

DOCKING SIMULATION OF 1,2,3-TRIAZOLO-INDOLE-2-CARBOXYLATE DERIVATIVES AS POTENTIAL HER2 INHIBITORS FOR BREAST CANCER THERAPY

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Abstract

HER2 is a tyrosine kinase receptor involved in cell proliferation, differentiation, and survival. Its overexpression promotes cancer progression and therapeutic resistance, indicating the need for new HER2 inhibitors. In this study, twelve 1,2,3-triazolo-indole-2-carboxylate derivatives were evaluated as potential HER2 inhibitors using *in silico* approaches. Drug-likeness was analyzed using SwissADME, ADMET properties were predicted with pkCSM, and molecular docking was performed using MOE. Docking analysis indicated that several compounds exhibited strong binding affinity toward HER2, with compounds 6b, 6c, 6d, 6e, and 9a identified as the most promising candidates. Among them, compound 6d showed the most balanced profile, combining strong binding affinity, favorable interactions comparable to lapatinib, moderate aqueous solubility, high Caco-2 permeability, non-substrate behavior toward P-gp, and non-mutagenic properties. ADMET evaluation revealed that all compounds complied with Lipinski's rule and exhibited high total clearance. However, limitations were observed in distribution parameters (VDss, Fu, and BBB), potential hepatotoxicity, and inhibition of several CYP enzymes, except CYP2D6. Overall, compound 6d is proposed as a promising HER2 inhibitor candidate, although further *in vitro* and *in vivo* validation is required to improve safety and pharmacokinetic profiles.

Keywords: Molecular docking, Breast Anticancer, 1,2,3-Triazolo-Indole-2-Carboxylate, ADMET, HER2

Abstrak

HER2 merupakan reseptor tirosin kinase yang berperan dalam proliferasi, diferensiasi, dan kelangsungan hidup sel. Overekspresinya mendorong perkembangan kanker serta resistensi terhadap terapi, sehingga menunjukkan perlunya pengembangan inhibitor HER2 baru. Dalam penelitian ini, dua belas turunan 1,2,3-triazolo-indole-2-karboksilat dievaluasi sebagai kandidat inhibitor HER2 menggunakan pendekatan *in silico*. Analisis *drug-likeness* dilakukan menggunakan SwissADME, prediksi sifat ADMET menggunakan pkCSM, dan *molecular docking* dilakukan dengan MOE. Hasil *docking* menunjukkan bahwa beberapa senyawa memiliki afinitas ikatan yang kuat terhadap HER2, dengan senyawa 6b, 6c, 6d, 6e, dan 9a teridentifikasi sebagai kandidat paling menjanjikan. Di antara senyawa tersebut, senyawa 6d menunjukkan profil paling seimbang, dengan kombinasi afinitas ikatan yang kuat, interaksi yang menguntungkan dan sebanding dengan lapatinib, kelarutan air sedang, permeabilitas Caco-2 tinggi, bukan substrat P-gp, serta sifat non-mutagenik. Evaluasi ADMET mengungkapkan bahwa seluruh senyawa memenuhi aturan Lipinski dan menunjukkan *total clearance* yang tinggi. Namun, ditemukan keterbatasan pada parameter distribusi (VDss, Fu, dan BBB), potensi hepatotoksitas, serta inhibisi terhadap beberapa enzim CYP, kecuali CYP2D6. Secara keseluruhan, senyawa 6d diusulkan sebagai kandidat inhibitor HER2 yang menjanjikan, meskipun validasi lebih lanjut secara *in vitro* dan *in vivo* masih diperlukan untuk meningkatkan keamanan dan profil farmakokinetiknya.

Kata Kunci: Penambatan Molekuler, Antikanker Payudara, 1,2,3-Triazolo-Indol-2-Karboksilat, ADMET, HER2

1. Introduction

Cancer remains one of the most pressing global health challenges of the 21st century. According to the International Agency for Research on Cancer (IARC) report in 2022, there were approximately 20 million new cancer cases and 9.7 million cancer-related deaths worldwide, with new cases projected to increase to 35 million by 2050. Among various cancer types, breast cancer

is the most frequently diagnosed malignancy in women and is one of the leading causes of cancer-related mortality globally (Gautama, 2022; Akbar *et al.*, 2025). In 2022, around 2.3 million new breast cancer cases and more than 670,000 deaths were recorded worldwide (Akbar *et al.*, 2025). In Indonesia, breast cancer is the most common cancer among women and one of the leading causes of cancer-related death, accounting for 9.1% of all cancer cases (Bray *et al.*, 2024; Utama *et al.*, 2025).

Breast cancer is a malignant disease originating from breast tissue and can metastasize to other parts of the body if not properly treated (Shil and Ankar, 2025). Risk factors include increasing age, family history, genetic mutations, radiation exposure, hormone replacement therapy, and unhealthy lifestyles such as high-fat diets and excessive alcohol consumption (Toni and Azra, 2022; Akbar *et al.*, 2025; Shil and Ankar, 2025). Common therapies for breast cancer patients include surgery, radiation therapy, chemotherapy, and endocrine therapy (Nikakhtar *et al.*, 2025). However, treatment responses may vary among patients due to differences in molecular characteristics across breast cancer subtypes. Among these, HER2-positive breast cancer, accounting for approximately 15–20% of cases, is associated with more aggressive tumor behavior and poorer prognosis (Fisusi and Akala, 2019; Akbar *et al.*, 2025). HER2 also serves as a prognostic biomarker associated with lower survival rates (Kavarthapu, Anbazhagan and Dufau, 2021). Although HER2-targeted therapies such as lapatinib have improved survival outcomes, resistance and adverse effects remain significant challenges (Moy and Goss, 2007; Akbar *et al.*, 2025). Therefore, the development of new HER2 inhibitors with improved efficacy and safety remains an important challenge in breast cancer treatment.

In addition, conventional drug development still faces several limitations, including time-consuming processes, high costs, and low success rates (Toni and Azra, 2022; Solanki *et al.*, 2024). To overcome these limitations, computational-based approaches can be used as a more efficient initial step in drug discovery. Molecular docking can predict interactions between ligands and receptors at the molecular level, while drug-likeness evaluation and ADMET prediction provide insights into pharmacokinetic properties and compound safety before experimental validation (Akbar *et al.*, 2025; Okon *et al.*, 2025; Rajkumar *et al.*, 2025).

This approach can be applied to evaluate potential drug candidates, including 1,2,3-triazolo-indole-2-carboxylate derivatives. Anantoju *et al.* (2024) developed twelve derivatives based on chalcone, indole, and triazole scaffolds, which showed cytotoxic activity against several cancer cell lines, including MCF-7 and MDA-MB-231 breast cancer cells.

