



The potential of 5-O-acylpinostrobin derivatives against progesterone and EGFR-HER2 receptors as anti-breast cancer: Docking, molecular dynamics simulations, and ADMET prediction

[Potencial de los derivados de 5-O-acilpinostrobin contra los receptores de progesterona y EGFR-HER2 como anticáncer de mama: acoplamiento, simulación dinámica molecular y predicción ADMET]

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Abstract

Context: Breast cancer involves uncontrolled proliferation of breast tissue and remains the leading cause of cancer-related mortality in women. Progesterone receptors modulate estrogen- α receptor signaling, while EGFR-HER2 overexpression promotes cancer cell proliferation and therapy resistance. Pinostrobin, isolated from *Boesenbergia pandurata*, exhibits anticancer activity, and its structural modification to 5-O-acylpinostrobin derivatives may enhance potency.

Aims: To predict the potential of 5-O-acylpinostrobin derivatives against progesterone and EGFR-HER2 receptors through molecular docking, molecular dynamics simulations, and ADMET predictions.

Methods: Molecular docking was performed using MOE 2022.02, followed by 100 ns molecular dynamics simulations with AMBER 20, and absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties were evaluated using ADMETlab.

Results: All derivatives showed stronger binding affinities than pinostrobin, with pinostrobin butyrate demonstrating the highest stability during molecular dynamics to both receptors. ADMET predictions indicated favorable pharmacokinetics, although with potential carcinogenicity.

Conclusions: These findings indicate that pinostrobin butyrate exhibits promising candidate for further preclinical development as an anti-breast cancer agent.

Keywords: 5-O-acylpinostrobin; breast cancer; EGFR-HER2; *in silico*; progesterone.

Resumen

Contexto: El cáncer de mama implica una proliferación descontrolada del tejido mamario y sigue siendo la principal causa de mortalidad por cáncer en las mujeres. Los receptores de progesterona modulan la señalización del receptor de estrógeno α , mientras que la sobreexpresión de EGFR-HER2 promueve la proliferación de células cancerosas y la resistencia a la terapia. La pinostrobin, aislada de *Boesenbergia pandurata*, exhibe actividad anticancerígena y su modificación estructural en derivados de 5-O-acilpinostrobin puede aumentar su potencia.

Objetivos: Predecir el potencial de los derivados de 5-O-acilpinostrobin contra los receptores de progesterona y EGFR-HER2 mediante acoplamiento molecular, simulaciones de dinámica molecular y predicciones ADMET.

Métodos: El acoplamiento molecular se realizó con MOE 2022.02, seguido de simulaciones de dinámica molecular de 100 ns con AMBER 20, y las propiedades de absorción, distribución, metabolismo, excreción y toxicidad (ADMET) se evaluaron con ADMETlab.

Resultados: Todos los derivados mostraron afinidades de unión más fuertes que la pinostrobin, y el butirato de pinostrobin demostró la mayor estabilidad durante la dinámica molecular para ambos receptores. Las predicciones de ADMET indicaron una farmacocinética favorable, aunque con potencial carcinógeno.

Conclusiones: Estos hallazgos indican que el butirato de pinostrobin es un candidato prometedor para un mayor desarrollo preclínico como agente contra el cáncer de mama.

Palabras Clave: 5-O-acilpinostrobin; cáncer de mama; EGFR-HER2; *in silico*; progesterona.

ARTICLE INFO

Received: May 4, 2025.

Accepted: November 12, 2025.

Available Online: March 6, 2026.

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INTRODUCTION

Breast cancer is the most prevalent cancer worldwide, with an estimated 19.3 million cases and 10 million deaths in 2022 (GLOBOCAN, 2022). In Indonesia, it accounts for 30.1% of all cancer diagnoses, with a mortality rate of 19.8%. Current therapies, such as doxorubicin, are effective but associated with cardiotoxicity and multidrug resistance (Jalali et al., 2024; Kciuk et al., 2023; Lovitt et al., 2018). Thus, the development of novel agents with improved selectivity and reduced toxicity remains essential. Flavonoids, including pinostrobin from *Boesenbergia pandurata* (Roxb.) Schltr., a synonym of *B. rotunda* (L.) Mansf. (family Zingiberaceae), have demonstrated anticancer activity (Jongjang et al., 2025).

