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In Silico Study of Indole-Tetrazole Hybrid Derivatives as Potential Breast Cancer Anticancer Candidates Through Molecular Docking Against HER2, ADMET Profile Prediction, and Drug-Likeness Assessment

Zafrinaldi, Fajriah Azra*

Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Negeri Padang, West Sumatra, Indonesia
*e-mail: bunda_syasfa@yahoo.com

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Abstract: Breast cancer remains one of the leading causes of mortality among women worldwide, highlighting the urgent need for the development of more effective therapeutic agents with fewer adverse effects. This study aimed to analyze the potential of indole–tetrazole hybrid derivatives as anti-breast cancer agents by comparing their performance with the reference compound Bazedoxifen. The design of indole–tetrazole hybrid compounds, which integrates two pharmacologically active moieties within a single molecular framework, is expected to enhance biological activity and strengthen interactions with target proteins. The methods employed in this study included molecular docking to evaluate ligand binding affinity to the HER2 protein (PDB ID: 7PCD), Lipinski's Rule of Five analysis to assess drug-likeness for oral administration, and ADMET prediction to evaluate pharmacokinetic and toxicity profiles. SwissADME and pkCSM were used to assess the drug-likeness of the compounds based on Lipinski's Rule of Five and to predict their ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties. The key parameters analyzed in the docking study were binding affinity (ΔG), root mean square deviation (RMSD), and the types of interactions with amino acid residues at the active site. The results indicated that most compounds satisfied Lipinski's criteria and exhibited good absorption profiles, as well as non-mutagenic properties based on Ames test predictions. Compound 10 exhibited the best binding affinity (−13.0444 kcal/mol) and showed interactions with key amino acid residues, indicating a stable ligand–protein complex. Overall, compound 10 was identified as the most promising candidate for further development as an anti-breast cancer agent. However, further experimental validation through both in vitro and in vivo studies is required to confirm the compound's pharmacological potential and safety profile before it can be considered for drug development.

Keywords: ADMET; Breast Cancer; Drug-Likeness Assessment; Indole–tetrazole; Molecular Docking.

Introduction

Cancer is a disease characterized by uncontrolled cell proliferation, which leads to abnormal cell growth that can invade surrounding tissues and subsequently spread to other parts of the body. This complex pathological process remains a major challenge in modern medicine [1]. According to the GLOBOCAN 2022 report, approximately 20 million new cancer cases were recorded worldwide, with an estimated 9.7 million deaths. Among these, breast cancer is one of the most commonly diagnosed cancers in women and accounts for approximately 0.5 million deaths globally [2].

Breast cancer (carcinoma mammae) is a malignant disease originating from breast tissues, either in the ductal structures or the milk-producing glands (lobules). It occurs when breast cells lose control over their growth, leading to abnormal, rapid, and uncontrolled proliferation [3]. Breast cancer is one of the leading causes of cancer-related mortality among individuals from adolescence to adulthood. In women, the risk of mortality has shown a consistent increase in recent years. For instance, the risk was approximately 1 in 49 individuals in 2020 and increased to 1 in 48 by 2024, particularly among women under the age of 50 [4].

One of the primary treatment approaches for breast cancer patients is chemotherapy. Chemotherapy involves the use of specialized drugs to eliminate cancer cells and can be administered through various routes, including injection and oral forms such as tablets or syrups. These anticancer agents generally act by inhibiting or disrupting tumor growth and metastasis, thereby preventing the proliferation of cancer cells. Unlike surgery or radiotherapy, which target specific localized areas, chemotherapeutic agents are distributed systemically throughout the body via the bloodstream [5].

However, the use of chemotherapeutic agents is often associated with toxic side effects, the severity of which may vary among individuals [6]. Common adverse effects include nausea, vomiting, peripheral neuropathy, diarrhea, hair loss (alopecia), increased susceptibility to infections, oral inflammation (stomatitis), and muscle pain (myalgia) [7].

Therefore, to improve therapeutic efficacy, enhance biological activity, and minimize the adverse effects associated with currently available treatments, the development of novel therapeutic agents is highly warranted. In a previous study [8], a search for novel therapeutic agents against breast cancer was conducted using the compound 1-(4-Decylbenzoyl)-3-methylthiourea, which targets the HER2 receptor, resulting in a binding affinity of −8.64

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kcal/mol. HER2 is a transmembrane receptor tyrosine kinase that plays a crucial role in regulating cell growth, proliferation, and division. This protein can dimerize with itself or with other members of the epidermal growth factor receptor (EGFR) family through both ligand-dependent and ligand-independent mechanisms. These interactions subsequently activate various intracellular signaling pathways that contribute to enhanced cellular proliferation, survival, and migration [9]. The PI3K/AKT/mTOR pathway is a major signaling cascade that regulates cell growth, proliferation, and survival. Activation of this pathway is initiated by the binding of growth factors to receptor tyrosine kinases (RTKs), which triggers the conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) into phosphatidylinositol 3,4,5-trisphosphate (PIP3) by phosphoinositide 3-kinase (PI3K). Subsequently, PIP3 activates AKT through phosphorylation mediated by phosphoinositide-dependent kinase 1 (PDK1) and mammalian target of rapamycin complex 2 (mTORC2), leading to the activation of various cellular responses that promote proliferation and inhibit apoptosis [10].

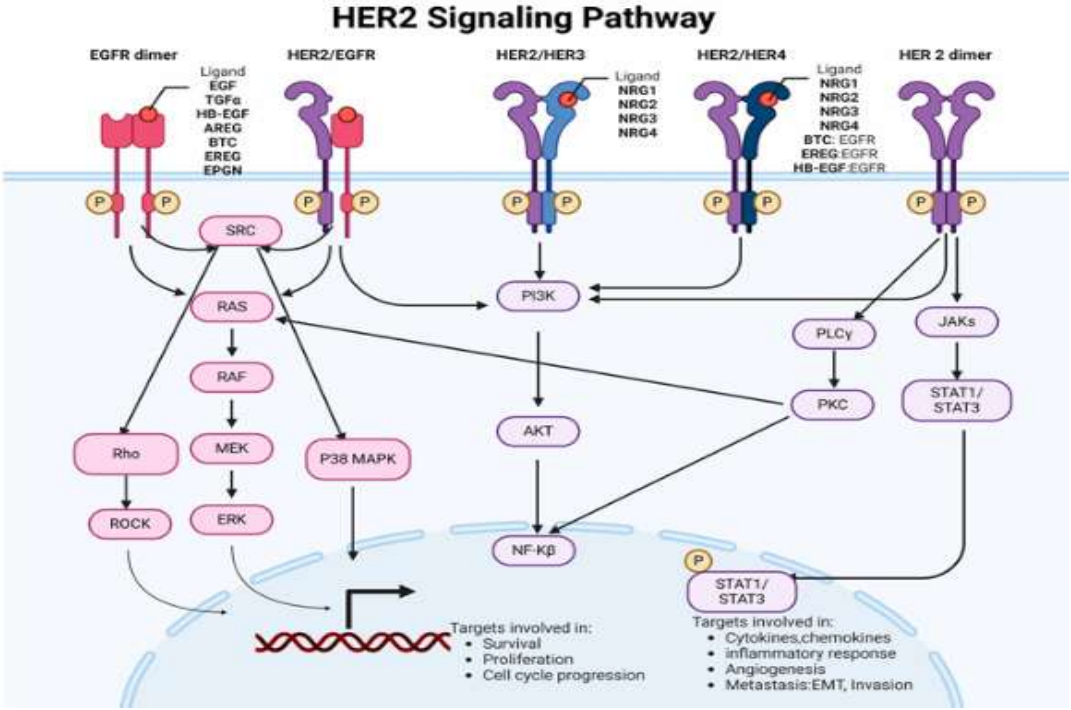


Figure 1. Schematic representation of the HER2 signaling pathways. These pathways contribute to the regulation of gene expression, cell cycle progression, cell motility, and other cellular functions.