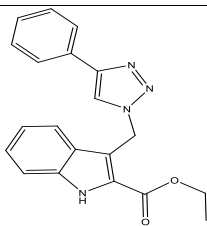
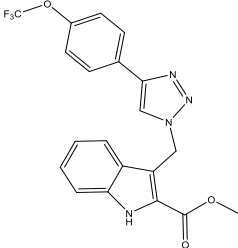
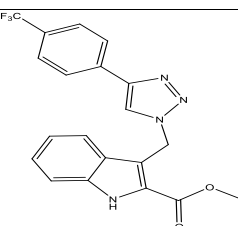
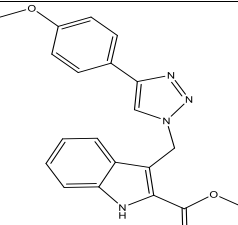
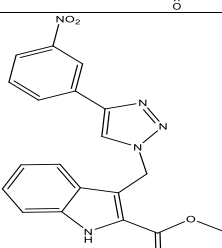
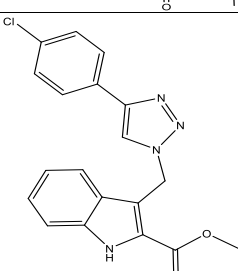
Despite the promising cytotoxic activity of 1,2,3-triazolo-indole-2-carboxylate derivatives reported in previous studies, their potential as HER2-targeted anticancer agents remains unclear. Previous studies have not investigated their interactions with the HER2 receptor at the molecular level, nor evaluated their drug-likeness and pharmacokinetic and toxicity profiles (ADMET). This lack of comprehensive evaluation limits the understanding of their suitability as drug candidates. Therefore, this study addresses these limitations by combining molecular docking, drug-likeness analysis based on Lipinski's Rule of Five, and ADMET prediction to identify the potential of these compounds as effective and safe HER2-targeted breast cancer drug candidates.

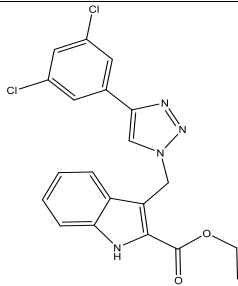
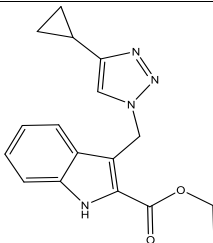
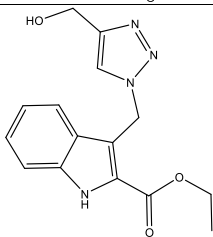
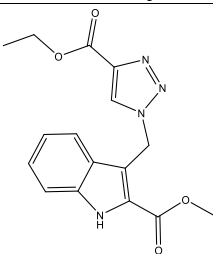
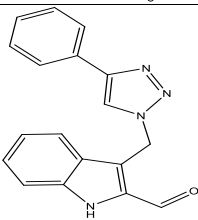
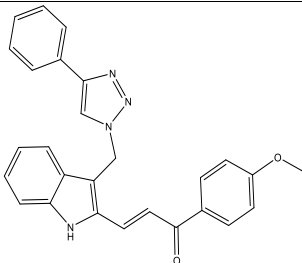
2. Methodology

2.1. Equipment, Software, and Materials

The hardware used in this study consisted of an ASUS VivoBook E410MAB_E410MA laptop (Intel® Celeron® N4020, 1.10 GHz; 4096 MB RAM; Windows 11). The software and websites utilized included Chemdraw Professional 16.0, Molecular Operating Environment (MOE) v2019.0102, Biovia Discovery Studio Visualizer 2025 Client (DSV), Protein Data Bank (RCSB) (<https://www.rcsb.org/>), SwissADME (<http://www.swissadme.ch/>), and PKCSM (<https://biosig.lab.uq.edu.au/pkcsm/prediction>). The materials included the HER2 protein structure (PDB ID: 7PCD), lapatinib as a positive control, and 1,2,3-triazolo-indole-2-carboxylate derivatives (6a–j, 8a, 9a) as test ligands (Table 1).

Table 1. Structures of 1,2,3-triazolo-indole-2-carboxylate derivatives synthesized by (Anantoju et al. (2024)

No	Compounds	IC ₅₀ in μM^a (MCF-7 ^b)	Structure
1	6a	0.95 ± 0.06	
2	6b	0.44 ± 0.052	
3	6c	1.53 ± 0.85	
4	6d	1.98 ± 0.39	
5	6e	18.2 ± 5.66	
6	6f	2.05 ± 1.35	

7	6g	4.98 ± 2.81	
8	6h	15.2 ± 7.56	
9	6i	5.82 ± 2.64	
10	6j	13.8 ± 6.13	
11	8a	0.027 ± 0.0085	
12	9a	3.66 ± 2.77	

^aData are expressed as mean $\pm$ SD from three independent experiments conducted in triplicate.

^bMCF-7: human breast cancer cell line.

2.2. Protein Preparation

The HER2 protein was prepared by removing the natural ligand and water molecules (Kamel *et al.*, 2025) using Biovia DSV. Further protein preparation was conducted in MOE by adding partial charges (AMBER10: EHT force field) and polar hydrogens. Subsequently, the quick prep menu was applied to stabilize the structure (RMS = 0.001 kcal/mol/Å²).

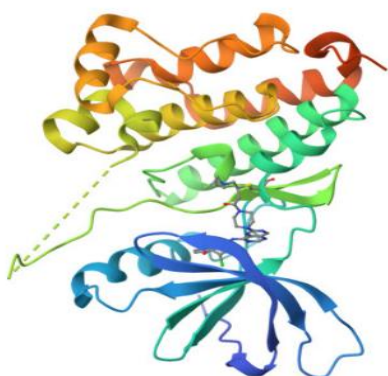


Figure 1. Crystallographic structure of HER2 (PDB ID: 7PCD)

2.3. Preparation of Test Ligands and Positive Control

All ligands were drawn using ChemDraw. In MOE, energy minimization was carried out via the energy minimize menu using the MMFF94x force field, along with charge fixing (fix charge) and hydrogen adjustment (fix hydrogen), with a gradient of 0.0001 kcal/mol/Å².

2.4. Active Site Determination (Site Finder)

The binding site was identified using the site finder feature in MOE. In MOE, active site prediction was based on alpha spheres (Shrestha *et al.*, 2022). The natural ligand was used as a reference, and dummy atoms were added to mark the binding site location (Zaman *et al.*, 2024). Figure 2 illustrates the HER2 binding pocket, displaying the predicted binding site and amino acid residues through dummy atoms. Afterward, docking and redocking simulations were performed.