Molecular modelling with the addition of an acyl group has been shown to modify pharmacological effects as well as lipophilic, electronic, and steric properties. These modifications enhance the ability of compounds to penetrate biological membranes and interact with target receptors, thereby increasing their biological activity (Siswandono, 2016). This result was supported by *in silico* studies, which predicted that 5-O-acylpinostrobin derivatives possess anti-breast cancer potential (Siswandono et al., 2020). Moreover, prior *in silico* analyses based on previous research indicated that these derivatives may interact with the estrogen receptor α (ER α) (Susilawati et al., 2024). The cytotoxicity and selectivity of two derivatives, pinostrobin propionate and pinostrobin butyrate, were evaluated against T47D cells, and both were found to be more effective and selective than the lead compound, pinostrobin (Widiandani et al., 2023).

Based on this study, 5-O-acylpinostrobin derivatives need to be further analysed against critical breast cancer targets, such as the progesterone receptor and the EGFR-HER2 receptors. *In silico* approaches,

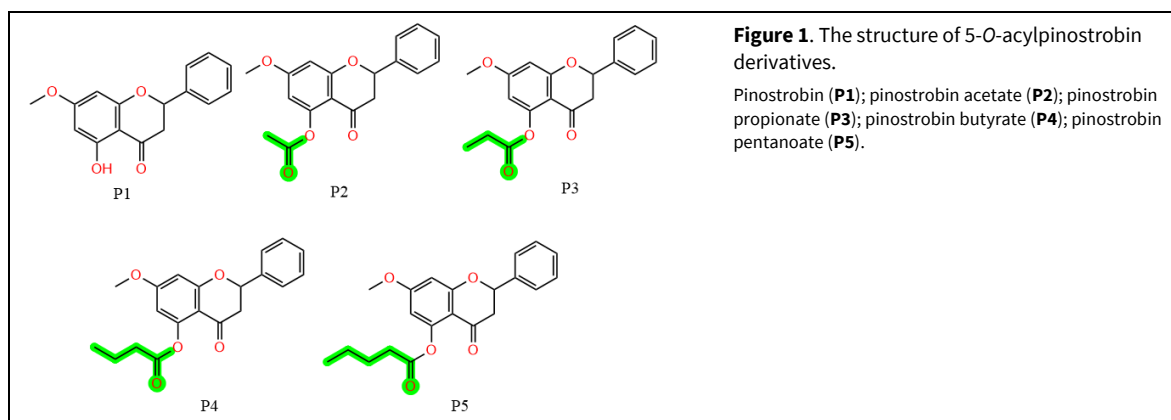
including molecular docking, molecular dynamics simulations, and absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction, were applied to predict ligand-receptor interactions, evaluate complex stability, and estimate pharmacokinetic properties and toxicity. This study aims to predict the potential of 5-O-acylpinostrobin derivatives as anti-breast cancer candidates against the progesterone and EGFR-HER2 receptors using docking, molecular dynamics, and ADMET prediction.