Under abnormal conditions, amplification of the HER2 gene may occur, resulting in the overexpression of HER2 receptors on the surface of cancer cells. This elevated expression leads to excessive activation of growth signaling pathways, thereby promoting uncontrolled cell proliferation and contributing to the progression of more aggressive tumors. Approximately 15–20% of breast cancer cases exhibit HER2 overexpression and are classified as HER2-positive breast cancer [11]. Trastuzumab is a monoclonal antibody that targets the HER2 receptor and is widely used in the treatment of HER2-positive breast cancer. The drug has been approved by the Food and Drug Administration and the European Medicines Agency for the management of HER2-positive breast cancer in adjuvant, neoadjuvant, and metastatic settings. Despite its proven clinical efficacy, trastuzumab therapy may be associated with cardiotoxic effects, including reduced left ventricular function and congestive heart failure [12]. Therefore, HER2 has emerged as a critical molecular target in the development of anticancer therapies, particularly for breast cancer, due to its pivotal role in tumor growth, progression, and disease aggressiveness. [13]. However, based on previous research conducted [8], The binding affinity of the compound toward the HER2 receptor, with a value of −8.64 kcal/mol, was considered suboptimal. [14] Previous studies have also investigated the HER2 receptor and reported compounds with favorable binding affinities and stable interactions with the target protein. However, these studies primarily focused on molecular docking results and the stability of the protein–ligand complexes. Such an approach does not provide a comprehensive assessment of the suitability of these compounds as drug candidates, as it excludes drug-likeness evaluation based on Lipinski's Rule of Five or ADMET profiling. Indeed, compounds exhibiting high binding affinity do not necessarily possess favorable pharmacokinetic properties or acceptable toxicity profiles for therapeutic use. Therefore, a more comprehensive approach that integrates molecular docking with Lipinski's Rule of Five and ADMET analyses is required to ensure that the selection of potential HER2 inhibitors is based not only on their binding affinity for the target protein but also on their overall drug-likeness and pharmacokinetic suitability. Accordingly, the present study aimed to identify compounds that not only exhibit stronger binding affinities toward the HER2 receptor but also demonstrate favorable drug-likeness and ADMET profiles, thereby improving their potential for further drug development.

Heterocyclic compounds have been widely utilized in the treatment of various diseases, including cancer. This is primarily because heterocyclic rings are commonly found in

essential biological molecules such as DNA, RNA, and vitamins, making them highly relevant in medicinal chemistry. Many anticancer drugs contain heterocyclic ring systems, among which indole and tetrazole are of particular interest [15]. Indole-based compounds are known to exhibit significant potential as chemotherapeutic agents, for example, indole-3-carbinol has been reported to inhibit the growth of estrogen-dependent breast cancer cells [16]. A study by [17] on indole-based derivatives demonstrated that the indole scaffold is a promising structural framework for developing anticancer agents, particularly as HER2 inhibitors. One of the investigated compounds exhibited the strongest inhibitory activity against both HER2 and CDK-1/cyclin B, highlighting its potential as a multitarget inhibitor. Molecular docking analysis revealed that the indole scaffold interacted favorably with the HER2 protein, resulting in a stable binding mode. Furthermore, the therapeutic potential of the compound was supported by both in vitro and in silico findings, which consistently demonstrated its biological activity. Collectively, these findings suggest that the indole scaffold is a promising molecular framework for further structural optimization to enhance its biological activity and selectivity as a potential anticancer agent. Indole alkaloids possess diverse therapeutic activities, largely due to their basic chemical characteristics conferred by the nitrogen-containing pyrrole ring, which plays an important role in mediating biological interactions and pharmacological effects [18].

In addition, the tetrazole moiety has gained increasing attention in anticancer drug development due to its structural similarity to other functional groups, allowing it to act as a bioisostere. Tetrazole derivatives also demonstrate favorable metabolic stability, making them suitable candidates for drug development [19]. Therefore, the combination of indole and tetrazole structures into a single hybrid molecule may result in compounds with enhanced biological activity and improved stability within the body. A previous study [20] demonstrated that the hybridization of indole and tetrazole scaffolds resulted in compounds with promising anticancer activity, favorable drug-likeness properties, and strong molecular docking performance. However, the study used estrogen receptor alpha (ER-α) as the molecular target rather than HER2.

Numerous studies have demonstrated that both indole and tetrazole derivatives possess promising anticancer activities and have been widely employed in the development of novel heterocyclic compounds. Tetrazole derivatives are known to enhance metabolic stability, improve bioavailability, and strengthen binding affinity toward biological targets, whereas indole derivatives exhibit broad-spectrum anticancer activity against a variety of molecular targets. Nevertheless, most previous studies have evaluated these scaffolds either individually or in combination with other pharmacophores targeting proteins other than HER2. Consequently, studies specifically investigating the potential of indole–tetrazole hybrid derivatives as HER2 inhibitors using a molecular docking approach remain limited.

Based on the aforementioned background, this study aimed to evaluate the potential of indole–tetrazole hybrid derivatives as inhibitors of breast cancer cell growth by targeting the HER2 protein using an in silico approach. In addition to molecular docking, the study incorporated ADMET profile prediction and drug-likeness assessment to provide a comprehensive evaluation of the pharmacological potential, pharmacokinetic properties, and drug-like characteristics of the investigated compounds. The findings of this study are expected to provide preliminary scientific insights into the development of more effective anti-breast cancer drug candidates.

Research Methods

Software and Hardware

The in silico analysis using molecular docking was performed on a laptop equipped with an Intel® Core™ i5-6300U processor (2.50 GHz) and 8.00 GB of installed RAM (7.88 GB usable). The Molecular Operating Environment (MOE) software version 2019.0102 was used for protein and ligand preparation and docking simulations. Protein structures were obtained from the Protein Data Bank (PDB). In addition, SwissADME and pkCSM web servers were utilized to evaluate the Lipinski's Rule of Five parameters and ADMET profiles of the studied compounds.

Materials

The tyrosine kinase protein HER2 (PDB ID: 7PCD) was retrieved from the Protein Data Bank. The ligands used in this study were synthetic indole–tetrazole hybrid derivatives, as described in the referenced article [20].

Protein Optimization

The downloaded PDB file was imported into MOE. Unnecessary components, such as the co-crystallized ligand and water molecules, were removed using the sequence editor. Protonation was then performed using the Protonate 3D feature to simulate physiological conditions at neutral pH. Subsequently, partial atomic charges were calculated, followed by energy minimization to stabilize the protein structure. The prepared protein was then saved in PDB or MDB format for further docking analysis.