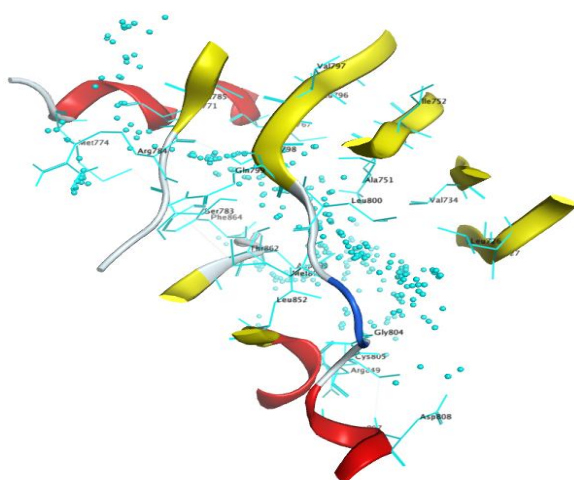


Figure 2. Visualization of the binding pocket on HER2

2.5. Docking Simulation

Docking simulations were performed on the test ligands. Docking used the AMBER10:EHT force field with a gradient value of 0.01 kcal/mol/Å². The placement method was Triangular Matcher, with London dG and WSA/GBVI dG used as scoring and rescoring methods, respectively (Qasem, 2025). Additionally, the induced fit mode was applied. For all ligands, London dG scoring ranked 50 docking poses, followed by optimization of the best pose and rescoring using WSA/GBVI dG to generate 10 final poses (Lina *et al.*, 2025). The dummy atoms previously defined in the active site selection were also set in the docking settings.

The best docking result was determined based on the lowest binding affinity and RMSD < 2 (Oktomalioputri *et al.*, 2025). Generally, binding energies below −5.0 kcal/mol indicate good binding activity, and values below −7.0 kcal/mol indicate stronger interactions (Lina *et al.*, 2025).

2.6. Visualization of Docking Results

Docking and redocking results were visualized using Biovia Discovery Studio Visualizer 2025 Client to observe ligand–protein interactions.

2.7. ADMET Prediction and Lipinski's Rule Assessment

Compounds were converted into SMILES format and analyzed using SwissADME (Lipinski's rule) and pkCSM (ADMET). These predictions were used to evaluate pharmacokinetic and toxicity properties.

3. Results and Discussion

3.1. Molecular Docking

The molecular docking results of 1,2,3-triazolo-indole-2-carboxylate derivatives against the HER2 protein are presented in Table 2. HER2 is known to play a crucial role in breast cancer progression, as it regulates cell proliferation, differentiation, and survival through the activation of downstream signaling pathways (Li and Huang, 2025). Overexpression of HER2 may induce invasion, migration, differentiation, angiogenesis, and resistance to chemotherapy (Pan *et al.*, 2024). Therefore, inhibition of the HER2 tyrosine kinase domain is considered an important strategy to suppress cancer cell progression (Mariam Raju *et al.*, 2024).

Table 2. Docking Scores (S) and RMSD values of the compounds docked against the HER2 protein

Compounds	S (kcal/mol)	RMSD (Å)
6a	-7.422	0.8038
6b	-8.178	1.982
6c	-8.149	1.827
6d	-8.321	1.363
6e	-8.328	0.7928
6f	-7.821	1.335
6g	-7.717	1.514
6h	-7.275	1.11
6i	-6.857	1.957
6j	-7.503	1.342
8a	-7.005	1.832
9a	-8.974	1.259
Lapatinib	-9.123	1.781

The docking results showed that compound 9a exhibited the lowest binding energy (−8.974 kcal/mol), indicating the strongest and most stable interaction between the ligand and the protein (Aini *et al.*, 2022). Compound 6e ranked second with −8.328 kcal/mol, followed by 6d with −8.321 kcal/mol, compound 6b (−8.178 kcal/mol), and compound 6c (−8.149 kcal/mol). These compounds still demonstrated strong binding interactions, although slightly weaker than 9a. All compounds exhibited RMSD values below 2 Å, which were used as the validation threshold in this docking analysis (Oktomalioputri *et al.*, 2025).

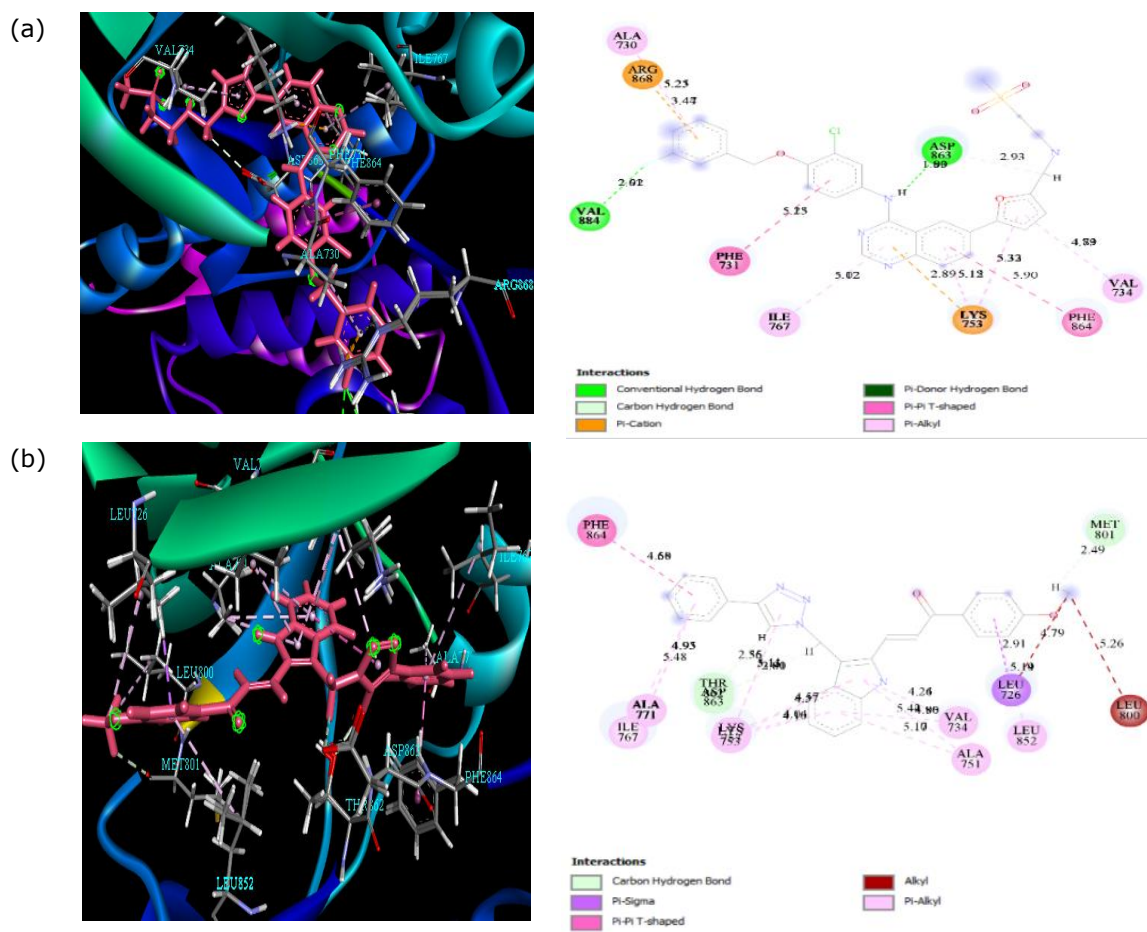
The interaction between the ligands and the HER2 receptor was further analyzed. Among all tested compounds, compound 9a exhibited the strongest binding potential. It formed three carbon–hydrogen bonds with MET801, THR862, and ASP863. In addition, compound 9a was stabilized by hydrophobic interactions, including π – π T-shaped interaction with PHE864, π –sigma interaction

with LEU726, and alkyl or π -alkyl interactions involving LEU726, LEU800, VAL734, LYS753, ALA771, and ILE767, supporting its favorable binding mode (Misran *et al.*, 2025).

