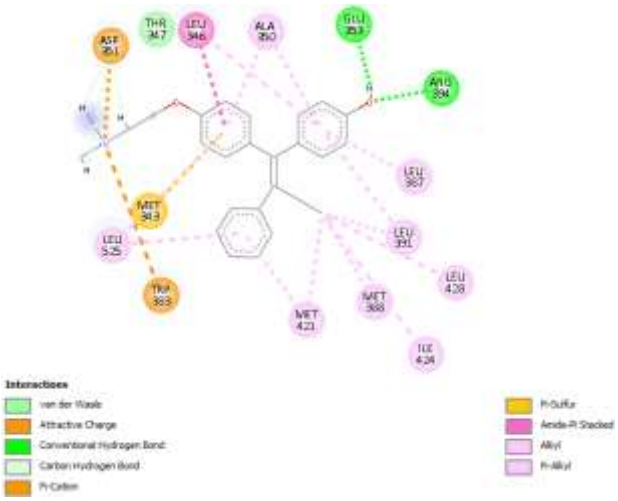

**Figure 3**. Two-dimensional interaction diagram of the re-docked native ligand (4-hydroxytamoxifen, OHT) within the binding pocket of ER-α (PDB ID: 3ERT).

**Table 1.** Results of the re-docking of the ER-α protein (PDB ID: 3ERT)

| 3ERT | Docking Score | RMSD | Hydrogen bonds | Non hydrogen bonds |
|---|---|---|---|---|
| Before re-docking | - | - | Arg394, Glu353, Asp351 | Met421, Met388, Ile424, Leu391, Leu428, Leu387, Ala350, Met 343, Leu346, Thr347, Leu525 |
| After Re-docking | -11.9696 | 1.8596 | Arg394, Glu353 | Met421, Met388, Ile424, Leu428, Leu391, Leu387, Ala350, Leu346, Asp351, Met343, Trp383, Leu525, Thr347 |

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**Molecular Docking**

Molecular docking is performed to predict the interaction between a biologically active compound and a target protein. This method can determine the binding position, the strength of the interaction, and the type of bond formed between the ligand and its receptor (Jawarkar et al., 2024). In this study, this method was used to evaluate imidazole-morpholine-1,2,4-oxadiazole as a candidate breast cancer drug through its interaction with ER-α.

Based on the binding results of the 15 compounds shown in Table 2, all imidazole-morpholine-1,2,4-oxadiazole derivatives demonstrated the ability to bind to the ER-α receptor, as indicated by their binding energy values. The lower the binding energy value of a compound, the stronger the complex formed between the ligand and the receptor (Anastasya et al., 2023). Among all the test compounds, compounds 7f, 7h, 7j, and 7m had the lowest binding energy values of -7.43247747 kcal/mol, -7.06977987 kcal/mol, -7.03865147 kcal/mol, and -7.07602549 kcal/mol, respectively, with RMSD values < 2 Å. However, when compared to tamoxifen, the binding energy value for tamoxifen is lower than that of the four tested ligand compounds, at approximately -8.90786552 kcal/mol. Based on these values, compounds 7f, 7h, 7j, and 7m have slightly lower potential than tamoxifen for interacting with the receptor.

Compounds 7f, 7h, 7j, and 7m exhibited less favorable predicted binding affinities toward ER-α than tamoxifen, suggesting weaker predicted binding to the receptor. These differences may be associated with variations in their molecular structures and interaction patterns within the ER-α binding pocket (Gaur et al., 2026). Tamoxifen has a triphenylethylene framework made up of three aromatic rings, which allows it to form extensive hydrophobic interactions with the receptor's active pocket. Additionally, its phenolic hydroxyl group contributes to hydrogen bonding with key amino acid residues, while its amine chain helps maintain the ligand's orientation within the binding pocket. On the other hand, imidazole–morpholine–1,2,4-oxadiazole derivatives have a different molecular framework. Although the imidazole, morpholine, and 1,2,4-oxadiazole groups contain nitrogen and oxygen atoms that can act as hydrogen bond donors or acceptors, these three heterocyclic groups generate a smaller hydrophobic surface area compared to the triphenylethylene framework in tamoxifen.