Ligand preparation

Fifteen indole–tetrazole hybrid derivatives were obtained from a previously published study [20], in which the compounds had been successfully synthesized and demonstrated anticancer activity against the MCF-7 breast cancer cell line. The chemical structures of all compounds were available in two-dimensional (2D) format, enabling their conversion into three-dimensional (3D) models for subsequent molecular docking studies.

Initially, the 2D structures of the fifteen indole–tetrazole derivatives were drawn using ChemDraw Pro 8.0 and saved in MOL format. The resulting files were then imported into the Molecular Operating Environment (MOE) software for ligand preparation. Each structure was processed using the Wash function, followed by the addition of hydrogen atoms, calculation of partial atomic charges, and energy minimization using the MMFF94X force field. Finally, the optimized ligand structures were saved in MDB format for subsequent molecular docking analysis.

Validation of Docking Methods

The molecular docking protocol was validated using a re-docking approach involving the native ligand and the prepared HER2 protein structure (PDB ID: 7PCD). The 7PCD structure was selected because it contains a co-crystallized ligand that serves as a reliable reference for validating the docking protocol. In addition, this protein structure possesses high crystallographic resolution, providing accurate and reliable three-dimensional structural information for molecular interaction analysis. The active site of the HER2 protein also contains key amino acid residues involved in interactions with the co-crystallized ligand, facilitating the identification of the ligand-binding region. Structural information for the HER2 protein (PDB ID: 7PCD) was obtained from the RCSB Protein Data Bank.

The re-docking procedure was performed to evaluate the accuracy of the docking protocol by comparing the position and conformation of the re-docked ligand with those of the native ligand in the original crystal structure. All validation procedures were performed using the Molecular Operating Environment (MOE) software under the same docking conditions used for the test compounds. Initial ligand placement was performed using the Triangle Matcher algorithm, followed by pose refinement using the Induced Fit protocol. Both the initial and final docking poses were evaluated using the London dG scoring function.

Molecular Docking

The prepared protein and ligand structures were imported into the MOE software for docking simulations. The docking process was carried out using the Triangle Matcher algorithm for initial ligand placement, followed by the Induced Fit protocol to allow structural adjustments within the binding site. Both initial and final scoring were performed using the London dG scoring function. The docking results were subsequently saved and analyzed based on binding affinity values and the interactions between the ligands and the active site residues of the target protein.

Lipinski's Five-Rule Screening

The indole–tetrazole hybrid derivatives were systematically screened to evaluate their suitability as drug candidates. This process employed Lipinski's Rule of Five as an initial criterion to assess the compounds' potential for oral administration. The evaluated parameters included molecular weight (< 500 g/mol), the number of hydrogen bond donors (< 5), the number of hydrogen bond acceptors (< 10), and the partition coefficient (LogP < 5) [21]. These parameters serve as general guidelines to determine whether a compound possesses favorable drug-like properties. All parameters were calculated by inputting the SMILES structures of the indole–tetrazole hybrid derivatives into the SwissADME web server (https://www.swissadme.ch/).

Pharmacokinetic Studies

The pharmacokinetic and toxicological properties of the compounds were predicted to provide a preliminary assessment of their safety and biological profiles in a rapid and efficient manner prior to further experimental validation. Key parameters evaluated included absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles of the studied compounds [22]. These parameters were analyzed by inputting the SMILES structures of the indole–tetrazole hybrid derivatives into the pkCSM web server (https://biosig.lab.uq.edu.au/pkcsm/.

Results and Discussion

Lipinski's Rule of Five prediction

Lipinski's Rule of Five is an experimental and computational guideline used to estimate drug solubility in aqueous and lipid environments, membrane permeability, and overall pharmacological effectiveness in drug discovery. Pharmacologists and medicinal chemists have extensively investigated the physicochemical properties that characterize compounds with favorable oral bioavailability [23].

At this stage, four key parameters are generally identified as being associated with the solubility and permeability of a compound, namely molecular weight, LogP value, and the number of hydrogen bond donors and acceptors [21].

Tabel 1. Result of the Lipinski's Rule of Five screening

Compounds	Molecular Weight (<500 g/mol)	Proton Donor (<5)	Proton Acceptor (<10)	Log P	Rotable Bonds
1-benzyl-3-(2-(4-methylbenzyl)-2H-tetrazol-5-yl)-1H-indole	379.46	0	3	3.87	5
1-benzyl-3-(2-(3-chlorobenzyl)-2H-tetrazol-5-yl)-1H-indole	399.88	0	3	3.89	5
1-benzyl-3-(2-(3,4-dichlorobenzyl)-2H-tetrazol-5-yl)-1H-indole	434.32	0	3	4.04	5
1-benzyl-3-(2-(2,4-dichlorobenzyl)-2H-tetrazol-5-yl)-1H-indole	434.32	0	3	4.19	5
1-benzyl-3-(2-(4-chlorobenzyl)-2H-tetrazol-5-yl)-1H-indole	399.88	0	3	3.86	5
1-benzyl-3-(2-(4-fluorobenzyl)-2H-tetrazol-5-yl)-1H-indole	383.42	0	4	3.73	5
1-benzyl-3-(2-(3-methoxybenzyl)-2H-tetrazol-5-yl)-1H-indole	395.46	0	4	3.90	6
3-(2-benzyl-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	379.46	0	3	3.76	5

3-(2-(3-chlorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	393.48	0	3	4.13	5
3-(2-(3,4-dichlorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	448.35	0	3	3.39	5
3-(2-(2,4-dichlorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	448.35	0	3	4.26	5
3-(2-(4-chlorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	413.90	0	3	4.18	5
3-(2-(4-fluorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	397,45	0	4	4	5
3-(2-(3-methoxybenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	409.48	0	4	3.83	6
1-benzyl-3-(2-benzyl-2H-tetrazol-5-yl)-1H-indole	365.43	0	3	3.59	5
Bazedoxifen	470.60	2	4	4.06	7

Based on the data obtained, nearly all compounds met the required criteria. The majority of the compounds exhibited molecular weights ranging from 379.46 g/mol (compounds 1 and 8) to 448.35 g/mol (compounds 10 and 11), indicating they fall within the acceptable range. The LogP values of all analyzed compounds were consistent with the criteria of Lipinski's Rule of Five, remaining within the acceptable limit (≤ 5). The observed LogP values ranged from 3.39 (compound 10) to 4.26 (compound 11), suggesting that all compounds possess optimal lipophilicity.

Regarding hydrogen-bonding capacity, the analysis revealed that all compounds had zero hydrogen-bond donors. This indicates that the compounds lack functional groups capable of donating hydrogen atoms for hydrogen bond formation. According to Lipinski's Rule of Five, the acceptable limit for hydrogen bond donors is up to five; therefore, a value of zero remains within the permissible range and still qualifies the compounds as potential oral drug candidates [24]. From a molecular interaction perspective, the absence of hydrogen-bond donors may reduce the compounds' ability to form specific interactions with amino acid residues at the protein's active site. Nevertheless, the compounds can still interact through alternative mechanisms, such as hydrogen bond acceptors, hydrophobic interactions, and π–π interactions involving the indole aromatic ring, all of which contribute to the stability of the ligand–protein complex.