Compound 6e showed a binding pattern similar to 9a, forming hydrogen bonds with MET801, THR862, and LYS753, while ASP863 was involved only in carbon–hydrogen bonding in compound 9a. Hydrophobic interactions of compound 6e involved PHE864, LYS753, LEU726, ALA751, VAL734, and LEU852. Compound 6d exhibited additional interaction diversity, forming hydrogen bonds with the same residues as 6e, along with electrostatic interactions such as π -cation with LYS753 and π -anion with ASP863, as well as hydrophobic interactions involving VAL734, LEU800, LEU726, ALA751, and LEU852.

Compound 6b formed hydrogen bonds with MET801 and LYS753 and showed hydrophobic interactions with ILE767, LEU852, VAL734, ALA751, LYS753, ALA771, LEU726, and LEU800, as well as a halogen bond with MET801. Meanwhile, compound 6c formed a conventional hydrogen bond with LYS753, hydrophobic interactions with LEU726, ALA751, LEU852, ALA771, LEU785, PHE864, VAL734, LYS753, and LEU796, a π -anion interaction with VAL734, and a halogen bond with MET801.

Overall, the five test compounds (9a, 6e, 6d, 6b, and 6c) shared key interacting residues with the positive control lapatinib. Among them, compound 9a emerged as the most promising HER2 inhibitor candidate due to its lowest binding energy and more extensive interaction profile. The interaction visualizations are presented in Figure 3.



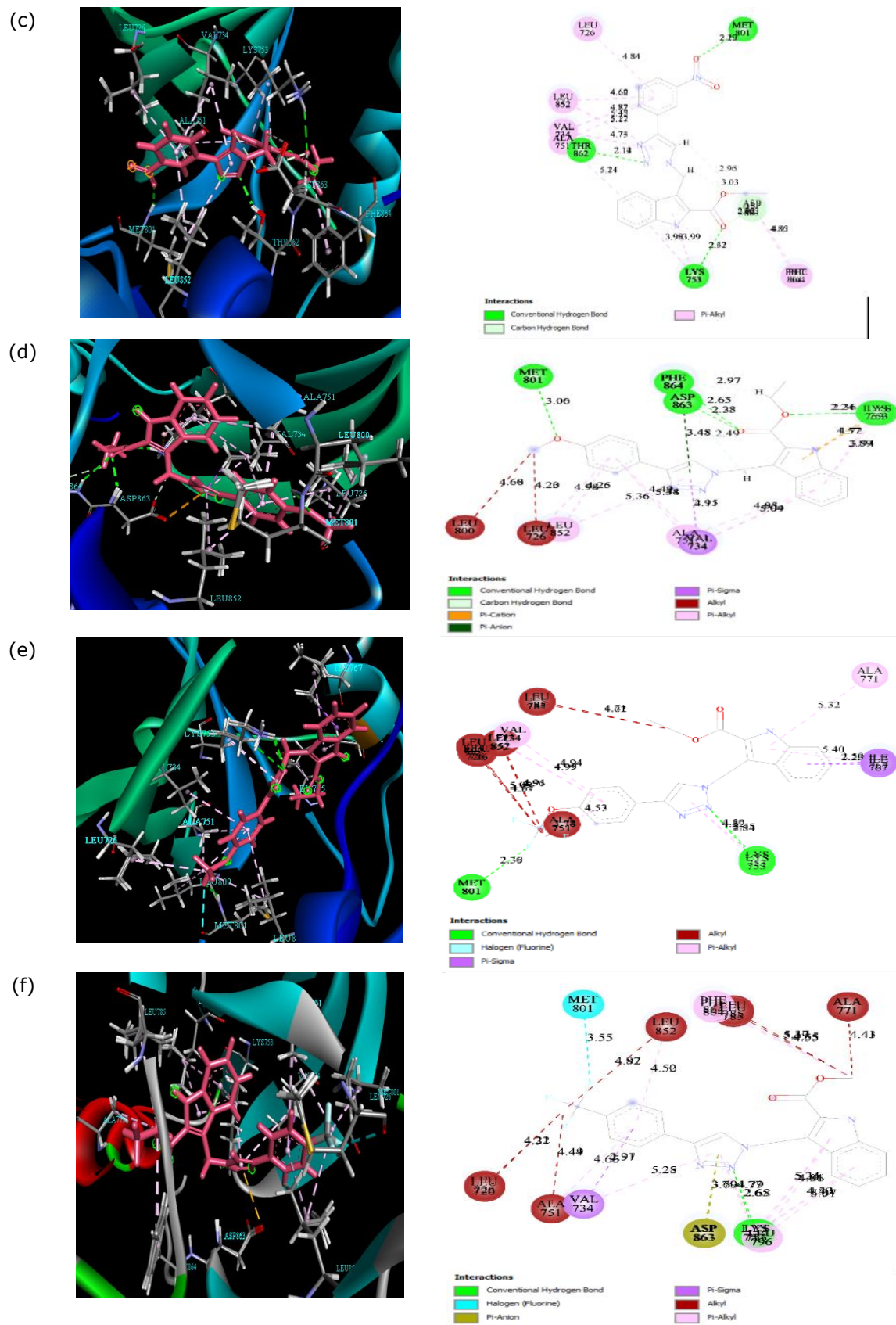


Figure 3. 2D and 3D visualization of compounds: (a) Lapatinib, (b) 9a, (c) 6e, (d) 6d, (e) 6b, and (f) 6c

3.2. Physicochemical Properties and Drug-Likeness

Table 3 presents the physicochemical properties and drug-likeness evaluation of all 1,2,3-triazolo-indole-2-carboxylate derivatives. These properties are crucial for understanding how the compounds behave within the body and their potential as anticancer agents (Aini *et al.*, 2022; Misran *et al.*, 2025). Drug-likeness assessment was based on Lipinski's Rule of Five, which includes the following criteria: molecular weight < 500 Da, Log P o/w < 5, hydrogen bond acceptors < 10, hydrogen bond donors < 5 (Zeki and Mustafa, 2024).