The molecular docking results shown in Table 2 indicate that fifteen imidazole-morpholine-1,2,4-oxadiazole derivatives form various interactions with amino acid residues in the ER-α binding pocket. These interactions include hydrogen bonds as well as non-hydrogen interactions that play a role in determining the stability of the ligand–receptor complex. Among the four best compounds, compound 7f has the lowest binding energy to the ER-α receptor. The 2D interaction visualization of compound 7f is shown in Figure 4. Based on Figure 4, compound 7f forms carbon hydrogen bonds with the Leu346

residue and the key Glu353 residue. In addition, compound 7f also forms several hydrophobic interactions with the residues Phe404, Met388, Met421, Leu391, Leu387, Leu349, Leu525, Ala350, and Met343 through π-π T-shaped, π-sulfur, alkyl, and π-alkyl interactions. Compared to compound 7f, compound 7h does not form hydrogen bonds with the amino acid residues in the ER-α binding pocket, so the interactions it generates are mostly non-hydrogen interactions. Meanwhile, compounds 7j and 7m each only form a single hydrogen bond with residues Leu346 and Thr347. The fewer number and simpler interactions of compounds 7h, 7j, and 7m compared to 7f suggest that the stability of the ligand–receptor complex for these three compounds is relatively lower. Therefore, compound 7f is predicted to have the best binding affinity among the four compounds because it can form more hydrogen interactions than the other three compounds (Mardianingrum et al., 2021). Compound 7f can also maintain interactions with the key Glu353 residue and form a broader network of hydrophobic interactions compared to compounds 7h, 7j, and 7m. This combination of interactions is expected to contribute to the stability of the ligand–receptor complex and result in a lower binding energy.