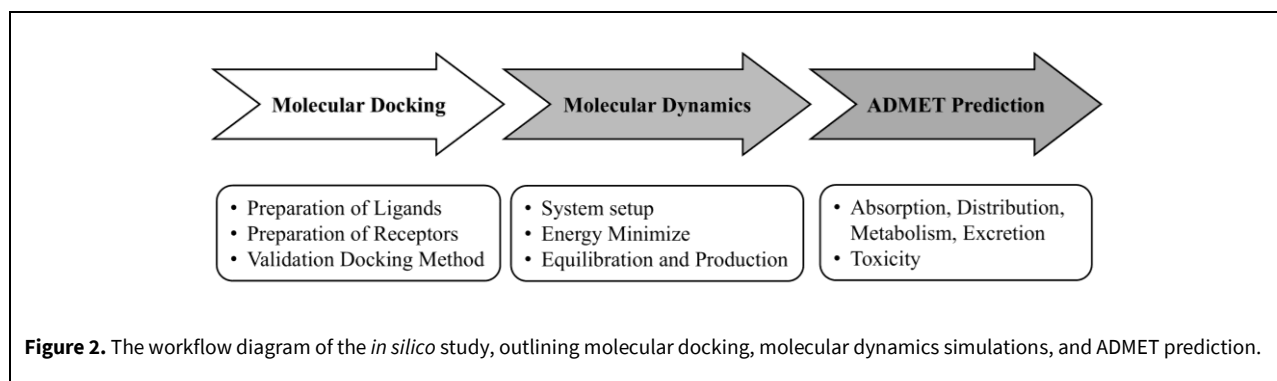
MATERIAL AND METHODS

Materials

ChemDraw 20.0, Discovery Studio 2021, MOE 2022.02 (academic license K22CCG679), and AMBER 20 were used. This study used pinostrobin (lead compound) and 5-O-acylpinostrobin derivatives structures designed (Fig. 1), pinostrobin acetate, pinostrobin propionate, pinostrobin butyrate, and pinostrobin pentanoate (Siswandono et al., 2020), progesterone (PDB ID 1E3K), and EGFR-HER2 receptors (PDB ID 3PP0).

Furthermore, the computational workflow consisted of three main steps, which are molecular docking, molecular dynamics, and absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction (Fig. 2). In the first step, ligands and receptors were prepared, docking method was validated, and docking was performed to predict the optimal binding poses and affinities of the ligands. The complex compounds were then subjected to molecular dynamics simulations. In addition, the ligands were analysed for their pharmacokinetic and toxicity properties. This study was conducted using *in silico* approaches without the involvement of human participants, animals, or clinical samples, the requirement for ethical approval was not applicable.





Ligand and receptor preparation

Pinostrobin and 5-O-acylpinostrobin derivative structures (Fig. 1) were drawn using MOE by putting the pharmacophore groups on the ligand, then saved in Tripos MOL2 (.mol2) file formats. The pharmacophore groups on each receptor can be seen on the site <https://proteins.plus/> (Ehrt et al., 2025).

Progesterone (PDB ID 1E3K) and EGFR-HER2 (PDB ID 3PP0) receptors were downloaded from the Protein Data Bank, which was freely accessible at <https://www.rcsb.org/> (Forli et al., 2016). Unused components at the receptor, such as water, solvent, unused chain, and ions, were removed, and the structure was prepared by three-dimensional protonation. The structure of receptors was corrected by protonate 3D with 300K of temperature, pH 7, and 0.1 of salt. The energy minimization of all atoms was performed with MOE 2022.02 using the Amber10: EHT force field. Amber parameters were used for proteins and nucleic acids (ff10). Meanwhile, EHT parameters were used for small molecules. The receptor was saved in MOE molecule file (.moe) (Case et al., 2023).

Validation of the docking method

Validation of the docking method was performed by re-docking the co-crystal ligand into each receptor using MOE 2022.02. The method was considered valid when the Root Mean Square Deviation (RMSD) of the redocked pose was $\leq 2\text{\AA}$ (Ruswanto et al., 2022). Validation was repeated three times to obtain the mean value and standard deviation.