The analysis revealed that all synthetic compounds comply with Lipinski's rule, whereas lapatinib violates one criterion, specifically its molecular weight (MW) which is > 500 Da. The molecular weight range of the synthesized compounds (300.31–434.49 Da) indicates favorable potential for oral absorption, distribution, and elimination within the body. Thus, these compounds may have better bioavailability compared to lapatinib (Okon *et al.*, 2025). An ideal molecular weight is crucial because it determines the rate of gastrointestinal absorption, ability to pass physiological membranes, potential to cross the blood–brain barrier, interaction with biological targets, and elimination processes from the body (Zeki and Mustafa, 2024).

Table 3. Evaluation of Physicochemical Properties and Drug-likeness of 1,2,3-triazolo-indole-2-carboxylate Derivatives

Compounds	Physicochemical Properties				Drug-likeness	
	MW (g/mol)	HBA	HBD	Log P	Lipinski's Rule	Bioavailability Score
6a	346.38	1	4	2.65	0	0.55
6b	430.38	8	1	2.67	0	0.55
6c	414.38	7	1	3.47	0	0.55
6d	376.41	5	1	2.34	0	0.55
6e	391.38	6	1	1.77	0	0.55
6f	380.83	4	1	3.14	0	0.55
6g	415.27	4	1	3.63	0	0.55
6h	310.35	4	1	2.17	0	0.55
6i	300.31	5	2	0.88	0	0.55
6j	342.35	6	1	1.59	0	0.55
8a	302.33	3	1	1.92	0	0.55
9a	434.49	4	1	3.04	0	0.55
Lapatinib	581.06	8	2	3.18	1, MW>500	0.55

In SwissADME, Lipinski's rule prediction employs the MLOGP model to determine partition coefficients, therefore this study followed the same approach. The analysis showed that compound 6i has a Log P value < 1, indicating low lipophilicity and highwater solubility. However, such compounds generally exhibit low gastrointestinal permeability and limited distribution, leading to rapid elimination and reduced capacity to interact with tissue and intracellular targets (Zeki and Mustafa, 2024).

Conversely, compounds with Log P > 3 namely 6c, 6f, 6g, and 9a exhibit high lipophilicity, enabling them to penetrate biological membranes and potentially cross the blood–brain barrier. However, excessive lipophilicity poses concerns regarding toxicity due to extensive distribution and slower elimination. The ideal Log P range for drug-like molecules is 1–3, as it offers a good balance between solubility and permeability; this range was fulfilled by compounds 6a, 6b, 6d, 6e, 6h, 6j, and 8a (Zeki and Mustafa, 2024).

The number of hydrogen bond acceptors (HBA) and donors (HBD) also complied with Lipinski's criteria. Compound 6b and lapatinib had the highest HBA count (8), while 6a exhibited the highest HBD value (4); the remaining compounds possessed 1–2 hydrogen bonds. Excessive hydrogen

bonding can enhance solubility but reduce membrane permeability, thus potentially hindering oral absorption (Zeki and Mustafa, 2024). The bioavailability scores for both synthetic compounds and lapatinib were moderate (0.55), indicating good absorption (Okon *et al.*, 2025).

Overall, the physicochemical analysis indicates that the 1,2,3-triazolo-indole-2-carboxylate derivatives possess properties that support oral bioavailability and meet the criteria of drug-like compounds, demonstrating promising potential as anticancer agents (Rampogu, 2025).

3.3. ADMET Analysis

The ADMET analysis of the 1,2,3-triazolo-indole-2-carboxylate derivatives was carried out to determine their safety profile and potential biological effects (table 4) (Okon *et al.*, 2025). A key pharmacokinetic parameter is aqueous solubility (Log S), which significantly influences drug absorption (Zeki and Mustafa, 2024; Rampogu, 2025). The Log S results indicated that compounds 6a–b, 6f–j, 8a, and 9a exhibited Log S values ranging from –2 to –3, which fall within the range of –4 to –2 and are therefore classified as soluble compounds. Meanwhile, lapatinib had a Log S value of –4.035, and compounds 6c, 6d, and 6e had values of –4.330, –4.237, and –4.029, respectively; these compounds belong to the moderately soluble class (Masudur Rahman Munna *et al.*, 2024). Highly water-soluble compounds are more easily dissolved in gastrointestinal fluids, thus enhancing oral absorption. However, excessive solubility could limit distribution into tissues, resulting in reduced volume of distribution and lower tissue penetration (Zeki and Mustafa, 2024; Rampogu, 2025).

Caco-2 permeability was evaluated to estimate intestinal absorption. Compounds with Log Papp > 0.9 (6a–d, 6f–h, 8a, and 9a) showed high permeability, whereas lapatinib, 6e, and 6i–j had values below 0.9, indicating low permeability (Saritha, Alivelu and Mohammad, 2024). High permeability indicates good intestinal barrier penetration, leading to increased absorption into the bloodstream and enhanced therapeutic effectiveness, whereas low permeability indicates the opposite (Sindi *et al.*, 2025). The analysis further revealed that all compounds, including lapatinib, were non-substrates of P-glycoprotein (P-gp), except for 6h, 6i, and 9a, suggesting that most compounds could bypass P-gp-mediated efflux and therefore exhibit good bioavailability and prolonged intracellular presence, enhancing pharmacological effects (Misran *et al.*, 2025; Rampogu, 2025). Conversely, if a compound is a P-gp substrate, its intracellular accumulation decreases, reducing biological effects such as anticancer activity (Misran *et al.*, 2025).

Following absorption, the compounds are distributed through the bloodstream and lymphatic system (Saritha, Alivelu and Mohammad, 2024). The Volume of Distribution at Steady State (VDss) provides insight into the extent of compound distribution within the body (Misran *et al.*, 2025). The results showed that none of the compounds exhibited VDss values greater than 0.45, which indicate extensive and relatively uniform distribution between tissues and plasma (Amen *et al.*, 2025). Compounds with low VDss values (VDss < –0.15), including lapatinib, 6a, 6e, and 6j, were predicted to preferentially distribute in the plasma rather than in tissues (Rampogu, 2025). Meanwhile, compounds 6b–6d, 6f–6i, and 8a exhibited moderate VDss values (–0.15 to 0.45).

The Fraction Unbound (Fu) parameter describes the proportion of drug not bound to plasma proteins (Flores-Holguín, Frau and Glossman-Mitnik, 2021). The Fu values of the derivatives were relatively low, ranging from 0.099 to 0.246 (Klimoszek *et al.*, 2024). Nevertheless, higher Fu values are associated with increased pharmacological activity due to reduced affinity for plasma proteins, which facilitates better membrane diffusion and transport (Ojuka *et al.*, 2023; Misran *et al.*, 2025).