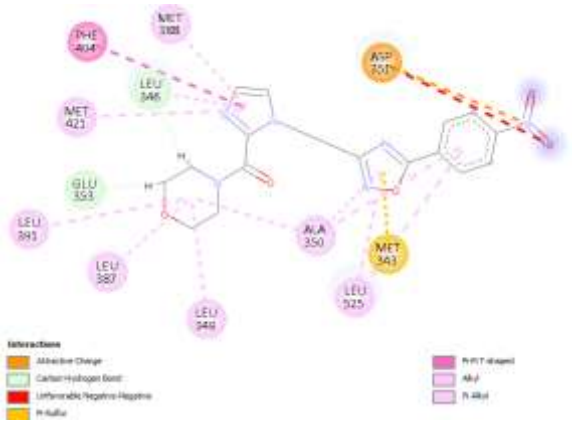

**Figure 4. I**nteractions of compound 7f with amino acid residues in ER-α

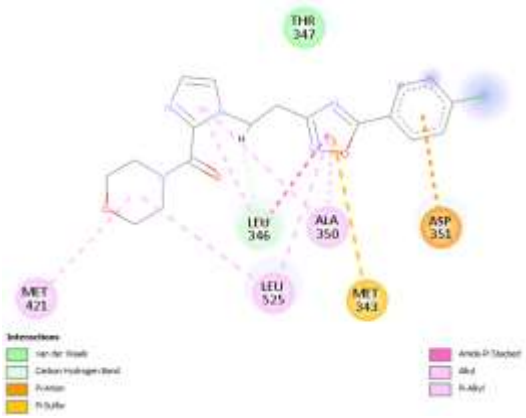

**Figure 5.** Amino acid residue interactions in compound 7j

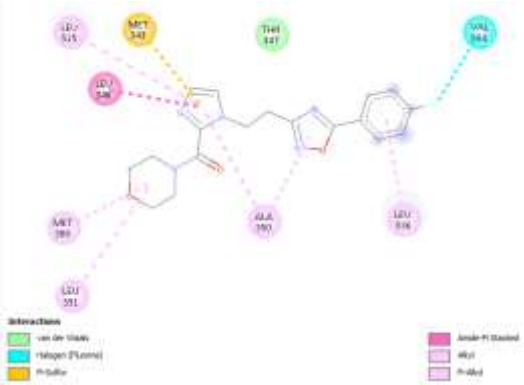

**Figure 6.** Amino acid residue interactions in compound 7h

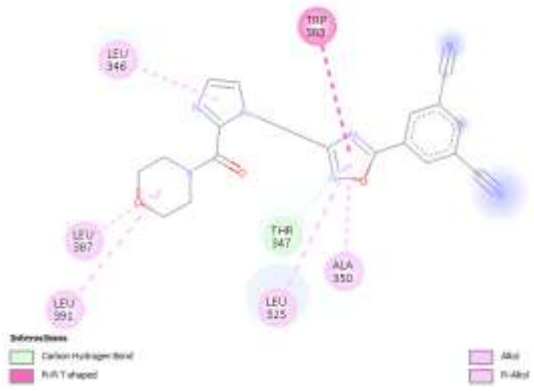

**Figure 7.** Amino acid residue interactions in compound 7m

**Table 2**. Molecular docking results for imidazole-morpholine-1,2,4-oxadiazole derivatives

| Compounds | Binding Affinity | RMSD (Root Mean Square Deviation) | Hydrogen bonds | Non-hydrogen bonds |
|---|---|---|---|---|
| 7a | -5.52582455 | 1.28740644 | Leu346 | Glu353, Leu387, Met388, Met421, Met343, Leu525, Thr347, Ala350 |
| 7b | -5.51959467 | 1.9294498 | - | Met388, Leu384, Ile424, Leu525, Ala350, Met421, Trp383, Leu346, Met343 |
| 7c | -6.39592934 | 1.45198119 | Glu353, Lys449 | Arg354, Ile326, Leu320, Glu323, Pro324, Met357, Leu387 |
| 7d | -6.77824497 | 1.05686057 | Lys449, Trp393, Glu323, Pro324, Arg394, Ile386, Glu353 | Met357, Ile326 |
| 7e | -6.90481091 | 1.30516267 | Glu353, Thr347, Asp351 | Leu525, Ala350, Leu349, Ile424, Met421, Leu428, Met388, Trp383, Leu346 |
| 7f | -7.43247747 | 1.83123922 | Leu346, Glu353 | Met388, Phe404, Met421, Leu391, Leu387, Leu349, Ala350, Leu525, Met343, Asp351, |
| 7g | -5.7771821 | 1.59262729 | - | Met388, Leu387, Leu391, Met421, Met343, Leu346, Leu525, Thr347, Ala350, Asp351 |
| 7h | -7.06977987 | 1.52042353 | - | Met388, Leu391, Ala350, Leu536, Val534, Thr347, Met343, Leu525, Leu346 |
| 7i | -6.77375507 | 0.960575104 | Leu536 | Val533, Cys530, Leu525, Ala350, Met343, Leu346, Met421 |
| 7j | -7.03865147 | 1.56146097 | Leu346 | Met421, Leu525, Ala350, Met343, Asp351, Thr347 |
| 7k | -6.61818838 | 1.34207022 | Glu353 | Leu387, Leu391, Leu349, Leu346, Ala350, Thr347, Met343, Leu525, Leu536, Asp351, Leu354, Leu384, Met388 |
| 7l | -5.60186148 | 1.39999223 | Asp351 | Ala350, Trp383, Val533, Leu536, Met58, Leu525 |
| 7m | -7.07602549 | 1.30058944 | Thr347 | Leu525, Ala360, Trp383, Leu346, Leu387, Leu391 |
| 7n | -5.62583256 | 1.53861463 | Lys467, Ser468, Asp374 | His373, Asp538, Tyr537, Leu462 |
| 7o | -6.96924925 | 1.75148928 | Met388, Gly521, Glu419, Glu535 | Met421, Leu525, Leu346, Ala350, Leu391, Leu349, Leu387 |
| Tamoxifen | -8.90786552 | 1.11637342 | - | Met343, Leu525, Met421, Phe404, Leu346, Leu387, Leu391, Ala350 |