A low or zero number of hydrogen-bond donors generally increases a compound's lipophilicity, which may enhance membrane permeability and support oral absorption. However, increased lipophilicity can potentially reduce aqueous solubility; therefore, a balance between solubility and permeability must be carefully considered in further evaluations [25]. Although a hydrogen bond donor value of zero is still considered acceptable, the results should not be interpreted from a single parameter alone. Other physicochemical and pharmacokinetic properties must also be taken into account to more accurately assess the compound's potential as an effective drug candidate. Regarding hydrogen-bond acceptors, all compounds exhibit values ≤ 5, indicating they remain within the acceptable range.

Overall, the analysis indicates that the compounds possess physicochemical properties consistent with the criteria for ideal oral drug candidates. Based on the evaluated data, these compounds are considered suitable for further investigation as potential anticancer drug candidates.

ADMET Validation

ADMET is a term in pharmacology used to describe how a drug behaves within the body. After administration, whether oral, intravenous, or via other routes, a drug undergoes several sequential processes: absorption (A), distribution throughout the body (D), metabolic transformation (M), excretion (E), and potential for toxic effects (T). These processes are critical to evaluate, as they determine whether a drug can reach its target site, exert its therapeutic effect effectively, and maintain an acceptable safety profile without inducing harmful side effects [26].

To assess whether the test compounds can function effectively as drugs in the body, their properties were evaluated using ADMET parameters. The analysis includes key parameters such as aqueous solubility, volume of distribution (VD), plasma protein binding (PPB), blood–brain barrier (BBB) permeability, potential inhibition of cytochrome P450 (CYP450) enzymes, and toxicity profiles, including AMES test results, hepatotoxicity, and LD_{50} values. This evaluation is essential to determine whether the compounds are both safe and effective for further development as therapeutic agents. Based on the ADMET analysis, all test compounds exhibit diverse pharmacokinetic profiles, thereby requiring a comprehensive evaluation to identify the most promising candidates for drug development. The detailed results are presented in Table 2.

In terms of absorption, the aqueous solubility (log S) values range from −3.45 (compound 7) to −6.50 (compound 15), indicating that most compounds exhibit relatively low solubility. However, the Caco-2 permeability values for all compounds are approximately 1.0, suggesting good absorption capacity across the intestinal membrane. Furthermore, none of the compounds are predicted to be substrates of P-glycoprotein, indicating a low likelihood of efflux from cells, which could otherwise reduce drug bioavailability.

For the distribution parameters, the volume of distribution at steady state (VDss) ranges from −0.43 (compound 7) to 0.069 (compound 10), indicating relatively

low values overall. This suggests that most compounds are retained in plasma rather than extensively distributed into tissues. Meanwhile, the blood–brain barrier (BBB) permeability values show a considerable range: compounds 1–6 exhibit values around 0.8, indicating a higher potential to penetrate the central nervous system, whereas compounds 7–15 display lower values ranging from 0.4 to 0.1, suggesting limited CNS penetration. This distinction is important, as it is associated with the potential for central nervous system–related side effects.

Tabel 2. In Silico ADMET Evaluation of Indole–Tetrazole Hybrid Derivatives

Compounds	Parameters												
	Absorption			Distribution			Metabolism			Excretion	Toxicity		
	Water solubility (log mol/L)	Caco-2 Permeability (log Papp 10-6 cm/s)	Pgp-substrate	VD	PPB (%)	BBB	CYP1A2 inhibitor	CYP2C9 inhibitor	CYP3A4 inhibitor	CL	AMES Toxicity	Hepatoxicity	LD50
1-benzyl-3-(2-(4-methylbenzyl)-2H-tetrazol-5-yl)-1H-indole	-3.888	1.089	No	-0.26	-	0.841	Yes	Yes	No	0.465	No	Yes	2.45
1-benzyl-3-(2-(3-chlorobenzyl)-2H-tetrazol-5-yl)-1H-indole	-3.785	1.086	No	-0.296	-	0.802	No	Yes	No	0.117	No	Yes	2.421
1-benzyl-3-(2-(3,4-dichlorobenzyl)-2H-tetrazol-5-yl)-1H-indole	-3.92	1.083	No	-0.211	-	0.827	No	Yes	No	0.244	No	Yes	2.429
1-benzyl-3-(2-(2,4-dichlorobenzyl)-2H-tetrazol-5-yl)-1H-indole	-3.948	1.089	No	-0.19	-	0.792	No	Yes	No	0.104	No	Yes	2.481
1-benzyl-3-(2-(4-chlorobenzyl)-2H-tetrazol-5-yl)-1H-indole	-3.895	1.086	No	-0.25	-	0.828	Yes	Yes	No	0.116	No	Yes	2.437
1-benzyl-3-(2-(4-fluorobenzyl)-2H-tetrazol-5-yl)-1H-indole	-3.868	1.087	No	-0.328	-	0.821	Yes	Yes	No	0.331	No	Yes	2.45
1-benzyl-3-(2-(3-methoxybenzyl)-2H-tetrazol-5-yl)-1H-indole	-3.452	1.086	No	-0.434	-	0.435	No	Yes	Yes	0.492	No	Yes	2.447
3-(2-benzyl-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	-5.617	1.069	No	-0.089	-	0.317	Yes	Yes	No	0.386	No	Yes	2.123
3-(2-(3-chlorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	-5.658	1.056	No	-0.001	-	0.252	Yes	Yes	Yes	0.054	No	Yes	2.183
3-(2-(3,4-dichlorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	-5.632	1.049	No	0.069	-	0.222	Yes	Yes	No	0.177	No	Yes	2.226
3-(2-(2,4-dichlorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	-5.713	1.033	No	0.002	-	0.243	Yes	Yes	Yes	0.043	No	Yes	2.21
3-(2-(4-chlorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	-5.64	1.057	No	-0.034	-	0.274	Yes	Yes	Yes	0.05	No	Yes	2.178
3-(2-(4-fluorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	-4.772	1.111	No	-0.171	-	0.187	Yes	Yes	No	0.287	No	Yes	2.312
3-(2-(3-methoxybenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	-3.486	1.076	No	-0.394	-	0.406	No	Yes	Yes	0.493	No	Yes	2.512
1-benzyl-3-(2-benzyl-2H-tetrazol-5-yl)-1H-indole	-6.506	1.086	No	0.018	-	0.301	Yes	Yes	Yes	0.365	Yes	Yes	1.991
Bazedoxifen	-3.873	1.068	Yes	-0.478	-	-0.367	Yes	No	Yes	0.834	No	No	2.663

Regarding metabolic parameters, most compounds demonstrate potential as inhibitors of cytochrome P450 enzymes, particularly CYP2C9. In addition, several compounds (7, 9, 11, 12, 14, and 15) are also predicted to inhibit CYP1A2 and CYP3A4. This finding warrants careful consideration, as inhibition of cytochrome P450 enzymes may increase the risk of drug–drug interactions when the compounds are co-administered with other medications. Therefore, although these compounds exhibit promising biological activity, their metabolic stability and potential for metabolic interactions require further investigation.

In terms of excretion, the clearance values of all compounds vary considerably. Compounds 1, 7, and 14 exhibit relatively high clearance values (>0.4), indicating rapid elimination from the body and potentially a shorter duration of action. In contrast, compounds 11 and 12 exhibit very low clearance values (<0.1), indicating slower elimination. This condition may be advantageous for achieving a longer therapeutic effect.