Blood–brain barrier (BBB) permeability was also evaluated to determine CNS distribution (Amen *et al.*, 2025). Compounds 6b, 6e, and 6j, with Log BB < –1, were predicted to have low brain distribution. This indicates that these compounds do not have the potential to cause brain-related side effects (Saritha, Alivelu and Mohammad, 2024). Only compound 8a showed Log BB > 0.3, indicating high BBB penetration (Flores-Holguín, Frau and Glossman-Mitnik, 2021; El Rhabori *et al.*, 2024). Additionally, several compounds exhibited moderate BBB permeability, with Log BB values ranging from –0.478 to –1.217 (Muharrami, Santoso and Fatmawati, 2024).

Metabolism was assessed based on interactions with cytochrome P450 enzymes. In silico evaluation revealed that none of the compounds inhibited CYP2D6, while all compounds except

lapatinib inhibited CYP1A2. For CYP2C19, only 6i and 6j were non-inhibitors. Regarding CYP2C9 and CYP3A4, all compounds except 6h–6j acted as inhibitors. Inhibition of CYP enzymes may increase active drug concentration, potentially leading to drug–drug interactions, reduced efficacy, or adverse effects (Masudur Rahman Munna *et al.*, 2024; Saritha, Alivelu and Mohammad, 2024). Therefore, careful dose adjustment is required for CYP450 enzyme inhibitors to prevent unexpected metabolic alterations (Bultum *et al.*, 2022).

In the excretion phase, total clearance (CL) values indicated that lapatinib, 6a, 6c–e, 6h–j, and 9a had $CL > 0.5$, suggesting efficient elimination and reduced risk of drug accumulation and toxicity (Khedraoui *et al.*, 2025). Meanwhile, 6b, 6f, and 8a exhibited $CL < 0.5$, indicating slower elimination, prolonged systemic retention, and the potential for enhanced pharmacological activity allowing lower doses to be effective against target cells (Aloui *et al.*, 2024; Masudur Rahman Munna *et al.*, 2024).

Besides ADME parameters, toxicity assessment is critical to ensure safe drug development (Masudur Rahman Munna *et al.*, 2024). AMES toxicity tests showed that only 6e, 6h, and 9a were mutagenic and potentially carcinogenic (Flores-Holguín, Frau and Glossman-Mitnik, 2021; Ramadhan *et al.*, 2025). Hepatotoxicity results indicated that all compounds were predicted to be hepatotoxic, warranting caution in their future application. Maximum tolerated dose (MTD) was used to predict potential toxicity. Compounds with $MTD \leq 0.477 \log (\text{mg/kg/day})$ including 6a, 6e–j, 8a, and 9a were classified as low-toxicity compounds, whereas lapatinib and 6b–d, with $MTD > 0.477$, were considered to have higher toxicity risks (Liu, Tawa and Wallqvist, 2012; Jibrin *et al.*, 2025).

Based on the in silico evaluation, compounds 6b, 6c, 6d, 6e, and 9a were identified as the most promising 1,2,3-triazolo-indole-2-carboxylate derivatives targeting HER2. All compounds complied with Lipinski's rule and exhibited high total clearance; however, they shared several ADMET limitations, including moderate to low VDss and BBB values, relatively low Fu, inhibition of several CYP enzymes (except CYP2D6), and potential hepatotoxicity.

Among the evaluated compounds, 6d emerged as the most promising candidate due to its strong binding affinity toward HER2, moderate aqueous solubility, high Caco-2 permeability, non-substrate behavior toward P-gp, and non-mutagenic properties. Although it showed moderate VDss, Log BB, and a high MTD, compound 6d demonstrated advantages over lapatinib, which exhibited lower Caco-2 permeability, lower VDss, and P-gp substrate behavior. Compound 6c showed a similar ADMET profile to 6d but had a lower docking score.

Compound 9a exhibited the highest docking score, indicating strong HER2 affinity; however, its lower VDss, positive AMES toxicity, and moderate BBB penetration limited its overall potential, despite favorable solubility, high Caco-2 permeability, and non-P-gp substrate behavior. Compound 6e showed a better docking score than 6d but was limited by low Caco-2 permeability, mutagenicity, P-gp substrate behavior, and lower VDss, making lapatinib superior in terms of toxicity profile. Nonetheless, compound 6e also demonstrated some favorable characteristics, such as moderate aqueous solubility comparable to 6d, low BBB values, and a low MTD. Compound 6b demonstrated good solubility, high Caco-2 permeability, low BBB penetration, and negative AMES toxicity, but its high MTD, moderate VDss, and P-gp substrate behavior. While compound 6d was superior overall, compound 6b showed certain advantages compared to lapatinib, as lapatinib acted as a P-gp substrate and exhibited lower VDss values. Overall, compound 6d displayed the most balanced docking and ADMET profile among the tested compounds, supporting its selection for further experimental investigation.

Table 4. ADMET Analysis

Compounds	Parameters														
	Absorption			Distribution			Metabolism					Excretion	Toxicity		
	Log S (log mol/L)	Caco-2 permeability (log Papp 10 ⁻⁶ cm/s)	P-gp substrate	VDss (log L/kg)	Fu	BBB (log BB)	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	CL (log ml/min/kg)	AMES toxicity	Hepato toxicity	MTD (Log mol/kg/day)
lapatinib	-4.035	0.148	✓	-0.34	0.246	-0.732	x	✓	✓	x	✓	0.559	x	✓	0.578
6a	-3.666	1.211	x	-0.206	0.108	-0.537	✓	✓	✓	x	✓	0.939	x	✓	0.419
6b	-3.916	1.239	✓	-0.092	0.112	-1.217	✓	✓	✓	x	✓	0.472	x	✓	0.472
6c	-4.330	1.234	x	0.01	0.108	-0.699	✓	✓	✓	x	✓	0.52	x	✓	0.891
6d	-4.237	1.214	x	-0.109	0.112	-0.524	✓	✓	✓	x	✓	0.907	x	✓	0.869
6e	-4.029	-0.416	✓	-0.83	0.099	-1.039	✓	✓	✓	x	✓	0.887	✓	✓	0.226
6f	-3.757	1.225	x	-0.092	0.116	-0.727	✓	✓	✓	x	✓	0.44	x	✓	0.407
6g	-3.836	1.159	✓	-0.043	0.125	-0.888	✓	✓	✓	x	✓	0.354	x	✓	0.354
6h	-3.071	1.059	x	0.144	0.154	-0.478	✓	✓	x	x	x	0.867	✓	✓	-0.161
6i	-2.663	-0.077	✓	0.127	0.216	-0.591	✓	x	x	x	x	0.772	x	✓	0.14
6j	-3.655	0.726	x	-0.368	0.224	-1.005	✓	x	x	x	x	0.809	x	✓	0.316
8a	-3.426	1.246	x	-0.059	0.142	0.467	✓	✓	✓	x	✓	0.437	x	✓	0.326
9a	-3.766	1.08	x	-0.741	0.224	-0.61	✓	✓	✓	x	✓	0.6	✓	✓	0.439

Notes: BBB = Blood-Brain Barrier; P-gp = P-glycoprotein; VDss = Steady-State Volume of Distribution; Total CL = Total Clearance; MTD = Maximum Tolerated Dose (human)

4. Conclusion

Based on *in silico* molecular docking and ADMET evaluation, the 1,2,3-triazolo-indole-2-carboxylate derivatives demonstrated potential as HER2-targeted anticancer candidates. Among the evaluated compounds, 6d emerged as the most promising candidate due to its strong binding affinity toward HER2 and its balanced pharmacokinetic profile, including moderate aqueous solubility, high Caco-2 permeability, non-substrate behavior toward P-gp, and non-mutagenic properties.