**Drug-likeness**

Lipinski's Rules are guidelines used to evaluate the potential of a compound with pharmacological properties to serve as an effective oral drug in humans. When designing a drug compound, it is necessary to consider Lipinski's Rule of Five, which consists of the following criteria: molecular weight ≤ 500, hydrogen bond donors (HBD) ≤ 5, hydrogen bond acceptors (HBA) ≤ 10, and LogP value ≤ 5 (Lipinski et al., 1997). Molecular weight in Lipinski's Rule is related to drug distribution. If a compound's molecular weight exceeds the specified limits, it will have difficulty penetrating cell membranes. The Log P value is related to a compound's lipophilicity. When a compound has a high Log P value, it will be more lipophilic and tends to have lower water solubility, while a compound with a moderate Log P value can show better passive membrane permeability (Waring, 2010).

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Meanwhile, the number of HBA and HBD groups is related to the magnitude of a compound's biological activity (Mardianingrum et al., 2021). Based on the test results for the imidazole-morpholine-1,2,4-oxadiazole compounds, compounds 7f, 7h, 7j, and 7m meet all of Lipinski's rules and can be developed into oral drugs. The results of Lipinski's rules are shown in Table 3.

| Compounds | Molecular Weight (<500g/mol) | HBA (<10) | HBD (<5) | Log P |
|---|---|---|---|---|
| 7a | 367.4 | 6 | 0 | 1.35 |
| 7b | 381.43 | 6 | 0 | 1.70 |
| 7c | 353.38 | 6 | 0 | 0.99 |
| 7d | 383.4 | 7 | 0 | 0.93 |
| 7e | 413.43 | 8 | 0 | 0.87 |
| 7f | 400.39 | 8 | 0 | 0.18 |
| 7g | 378.38 | 7 | 0 | 0.74 |
| 7h | 371.37 | 7 | 0 | 1.36 |
| 7i | 432.27 | 6 | 0 | 1.68 |
| 7j | 387.82 | 6 | 0 | 1.60 |
| 7k | 422.27 | 6 | 0 | 2.20 |
| 7l | 511.17 | 6 | 0 | 2.36 |
| 7m | 403.39 | 8 | 0 | 0.50 |
| 7n | 447.4 | 10 | 4 | -0.61 |
| 7o | 354.36 | 7 | 0 | 0.18 |
| Tamoxifen | 371.51 | 2 | 0 | 6.06 |

Table 3. Prediction of Lipinski's Rule of Five.

**ADMET Prediction**

ADMET predictions are performed to identify the toxic properties of a compound, thereby reducing failures in drug development and preventing adverse effects on the human body (Anastasya et al., 2023). The parameters analyzed include Absorption (such as water solubility, Caco-2 permeability, and P-gp substrate), Distribution (consisting of VDss), Metabolism (such as CYP1A2, CYP2C9, and CYP3A4), Excretion (clearance (CL) values), and Toxicity (Ames toxicity, hepatotoxicity, and $LD_{50}$). The water solubility parameter indicates a compound's solubility in water. Drugs that are easily absorbed by the body are those with good water solubility compared to lipophilic compounds (Rakhmawati et al., 2025). Based on the ADMET prediction results, compounds 7f, 7h, 7j, and 7m have good water solubility compared to tamoxifen, suggesting they support their pharmacological activity as candidates for breast cancer drugs.

The Caco-2 permeability value is used as a parameter to predict drug absorption when administered orally. In the pkCSM model, Caco-2 permeability is considered high if the value is > 0.9 × $10^{-6}$ cm/s (Apriali et al., 2022). The ADMET prediction data in Table 4 show that compounds 7j and 7h have high permeability values of 1.470 and

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1.392, respectively, and are predicted to be able to penetrate cell membranes. Meanwhile, compounds 7f and 7m have low permeability values, with values as low as $0.9 \times 10^{-6}$ cm/s, which may affect their oral bioavailability. Therefore, structural and formulation optimization is required to improve the compound's absorption characteristics (Salsabila et al., 2023). Additionally, compounds 7f, 7h, 7j, and 7m are classified as substrates that may have a high potential for efflux, so this must be further considered in their structural optimization.