In terms of toxicity, nearly all compounds show negative results in the Ames test, indicating that they are non-mutagenic, which represents a favorable attribute for drug development. However, all compounds are predicted to be hepatotoxic, warranting further investigation into their safety for liver function. The LD_{50} values are relatively consistent across all compounds, with a value of 2, suggesting that their acute toxicity remains within an acceptable range. Nevertheless, these findings still require further validation through experimental studies.

Overall, the ADMET analysis revealed that most of the studied compounds exhibited favorable absorption properties and were predicted to be non-mutagenic. However, certain limitations were observed in their metabolic profiles and in their potential for hepatotoxicity. Based solely on the ADMET evaluation, 1-benzyl-3-(2-(3-chlorobenzyl)-2H-tetrazol-5-yl)-1H-indole demonstrated the most favorable pharmacokinetic and toxicity profile among the investigated compounds. In addition, 3-(2-(3,4-dichlorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole exhibited several characteristics supporting its potential as a drug candidate. Therefore, the selection of the most promising compound should not be based on a single parameter but rather on a comprehensive assessment that balances efficacy, safety, and pharmacokinetic stability, as well as the outcomes of drug-likeness evaluation and molecular docking studies.

Docking Validation

Molecular docking validation was performed using a re-docking approach, in which the native ligand bound to the receptor was re-docked using the same parameters as those used for the test compounds. This procedure aimed to verify the accuracy of the receptor's active site location through analysis of the Root Mean Square Deviation (RMSD) values [27]. The RMSD value is used as an indicator of the degree of conformity between the docked ligand position and its original conformation within the target protein [28]. The smaller the RMSD value obtained, the higher the accuracy of the docking method employed. In general, an RMSD value below 1 Å indicates highly accurate results, values within the range of 1–2 Å are considered good, values between 2–3 Å reflect moderate accuracy, whereas values above 3 Å suggest less reliable docking results [29].

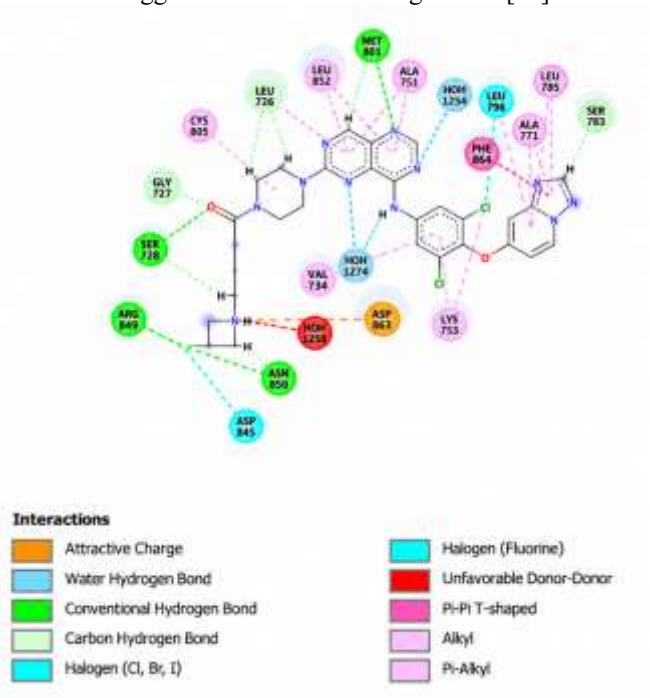


Figure 2. HER2 protein interaction with native ligand

The kinase domain of HER2 contains several key regions and amino acid residues that play essential roles in ligand recognition and the catalytic activity of the protein. Most HER2 inhibitors are designed to bind within the ATP-binding pocket, thereby blocking phosphate transfer and suppressing downstream signaling pathways involved in cancer cell proliferation. Among the critical residues within this binding site, Lys753 is directly involved in ATP binding, whereas Met801, located in the hinge region, frequently forms hydrogen bonds with kinase inhibitors. Thr798 functions as the gatekeeper residue, regulating ligand access to the active site, while Asp863, a component of the conserved DFG motif, is essential for the catalytic function of the kinase. In addition, Cys805 serves as a key target for irreversible inhibitors through covalent bond formation, whereas Phe864, Leu796, Glu770, and Asp871 contribute to stabilization of the protein–ligand complex through hydrophobic, electrostatic, and hydrogen-bonding interactions [30].

The re-docking results demonstrate that the ligand interacts with several key residues within the receptor's active site, including the formation of hydrogen bonds with MET801, carbon–hydrogen bonds with SER783, and hydrophobic π–alkyl interactions with CYS805. These interactions indicate the involvement of key residues in maintaining the stability of the ligand–receptor complex. The obtained RMSD value of 1.6319 Å demonstrates that the ligand conformation generated from re-docking closely matches the ligand position in the original crystal structure. This value suggests that the applied docking method has good accuracy in predicting ligand orientation within the target protein's active site. Therefore, the docking procedure used is considered valid and appropriate for evaluating the interactions between the test compounds and the target receptor.

Analysis of Molecular Docking Result

Molecular docking is a computational method widely used in drug discovery to predict how a compound (ligand) binds to and interacts with target proteins in the body [31]. This approach enables researchers to better understand the potential effectiveness of natural compounds (phytochemicals) at the molecular level. Key proteins identified from prior analyses are subsequently employed as targets to evaluate the binding affinity and interaction patterns of these natural compounds [32].

Molecular docking operates by predicting the position, orientation, and conformation of a ligand (drug candidate) when bound to a target protein. This method enables researchers to elucidate the interaction mechanisms between compounds and proteins, even prior to their experimental synthesis. Consequently, it allows for the estimation of binding affinity and facilitates the early-stage optimization of drug design [33].

The selected target protein structures were obtained from the RCSB Protein Data Bank (PDB). Prior to the docking process, unnecessary components such as water molecules and co-crystallized ligands were removed from the protein structures. The docking simulation identifies specific interactions, including hydrogen bonds and hydrophobic interactions, which are essential for understanding the binding mode and stability of the test compounds with the target proteins [34].

Based on molecular docking analysis of 15 compounds against the target protein, HER2 tyrosine kinase (PDB ID: 7PCD), their binding affinity was evaluated. The primary parameters assessed in this study are the binding affinity (ΔG) and the Root Mean Square Deviation (RMSD). Lower binding affinity values indicate stronger, more stable interactions, which are associated with higher biological activity. The values of these parameters are presented in Table 3.