Overall, ADMET data suggest that these compounds exhibit favorable absorption and elimination profiles; however, challenges remain in terms of distribution parameters (VDss, Fu, and BBB), potential hepatotoxicity, and CYP enzyme interactions. Therefore, further *in vitro* and *in vivo* studies, along with structural optimization, are necessary to improve distribution, safety, and metabolic stability prior to further drug development.

References

- Aini, N.S. *et al.* (2022) "In Silico Screening of Bioactive Compounds from *Garcinia mangostana* L. Against SARS-CoV-2 via Tetra Inhibitors," *Pharmacognosy Journal*, 14(5), pp. 575–579. Available at: <https://doi.org/10.5530/pj.2022.14.138>.
- Akbar, N.H. *et al.* (2025) "Screening, docking, and molecular dynamics analysis of *Mitragyna speciosa* (Korth.) compounds for targeting HER2 in breast cancer," *Current Research in Structural Biology*, 10. Available at: <https://doi.org/10.1016/j.crstbi.2025.100171>.
- Aloui, M. *et al.* (2024) "Design of novel potent selective survivin inhibitors using 2D-QSAR modeling, molecular docking, molecular dynamics, and ADMET properties of new MX-106 hydroxyquinoline scaffold derivatives," *Heliyon*, 10(19). Available at: <https://doi.org/10.1016/j.heliyon.2024.e38383>.
- Amen, L.N. *et al.* (2025) "An investigation of the drug discovery potential of phytochemicals from *Monodora* species through in silico ADMET profiling," *Scientific African*, 30. Available at: <https://doi.org/10.1016/j.sciaf.2025.e03060>.
- Anantoju, K.K. *et al.* (2024) "An efficient synthesis and anticancer evaluation of 1,2,3-triazolo-indole-2-carboxylate derivatives," *Results in Chemistry*, 7. Available at: <https://doi.org/10.1016/j.rechem.2024.101536>.
- Bray, F. *et al.* (2024) "Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA: A Cancer Journal for Clinicians*, 74(3), pp. 229–263. Available at: <https://doi.org/10.3322/caac.21834>.
- Bultum, L.E. *et al.* (2022) "In silico activity and ADMET profiling of phytochemicals from Ethiopian indigenous aloes using pharmacophore models," *Scientific Reports*, 12(1). Available at: <https://doi.org/10.1038/s41598-022-26446-x>.
- Fisusi, F.A. and Akala, E.O. (2019) "Drug Combinations in Breast Cancer Therapy," *Pharmaceutical Nanotechnology*, 7(1), pp. 3–23. Available at: <https://doi.org/10.2174/2211738507666190122111224>.
- Flores-Holguín, N., Frau, J. and Glossman-Mitnik, D. (2021) "In Silico Pharmacokinetics, ADMET Study and Conceptual DFT Analysis of Two Plant Cyclopeptides Isolated From Rosaceae as a Computational Peptidology Approach," *Frontiers in Chemistry*, 9. Available at: <https://doi.org/10.3389/fchem.2021.708364>.
- Gautama, W. (2022) "Breast Cancer in Indonesia in 2022: 30 Years of Marching in Place," *Indonesian Journal of Cancer*, 16(1), p. 1. Available at: <https://doi.org/10.33371/ijoc.v16i1.920>.
- Jibrin, A. *et al.* (2025) "Molecular design, ADMET evaluation, and molecular dynamic simulation of some potent sulfonamide-based compounds as anti-tuberculosis agents," *In Silico Research in Biomedicine*, 1, p. 100035. Available at: <https://doi.org/10.1016/j.insr.2025.100035>.
- Kamel, M.G. *et al.* (2025) "Utility of 6-aza-2-thiothymine in the synthesis of novel [1,2,4]triazolo[4,3-b][1,2,4]triazin-7-one derivatives: synthesis, structure elucidation, molecular docking and in vitro anti-lung cancer activity," *RSC Advances*, 15(8), pp. 6015–6031. Available at: <https://doi.org/10.1039/d4ra08958h>.
- Kavarthapu, R., Anbazhagan, R. and Dufau, M.L. (2021) "Crosstalk between PRLR and EGFR/HER2 signaling pathways in breast cancer," *Cancers*. MDPI. Available at: <https://doi.org/10.3390/cancers13184685>.