Furthermore, compounds 7f, 7h, 7j, and 7m are predicted to be substrates of P-glycoprotein (P-gp). P-gp is a transporter protein that pumps compounds out of cells, reducing their accumulation inside. Even though compound 7f is predicted to have low Caco-2 permeability and is a P-gp substrate, these results do not directly conflict with the cytotoxic activity against MCF-7 cells reported by Kannekanti et al. (2024). This is because the MTT assay was done directly on MCF-7 cells to assess the anticancer activity of the compounds, while the Caco-2 and P-gp predictions are used to estimate absorption and transport processes in the body. Therefore, structural optimization and substituent modification are needed to improve the permeability and pharmacokinetic characteristics of the test compounds.

**Table 4.** ADMET predictions result

| Compounds | Water solubility (Log mol/L) | Caco-2 Permeability (LogPap $10^{-6}$ cm/s | P-gp Substrate | VDss | CYP 1A2 inhibitor | CYP 2C9 inhibitor | CYP 3A4 inhibitor | CL | Ames toxicity | Hepatoxicity | $LD_{50}$ (mol/Kg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **7a** | -2. 963 | 1.48 | Yes | 0.459 | Yes | Yes | No | 0.695 | Yes | Yes | 2.013 |
| **7b** | -2.98 | 1.466 | Yes | 0.464 | Yes | Yes | No | 0.594 | Yes | Yes | 2.042 |
| **7c** | -3.152 | 1.462 | Yes | 0.436 | Yes | Yes | No | 0.694 | Yes | Yes | 1.979 |
| **7d** | -2.931 | 0.156 | Yes | 0.375 | Yes | No | No | 0.718 | Yes | Yes | 1.986 |
| **7e** | -2.913 | 0.214 | Yes | 0.274 | No | No | No | 0.65 | Yes | Yes | 2.57 |
| **7f** | -2.984 | 0.046 | Yes | 0.386 | No | No | No | 0.449 | Yes | Yes | 2.114 |
| **7g** | -2.931 | 0.06 | Yes | 0.377 | Yes | Yes | No | 0.711 | Yes | Yes | 1.955 |
| **7h** | -2.936 | 1.392 | Yes | 0.368 | Yes | Yes | No | 0.651 | Yes | Yes | 2.004 |
| **7i** | -2.975 | 1.466 | Yes | 0.446 | Yes | Yes | No | 0.664 | Yes | Yes | 2.043 |
| **7j** | -2.971 | 1.47 | Yes | 0.436 | Yes | Yes | No | 0.683 | Yes | Yes | 2.036 |
| **7k** | -2.995 | 1.448 | Yes | 0.417 | Yes | Yes | Yes | 0.44 | Yes | Yes | 2.087 |
| **7l** | -3.005 | 1.441 | Yes | 0.437 | Yes | Yes | Yes | 0.189 | Yes | Yes | 2.1 |
| **7m** | -2.891 | 0.014 | Yes | 0.259 | No | Yes | No | 0.61 | Yes | Yes | 1.911 |
| **7n** | -0.21 | -0.215 | Yes | 0.246 | No | Yes | No | 0.158 | No | Yes | 2.159 |
| **7o** | -2.81 | 0.657 | Yes | 0.281 | No | No | No | 0.682 | Yes | Yes | 1.907 |
| **Tamoxifen** | -6.34 | 0.971 | Yes | 0.469 | Yes | No | Yes | 0.475 | Yes | Yes | 2.59 |

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Regarding distribution parameters, the VDss value is used to indicate a compound's ability to distribute within the body. A favorable VDss value falls within the range of -0.15 to 0.45 (Dari et al., 2025). Based on the ADMET prediction results, some imidazole-morpholine-1,2,4-oxadiazole derivatives have moderate VDss values ranging from 0.246 to 0.464, indicating that they distribute fairly well between plasma and body tissues. Tamoxifen, on the other hand, has a higher VDss value and therefore tends to accumulate in the body.