Tabel 3. Molecular Docking Results of Indole–Tetrazole Hybrid Derivatives

No	Compounds	S score (kcal/mol)	RMSD	Type of Bond	Amino acid residue
1	1-benzyl-3-(2-(4-methylbenzyl)-2H-tetrazol-5-yl)-1H-indole	-10.6542	1.8138	pi-H	LEU 852 ASP 863 GLY 865
2	1-benzyl-3-(2-(3-chlorobenzyl)-2H-tetrazol-5-yl)-1H-indole	-11.1298	1.4459	pi-H	VAL 734 PHE 864
3	1-benzyl-3-(2-(3,4-dichlorobenzyl)-2H-tetrazol-5-yl)-1H-indole	-10.8746	1.4497	H-donor	THR 862
4	1-benzyl-3-(2-(2,4-dichlorobenzyl)-2H-tetrazol-5-yl)-1H-indole	-10.3533	1.9814	H-donor	GLU 770
5	1-benzyl-3-(2-(4-chlorobenzyl)-2H-tetrazol-5-yl)-1H-indole	-12.6672	1.2740	-	-
6	1-benzyl-3-(2-(4-fluorobenzyl)-2H-tetrazol-5-yl)-1H-indole	-11.3571	1.2889	H-donor H-acceptor pi-cation pi-H	ASP 863 LYS 753 LYS 753 ASP 863
7	1-benzyl-3-(2-(3-methoxybenzyl)-2H-tetrazol-5-yl)-1H-indole	-12.6784	0.6935	-	-
8	3-(2-benzyl-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	-11.5736	1.4979	pi-H	THR 862 ASP 863 PHE 864
9	3-(2-(3-chlorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	-12.3367	1.6018	-	-
10	3-(2-(3,4-dichlorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	-13.0444	1.7881	H-acceptor pi-H	GLY 729 ALA 730
11	3-(2-(2,4-dichlorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	-11.6488	1.2774	H-donor pi-H	ASP 863 LYS 753
12	3-(2-(4-chlorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	-11.9939	2.0541	pi-cation pi-H	LYS 753 PHE 864
13	3-(2-(4-fluorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	-10.7772	1.7468	-	-
14	3-(2-(3-methoxybenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	-11.5812	2.5137	pi-H	VAL 734
15	1-benzyl-3-(2-benzyl-2H-tetrazol-5-yl)-1H-indole	-11.0505	1.3973	pi-H	LEU 726
16	Bazedoxifen	-10.6883	1.6289	H-donor pi-H pi-H	MET 801 VAL 734 MET 801

Based on the molecular docking results, 15 indole–tetrazole hybrid compounds were compared with Bazedoxifene as the reference control by evaluating binding affinity values, RMSD, and amino acid residue interaction patterns. The control compound Bazedoxifen exhibited a

binding energy of −10.6883 kcal/mol with an RMSD value of 1.6289 Å, indicating a stable ligand–receptor complex.

In general, many of the test compounds exhibit more negative binding energies than Bazedoxifene, which theoretically indicates a higher binding affinity toward the target receptor [35]. However, this analysis should not be based solely on binding energy values; it must also consider other parameters such as RMSD and the nature of molecular interactions. In this context, several compounds, including compound 10 (−13.0444 kcal/mol), compound 7 (−12.6784 kcal/mol), and compound 5 (−12.6672 kcal/mol), display highly favorable binding energies; nevertheless, not all of them demonstrate specific interactions with key amino acid residues.

The RMSD values of all compounds are generally within the acceptable range (< 2 Å), although several compounds exhibit RMSD values exceeding 2 Å. These results indicate that the docked ligand poses largely remain in stable conformations, and the docking outcomes can be considered reliable for further analysis [29].

In terms of binding interactions, the control compound (Bazedoxifene) forms both hydrogen bonds and hydrophobic (π–H) interactions with key residues such as MET 801 and VAL 734. Among the test compounds, several exhibit more complex interaction patterns. For instance, compound 6 demonstrates a relatively comprehensive set of interactions, including hydrogen-bond donor, hydrogen-bond acceptor, π–cation, and π–H interactions with residues ASP 863 and LYS 753. Compared with compound 10, compound 6 exhibits a broader range of interaction types. However, its binding energy (ΔG) remains higher than that of compound 10, indicating that a greater number or diversity of interactions does not necessarily correlate directly with stronger binding affinity.

Based on the available data, although several compounds exhibit more favorable binding energy values than Bazedoxifene, the selection of the best candidates should not rely on a single parameter. A combination of low binding affinity (ΔG), stable RMSD values, and the presence of specific interactions with key residues constitutes the primary criteria for determining the biological potential of a compound. Based on these considerations, compounds 10 and 6 can be prioritized as the most promising candidates.

Tabel 4. Selection of the best compound based on Lipinski's Rule of Five, ADMET, and Molecular Docking

No	Compounds	Lipinski's	ADMET	Docking Molecular	Amino Acid Residues
10	3-(2-(3,4-dichlorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	Fulfilled	Good	Very Good	Gly 729 Ala 730
6	1-benzyl-3-(2-(4-fluorobenzyl)-2H-tetrazol-5-yl)-1H-indole	Fulfilled	Good	Very Good	Asp 863 Lys 753 Asp 863
2	1-benzyl-3-(2-(3-chlorobenzyl)-2H-tetrazol-5-yl)-1H-indole	Fulfilled	Very Good	Quite Good	Val 734 Phe 864
11	3-(2-(2,4-dichlorobenzyl)-2H-tetrazol-5-yl)-1-(4-methylbenzyl)-1H-indole	Fulfilled	Quite Good	Good	Asp 863 Lys 753
3	1-benzyl-3-(2-(3,4-dichlorobenzyl)-2H-tetrazol-5-yl)-1H-indole	Fulfilled	Very Good	Quite Good	Thr 862

Based on the results of the molecular docking analysis, Lipinski's Rule of Five assessment, and ADMET prediction, a comparative evaluation was conducted to identify the most promising HER2 inhibitor among the compounds investigated. Binding affinity for the HER2 receptor was considered the primary selection criterion, as it reflects the strength of the ligand-target protein interaction. This evaluation was further supported by an analysis of ligand interactions with key amino acid residues within the active site, compliance with Lipinski's Rule of Five, and the predicted pharmacokinetic and toxicity profiles obtained from the ADMET analysis. This integrated assessment provides a more comprehensive basis for compound selection, as high binding affinity alone does not necessarily translate into favorable drug-likeness properties or optimal pharmacokinetic behavior.

Compound 10 was identified as the most promising candidate based on its overall performance across molecular docking, drug-likeness, and ADMET evaluations. This compound exhibited the most favorable binding affinity toward the HER2 receptor, with a binding energy of −13.0444 kcal/mol, which was lower than those of all other tested compounds as well as the reference ligand, Bazedoxifene. This result indicates a stronger predicted interaction between Compound 10 and the HER2 protein.

Furthermore, Compound 10 formed interactions with the GLY729 and ALA730 residues, which may contribute to the stability of the protein–ligand complex. The obtained RMSD value of 1.7881 Å, which falls within the accepted docking validation threshold (< 2 Å), further supports the reliability of the predicted binding pose. From a drug-likeness perspective, the compound satisfied all criteria of Lipinski's Rule of Five and demonstrated a favorable ADMET profile. Notably, it exhibited high Caco-2 permeability, was not predicted to be a P-glycoprotein substrate, showed no inhibitory activity toward CYP3A4, and was classified as non-mutagenic based on the Ames toxicity prediction. Taken together, the combination of strong binding affinity, favorable interactions within the binding site, and desirable pharmacokinetic and toxicity characteristics suggests that Compound 10 possesses the most advantageous biological profile among the evaluated candidates and warrants further investigation as a potential HER2-targeted anticancer agent.