- Khedraoui, M. *et al.* (2025) "In silico exploration of Aloe vera leaf compounds as dual AChE and BChE inhibitors for Alzheimer's disease therapy," *Current Pharmaceutical Analysis*, 21(4), pp. 238–248. Available at: <https://doi.org/10.1016/j.cpan.2025.03.005>.
- Klimoszek, D. *et al.* (2024) "Study of the Lipophilicity and ADMET Parameters of New Anticancer Diquinothiazines with Pharmacophore Substituents," *Pharmaceuticals*, 17(6). Available at: <https://doi.org/10.3390/ph17060725>.
- Li, X. and Huang, T. (2025) "Advances in the intrinsic signaling pathway interactions and clinical translation of HR+/HER2+ breast cancer," *Breast Cancer*. Springer, pp. 1216–1243. Available at: <https://doi.org/10.1007/s12282-025-01779-3>.
- Lina, L. *et al.* (2025) "Purification and molecular docking of α -glucosidase inhibitory peptides from mung bean protein hydrolysates," *LWT*, 222. Available at: <https://doi.org/10.1016/j.lwt.2025.117545>.
- Liu, R., Tawa, G. and Wallqvist, A. (2012) "Locally weighted learning methods for predicting dose-dependent toxicity with application to the human maximum recommended daily dose," *Chemical Research in Toxicology*, 25(10), pp. 2216–2226. Available at: <https://doi.org/10.1021/tx300279f>.
- Mariam Raju, R. *et al.* (2024) "EGFR as therapeutic target to develop new generation tyrosine kinase inhibitors against breast cancer: A critical review," *Results in Chemistry*. Elsevier B.V. Available at: <https://doi.org/10.1016/j.rechem.2024.101490>.
- Masudur Rahman Munna, M. *et al.* (2024) "Unveiling promising phytochemicals from Moringa oleifera as dual inhibitors of EGFR(T790M/C797S) and VEGFR-2 in non-small cell lung cancer through in silico screening, ADMET, dynamics simulation, and DFT analysis," *Journal of Genetic Engineering and Biotechnology*, 22(3). Available at: <https://doi.org/10.1016/j.jgeb.2024.100406>.
- Misran, E. *et al.* (2025) "In silico evaluation of guarana's bioactive compounds for diabetes, inflammation, and oxidative stress: Insights from molecular docking and ADMET profiling," *Results in Chemistry*, 16. Available at: <https://doi.org/10.1016/j.rechem.2025.102394>.
- Moy, B. and Goss, P.E. (2007) "Lapatinib-Associated Toxicity and Practical Management Recommendations," *The Oncologist*, 12(7), pp. 756–765. Available at: <https://doi.org/10.1634/theoncologist.12-7-756>.
- Muharrami, L.K., Santoso, M. and Fatmawati, S. (2024) "Chemical profiles, in silico pharmacokinetic and toxicity prediction of bioactive compounds from Boesenbergia rotunda," *Case Studies in Chemical and Environmental Engineering*, 10. Available at: <https://doi.org/10.1016/j.cscee.2024.100992>.
- Nikakhtar, S. *et al.* (2025) "Novel phosphoramidate ligand shows promise as a cytotoxic agent against breast cancer: Molecular docking, ADMET studies and quantum studies," *Results in Chemistry*, 16. Available at: <https://doi.org/10.1016/j.rechem.2025.102520>.
- Ojuka, P. *et al.* (2023) "Phytochemistry of the Vepris genus plants: A review and in silico analysis of their ADMET properties," *South African Journal of Botany*. Elsevier B.V., pp. 106–114. Available at: <https://doi.org/10.1016/j.sajb.2023.03.057>.
- Okon, I.A. *et al.* (2025) "In silico molecular docking study and antihypertensive property of Gongronema latifolium Benth. ethanol leaf extract in dexamethasone-induced hypertension in Wistar rats," *Phytomedicine Plus*, 5(4). Available at: <https://doi.org/10.1016/j.phyplu.2025.100892>.
- Oktomalioputri, B. *et al.* (2025) "Network pharmacology, molecular docking, and molecular dynamics analyses to explore the molecular mechanism of paclitaxel in atherosclerosis therapy," *Narra J*, 5(2), p. e2140. Available at: <https://doi.org/10.52225/narra.v5i2.2140>.
- Pan, L. *et al.* (2024) "HER2/PI3K/AKT pathway in HER2-positive breast cancer A review," *Medicine (United States)*. Lippincott Williams and Wilkins, p. e38508. Available at: <https://doi.org/10.1097/MD.00000000000038508>.
- Qasem, A. (2025) "GC-MS Analysis, Antimicrobial Activity, and Genotoxicity of Pimpinella anisum Essential oil: In Vitro, ADMET and Molecular Docking Investigations," *Phyton-International Journal of Experimental Botany*, 94(3), pp. 809–824. Available at: <https://doi.org/10.32604/phyton.2025.062683>.
- Rajkumar, K. *et al.* (2025) "Anticancer evaluation of Myo-inositol through carbonic anhydrase IV inhibition activity: A spectroscopic, quantum computational, topological, drug-likeness and in-silico molecular docking studies," *Results in Chemistry*, 17. Available at: <https://doi.org/10.1016/j.rechem.2025.102605>.

- Ramadhan, M.A. *et al.* (2025) "Extraction of Morinda Citrifolia Leaves Essential Oils as EGFR Inhibitor in Non-Small Cells Lung Cancer: In Silico Approach," *J. Chem. Sci*, 14(2). Available at: <http://journal.unnes.ac.id/sju/index.php/ijcs>.
- Rampogu, S. (2025) "Structure-based pharmacophore modeling, molecular docking and ADMET analysis to discover potential hMPV inhibitors," *In Silico Research in Biomedicine*, 1, p. 100031. Available at: <https://doi.org/10.1016/j.insr.2025.100031>.
- El Rhabori, S. *et al.* (2024) "Design, 3D-QSAR, molecular docking, ADMET, molecular dynamics and MM-PBSA simulations for new anti-breast cancer agents," *Chemical Physics Impact*, 8. Available at: <https://doi.org/10.1016/j.chphi.2023.100455>.
- Saritha, K., Alivelu, M. and Mohammad, M. (2024) "Drug-likeness analysis, in silico ADMET profiling of compounds in Kedrostis foetidissima (Jacq.) Cogn, and antibacterial activity of the plant extract," *In Silico Pharmacology*, 12(2). Available at: <https://doi.org/10.1007/s40203-024-00240-1>.
- Shil, R. and Ankar, R. (2025) "Chemotherapy-Induced Peripheral Neuropathy in Breast Cancer Patients: A Narrative Review," *Archives of Breast Cancer*. Farname Inc., pp. 15–22. Available at: <https://doi.org/10.32768/abc.202512115-22>.
- Shrestha, A. *et al.* (2022) "Molecular Docking and Dynamics Simulation of Several Flavonoids Predict Cyanidin as an Effective Drug Candidate against SARS-CoV-2 Spike Protein," *Advances in Pharmacological and Pharmaceutical Sciences*, 2022. Available at: <https://doi.org/10.1155/2022/3742318>.
- Sindi, E.R. *et al.* (2025) "Assessment of Annona muricata Phytochemicals as 17 β -HSD1 Inhibitors through Molecular Docking, Dynamics Simulation, DFT, and ADMET Analyses," *Journal of Cellular and Molecular Medicine*, 29(21). Available at: <https://doi.org/10.1111/jcmm.70904>.
- Solanki, P. *et al.* (2024) "Targeting the cyclin-dependent kinase family in anticancer drug discovery: From computational to experimental studies," *Chemical Physics Impact*, 9. Available at: <https://doi.org/10.1016/j.chphi.2024.100768>.
- Toni, N.P.D. and Azra, F. (2022) "Modeling the Relationship of Net Atomic Charge with the Activity of 5-Aminopyrazole Derivative Compounds as Antioxidants with AM1 Method," *EKSAKTA: Berkala Ilmiah Bidang MIPA*, 23(04), pp. 242–252. Available at: <https://doi.org/10.24036/eksakta/vol23-iss04/334>.
- Utama, M.S. *et al.* (2025) "Barriers to radiotherapy completion in breast cancer patients: A retrospective analysis from a tertiary hospital in Indonesia," *Journal of Cancer Policy*, 44. Available at: <https://doi.org/10.1016/j.jcpo.2025.100574>.
- Zaman, H. *et al.* (2024) "Novel pyrimidine linked acyl thiourea derivatives as potent α -amylase and proteinase K inhibitors: design, synthesis, molecular docking and ADME studies," *RSC Advances*, 14(45), pp. 33235–33246. Available at: <https://doi.org/10.1039/d4ra05799f>.
- Zeki, N.M. and Mustafa, Y.F. (2024) "Digital alchemy: Exploring the pharmacokinetic and toxicity profiles of selected coumarin-heterocycle hybrids," *Results in Chemistry*, 10. Available at: <https://doi.org/10.1016/j.rechem.2024.101754>.