In metabolic analysis, cytochrome P450 (CYP) parameters are used to predict the metabolic processes of compounds in the liver. The CYP isoenzymes analyzed in this ADMET prediction include CYP1A2, CYP2C9, and CYP3A4. Based on the prediction results, compound 7f is not an inhibitor of CYP1A2, CYP2C9, or CYP3A4. This indicates that this compound does not interfere with the metabolism of other drugs, as drugs that do not undergo CYP metabolism typically have minimal drug interactions (Rakhmawati et al., 2025).

Regarding excretion parameters, the clearance values range from 0.158 to 0.718. The clearance values for compounds 7f, 7h, 7j, and 7m are 0.449, 0.651, 0.683, and 0.610, respectively. These values indicate that the compounds can be eliminated from the body fairly well. Compound 7f is relatively similar to tamoxifen in terms of its characteristics.

The AMES test can be used to assess a compound's toxicity. The AMES test is used to determine a compound's mutagenic potential. If a compound is mutagenic, it will yield a positive test result (Apriali et al., 2022). The AMES test results for all compounds listed in Table 4 indicate that these compounds are predicted to have mutagenic potential, except for compound 7e. The hepatotoxicity parameters also predict that all compounds could cause liver damage. In drug development, these prediction results must be taken into account through further evaluation using both in vitro and in vivo studies.

The predicted mutagenicity and hepatotoxicity of compound 7f may be associated with the presence of the nitro group (-$NO_2$). In medicinal chemistry, nitro groups are known to potentially increase toxicity in some compounds because they can form reactive metabolites in the body. These metabolites can interact with DNA or proteins, raising the risk of mutagenicity (Nepali et al., 2018). In addition, ADMET predictions in this study also showed potential hepatotoxicity, so the safety aspects of the compound still need to be further evaluated through substituent modifications and toxicity testing, both in vitro and in vivo. Modifying the $NO_2$ substituent can be done by replacing it with other electron-withdrawing groups, like a cyanide group, which could maintain biological activity while reducing toxic effects. The $LD_{50}$ value is used to assess a compound's short-term toxicity potential based on the single dose that causes a 50% mortality rate in test animals (Dari et al., 2025). Based on the ADMET prediction results, the $LD_{50}$ values of

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compounds 7f, 7h, 7j, and 7m are 2.114, 2.004, 2.036, and 1.911 mol/kg, respectively. These values are lower than tamoxifen (2.590 mol/kg), which indicates a higher predicted acute toxicity potential. However, $LD_{50}$ values only represent one aspect of toxicity and cannot be used as a basis to conclude the overall safety of a compound.

Overall, compounds 7f, 7h, 7j, and 7m show some predicted favorable ADMET characteristics, including good water solubility, acceptable distribution, and favorable metabolic properties, especially for compound 7f, which is predicted not to inhibit CYP1A2, CYP2C9, or CYP3A4. However, these compounds also show some predicted limitations, including low Caco-2 permeability (for compounds 7f and 7m), being P-glycoprotein substrates, positive Ames mutagenicity, predicted hepatotoxicity, and predicted $LD_{50}$ values lower than tamoxifen. Therefore, this prediction shows that even though these compounds have some predicted favorable pharmacokinetic characteristics, further structural optimization and experimental validation are needed to improve the overall ADMET profile and ensure their safety.

## CONCLUSION

Based on in silico molecular modelling and ADMET evaluation, imidazole-morpholine-1,2,4-oxadiazole derivatives have potential as cancer drug candidates targeting ER-α. Compound 7f was identified as the candidate with the best predicted profile among the evaluated compounds because it showed strong binding affinity to ER-α, with an affinity of -7.43247747 kcal/mol and an RMSD of 1.8. Compound 7f is predicted to have favorable metabolic characteristics since it is not expected to inhibit CYP1A2, CYP2C9, or CYP3A4. However, it also has some predicted drawbacks, such as low Caco-2 permeability, being a P-glycoprotein (P-gp) substrate, positive Ames mutagenicity, predicted hepatotoxicity, and a predicted $LD_{50}$ lower than tamoxifen, indicating higher acute toxicity. Therefore, further structural optimization and experimental validation through *in vitro* and *in vivo* studies are warranted to address the predicted ADMET liabilities and confirm the compound's safety and therapeutic potential before further drug development.

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