Compound 6 also demonstrated considerable potential as a HER2 inhibitor, despite exhibiting a slightly less favorable binding affinity than several of the top-ranked candidates. Notably, this compound displayed a diverse interaction profile within the HER2 active site, including a hydrogen bond with Asp863, a hydrogen bond acceptor

interaction and a π–cation interaction with Lys753, as well as a π–H interaction with Asp863. The presence of these complementary interactions suggests that compound 6 adopts a favorable binding orientation within the HER2 ATP-binding pocket, thereby contributing to the stability of the protein–ligand complex. Furthermore, the RMSD of 1.2889 Å, well below the accepted validation threshold of 2 Å, indicates a highly reliable docking pose. In addition to satisfying all criteria of Lipinski's Rule of Five, compound 6 exhibited a favorable predicted ADMET profile. Taken together, these findings support the prioritization of compound 6 as a promising HER2 inhibitor candidate for further investigation.

Compound 2 exhibited a favorable balance between molecular docking performance and predicted pharmacokinetic properties. Although its binding affinity was less favorable than those of compounds 10 and 6, it maintained interactions with the key active-site residues Val734 and Phe864, supporting its potential to bind effectively to the HER2 receptor. Furthermore, ADMET prediction indicated that compound 2 is not expected to inhibit CYP1A2 or CYP3A4, suggesting a lower risk of drug–drug interactions compared with several other candidates. The compound was also predicted to be non-mutagenic in the Ames test and satisfied all criteria of Lipinski's Rule of Five. Collectively, these findings indicate that compound 2 possesses favorable drug-like characteristics and remains a promising candidate for further development as a HER2 inhibitor.

Compound 11 also demonstrated a favorable biological profile, characterized by high binding affinity and interactions with the key active-site residues Asp863 and Lys753. These interactions suggest that the compound can bind effectively within the catalytic region of the HER2 protein. In addition, compound 11 fulfilled all criteria of Lipinski's Rule of Five, supporting its favorable physicochemical properties as a potential drug candidate. However, the predicted ADMET profile indicated that compound 11 is likely to inhibit more cytochrome P450 enzymes than compound 10, suggesting a higher potential for drug–drug interactions. Therefore, despite its promising molecular docking performance, the overall pharmacokinetic profile of compound 11 appears to be less favorable than that of the leading candidate.

Similarly, compound 3 exhibited a well-balanced biological profile, as evidenced by its interaction with the active-site residue Thr862 and its compliance with all criteria of Lipinski's Rule of Five. ADMET prediction further indicated that the compound is unlikely to inhibit CYP1A2 or CYP3A4 and was classified as non-mutagenic based on the Ames test. Although its binding affinity was less favorable than that of the leading candidates, the combination of favorable protein–ligand interactions, suitable physicochemical properties, and a predicted pharmacokinetic profile supports the potential of compound 3 as a promising HER2 inhibitor candidate for further investigation.

Conclusion

Based on the results of this study, indole–tetrazole hybrid derivatives demonstrate potential as candidate agents for breast cancer treatment based on an in silico approach. Lipinski's rule analysis indicates that most compounds satisfy the criteria for good oral drug candidates. Meanwhile, ADMET evaluation reveals that the compounds exhibit favorable absorption profiles and are non-mutagenic, although a potential risk of hepatotoxicity remains and warrants further investigation.

The molecular docking results indicate that several compounds exhibit more favorable binding affinities than the control, Bazedoxifene, suggesting greater interaction stability with the target protein. Among them, compound 10 demonstrates the most favorable binding affinity and also shows specific molecular interactions with key amino acid residues.

Overall, the findings indicate that the selection of potential HER2 inhibitors should not rely solely on binding affinity but should also incorporate the quality of ligand interactions with key active-site amino acid residues, compliance with Lipinski's Rule of Five, and the predicted ADMET profile. This integrated evaluation provides a more comprehensive framework for identifying compounds with the greatest potential for further development. Based on these criteria, compound 10 exhibited the most favorable overall biological profile and was therefore identified as the most promising HER2 inhibitor candidate among the evaluated indole–tetrazole derivatives.Nevertheless, further experimental validation through both in vitro and in vivo studies is essential to confirm the pharmacological efficacy, safety, and therapeutic potential of these compounds before they can be considered for further drug development.

Author's Contribution

Zafrinaldi: Developed and structured the research design, including the formulation of study objectives and approaches. She also collected and organized compound data and conducted molecular docking simulations. In addition, she established the research methodology, conducted a literature review in pharmacoinformatics, supervised in silico analyses and data processing, and contributed to the interpretation of the research findings. F. Azra: Developed the research concept, organized and prepared the manuscript framework, and conducted the final review and revisions prior to submission.

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References

[1] S. Bajaj, P. P. Roy, and J. Singh, "Synthesis, thymidine phosphorylase inhibitory and computational study of novel 1,3,4-oxadiazole-2-thione derivatives as potential anticancer agents," *Comput. Biol. Chem.*, vol. 76, pp. 151–160, 2018, doi: 10.1016/j.compbiolchem.2018.05.013.

[2] B. S. Lakshmi, J. K. Bidarur, H. G. Anilkumar, and B. S. Ravindranath, "Prioritization of phytochemical isolation and characterization against HER2 as a breast cancer target based on chromatographic methods , DFT," vol. 2, pp. 25103–25114, 2025, doi:

10.1039/d5ra01800e.
[3] E. D. O. Sihite, S. Nurchayati, and Y. Hasneli, "Gambaran Tingkat Pengetahuan Tentang Kanker Payudara Dan Perilaku Periksa Payudara Sendiri (Sadari)," *J. Ners Indones.*, vol. 9, no. 2, p. 8, 2019, doi: 10.31258/jni.10.1.8-20.
[4] D. Qian *et al.*, "Trends in the global , national , and regional burden of breast cancer among adolescents and young adults from 1990 to 2021 : Analyses of the 2021 global burden of disease study," *The Breast*, vol. 82, no. May, p. 104486, 2025, doi: 10.1016/j.breast.2025.104486.
[5] J. P. Arisanti, N. Saptarina, and Y. D. Andarini, "Evaluasi Penggunaan Obat Kemoterapi Pada Penderita Kanker Payudara Di Rsup Dr. Seoradji Tirtonegoro Periode 2018," *Pharm. J. Islam. Pharm.*, vol. 4, no. 2, p. 1, 2020, doi: 10.21111/pharmasipha.v4i2.4960.
[6] I. Nurjayanti, "DUKUNGAN KELUARGA PADA PASIEN KANKER PAYUDARA DENGAN KEMOTERAPI DI RUMAH SAKIT PKU MUHAMMADIYAH YOGYAKARTA," vol. 17, no. 1, pp. 1–23, 2019.
[7] M. Nilashi, H. Ahmadi, R. Ali, M. Alrizq, A. Alghamdi, and S. Alyami, "Heliyon Knowledge discovery of patients reviews on breast cancer drugs : Segmentation of side effects using machine learning techniques," *Heliyon*, vol. 10, no. 19, p. e38563, 2024, doi: 10.1016/j.heliyon.2024.e38563.
[8] Ruswanto, "DESAIN DAN STUDI IN-SILICO TURUNAN TIOUREA SEBAGAI KANDIDAT RADIOFARMAKA 131I-THIOUREA UNTUK KANKER PAYUDARA," vol. 8, no. 1, pp. 133–150, 2025.
[9] E. Rubin *et al.*, "Molecular Targeting of the Human Epidermal Growth Factor Receptor-2 (HER2) Genes across Various Cancers," vol. 2, 2024.
[10] Y. M. Panji Bachrudin, Agus Sulaeman, "PENDEKATAN TERAPI MOLEKULER PADA KANKER PAYUDARA TERHADAP PERAN EVEROLIMUS DAN TEMSIROLIMUS SEBAGAI PROTEIN KINASE INHIBITORS JALUR PI3K/AKT/MTOR," vol. 8, no. 1, pp. 179–191, 2025, doi: 10.36387/jifi.v8i1.2508.
[11] M. Arumí, M. Bellet, and C. Saura, "HER2-positive breast cancer : Current and new therapeutic strategies," vol. 39, pp. 80–88, 2018, doi: 10.1016/j.breast.2018.03.006.
[12] H. Rahma *et al.*, "Peran Human Epidermal Growth Factor Receptor-2 pada Kanker Payudara Role of Human Epidermal Growth Factor Receptor-2 in Breast Cancer," vol. 5, pp. 644–647, 2018.
[13] X. Cheng, "A Comprehensive Review of HER2 in Cancer Biology and Therapeutics," 2024.
[14] G. S. P. Matada *et al.*, "Pharmacophore modeling, virtual screening, molecular docking and dynamics studies for the discovery of HER2-tyrosine kinase inhibitors: An in-silico approach," *J. Mol. Struct.*, vol. 1257, p. 132531, 2022, doi: 10.1016/j.molstruc.2022.132531.
[15] R. K. Amewu, P. O. Sakyi, and D. Osei-safo, *Synthetic and Naturally Occurring Heterocyclic Anticancer Compounds with Multiple Biological Targets*. 2021.
[16] T. T. Y. Wang, M. J. Milner, J. A. Milner, and Y. S. Kim, "Estrogen receptor a as a target for indole-3-carbinol," pp. 3–8, 2006, doi: 10.1016/j.jnutbio.2005.10.012.
[17] A. Elkamhawy *et al.*, "Scaffold repurposing of in-house small molecule candidates leads to discovery of first-in-class cdk-1/her-2 dual inhibitors: In vitro and in silico screening," *Molecules*, vol. 26, no. 17, pp. 1–12, 2021, doi: 10.3390/molecules26175324.
[18] F. Islam *et al.*, "Indole alkaloids from marine resources: Understandings from therapeutic point of view to treat cancers," *Chem. Biol. Interact.*, vol. 383, no. July, p. 110682, 2023, doi: 10.1016/j.cbi.2023.110682.
[19] N. Dhiman, K. Kaur, and V. Jaitak, "Bioorganic & Medicinal Chemistry Tetrazoles as anticancer agents : A review on synthetic strategies , mechanism of action and SAR studies," *Bioorg. Med. Chem.*, vol. 28, no. 15, p. 115599, 2020, doi: 10.1016/j.bmc.2020.115599.
[20] K. Kaur, H. Verma, P. Gangwar, M. Dhiman, and V. Jaitak, "Design, synthesis, in vitro and in silico evaluation of indole-based tetrazole derivatives as putative anti-breast cancer agents," *RSC Med. Chem.*, vol. 15, pp. 1329–1347, 2024, doi: 10.1039/D3MD00730H.
[21] C. A. Lipinski, F. Lombardo, B. W. Dominy, and P. J. Feeney, "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings," *Adv. Drug Deliv. Rev.*, vol. 64, no. SUPPL., pp. 4–17, 2012, doi: 10.1016/j.addr.2012.09.019.
[22] L. Blanca, R. Estrada-tejedor, and E. a. Borrell, Jos I, "Evaluation of Free Online ADMET Tools for Academic or Small Biotech Environments," 2023.
[23] R. Roskoski, "Rule of five violations among the FDA-approved small molecule protein kinase inhibitors," *Pharmacol. Res.*, vol. 191, no. April, p. 106774, 2023, doi: 10.1016/j.phrs.2023.106774.
[24] G. Sampat, S. S. Suryawanshi, M. S. Palled, and A. S. Patil, "Drug Likeness Screening and Evaluation of Physicochemical Properties of Selected Medicinal Agents by Computer Aided Drug Design Tools," vol. 10, no. 4, pp. 234–246, 2022, doi: 10.13189/app.2022.100402.
[25] R. Feghali, R. P. Ribeiro, M. J. Ramos, and P. A. Fernandes, "The importance of intramolecular hydrogen bonds on the translocation of the small drug piracetam through a lipid bilayer †," pp. 899–908, 2021, doi: 10.1039/d0ra09995c.
[26] O. Nursanti, "Validasi Penambatan Molekul Untuk Mendapatkan Ligan Aktif Pada Reseptor Cyclooxygenase 2," *Pros. Semin. Inf. Kesehat. Nas.*, pp. 411–430, 2019.
[27] S. D. Lina Elfita, Anjas Apriadi, Supandi, "Studi Penambatan Molekuler dan Simulasi Dinamika Molekuler Senyawa Turunan Furanokumarin terhadap Reseptor Estrogen Alfa (ER-α) Sebagai Anti Kanker Payudara," pp. 255–264, 2022, doi: 10.25077/jsfk.9.3.255-264.2022.
[28] R. Zainul *et al.*, "In Silico Gene Transcription of 4-Hydroxycinnamic Acid from Broccoli Fruit (Brassica oleracea var . italica) with Estrogen Receptor Beta Protein," vol. 16, no. 4, pp. 791–796, 2024.
[29] D. Ramirez and J. Caballero, "Is It Reliable to Take the

Molecular Docking Top Scoring Position as the Best Solution without Considering Available Structural Data ?," pp. 1–17, 2018, doi: 10.3390/molecules23051038.

[30] D. T. Truong *et al.*, "Benchmarking the Ligand − HER2 Interactions Using Machine Learning and Molecular Dynamics Simulations," 2026, doi: 10.1021/acsomega.5c10459.

[31] Zoete, "Docking, virtual high throughput screening and in silico fragment-based drug design," *J. Cell. Mol. Med.*, vol. 13, no. 2, pp. 238–248, 2009, doi: 10.1111/j.1582-4934.2008.00665.x.

[32] Y. Mei *et al.*, "Letters in Drug Design & Discovery Mechanism of Yangxuetongmai Decoction in treating essential hypotension : A network pharmacology , Mendelian randomization and molecular docking strategy analysis," *Lett. Drug Des. Discov.*, no. February, p. 100008, 2025, doi: 10.1016/j.lddd.2025.100008.

[33] A. Grosdidier, "EADock: Docking of Small Molecules Into Protein Active Sites With a Multiobjective Evolutionary Optimization," *El Sist. argentino innovación Inst. Empres. y redes. El desafío la creación y apropiación Conoc.*, vol. 14, no. October 2006, pp. 659–664, 2013, doi: 10.1002/prot.

[34] W. Ouyang, C. Zhu, Y. Li, H. Huang, F. Li, and L. Ling, "Assessing the neurotoxic risks of triethyl citrate in daily environmental exposure using network toxicology and molecular docking," *Ecotoxicol. Environ. Saf.*, vol. 297, no. March, p. 118225, 2025, doi: 10.1016/j.ecoenv.2025.118225.

[35] N. Forouzesh and N. Mishra, "An Effective MM / GBSA Protocol for Absolute Binding Free," 2021.