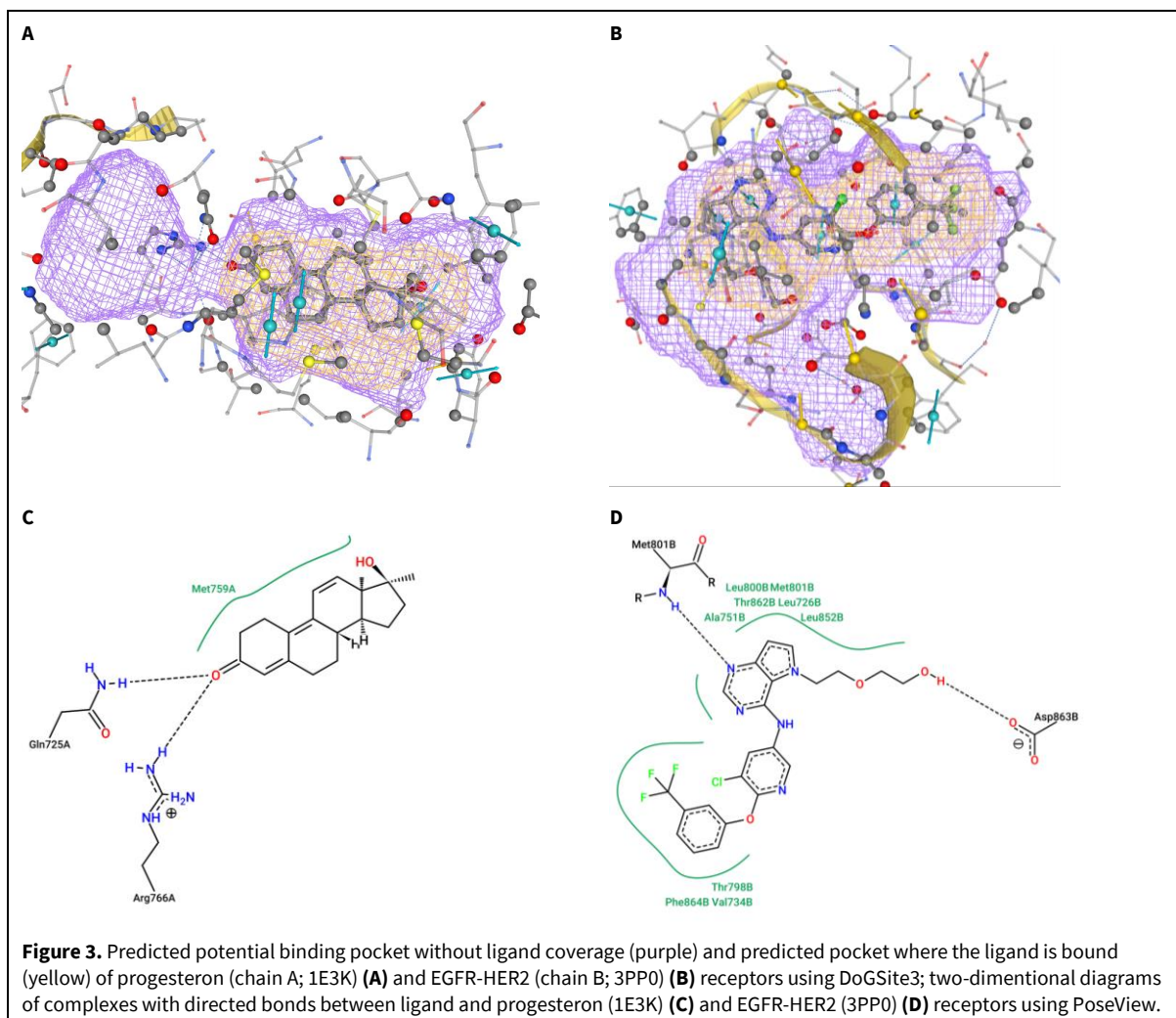
Molecular docking

Molecular docking was analyzed using the MOE 2022.02 program, with interactions between 5-O-acylpinostrobin derivatives and the human progesterone and EGFR-HER2 receptors, using the London dG scoring function, the Triangle Matcher placement algorithm with 100 poses, and rigid receptor refinement. The docking site was generated using the Surface and Maps module of MOE 2022.02, which automatically defines the binding pocket based on the co-crystallized

ligand and receptor cavity. This approach eliminates the need for manual grid dimension while ensuring accurate identification of the active site. The parameters analyzed were the binding free energy (S), which was compared with pinostrobin (the lead compound), and ligand-receptor interactions from amino acid similarity percentage interactions, which were compared with the native ligand on each receptor. As with validation of the docking method, molecular docking was repeated three times, and the resulting complex was saved in the Protein Data Bank (.pdb) format.

Molecular dynamics simulations

Molecular dynamics simulations were carried out on pinostrobin and 5-O-acylpinostrobin derivative complexes, based on the molecular docking results for each receptor, to analyze stability and flexibility during ligand-receptor interactions within the biological system of the body (Dermawan et al., 2019). The molecular dynamics simulations began with charge parameterization of the ligand using the semi-empirical quantum calculation method Austin Model 1 with Bond Charge Corrections (AM1-BCC) through the antechamber program (Wang et al., 2024), and the missing force field for the ligand was generated using the parmchk module. The ligand parameters were assigned using the General AMBER Force Field (GAFF). Receptor preparation is needed to complete missing atoms and determine residue protonation state using Force Field 2014 Stony Brook (FF14SB) through the antechamber program (Case et al., 2022). The ions, sodium (Na^+) or chloride (Cl^-), were added around the ligand-receptor complexes to neutralize the system. The complex and the box boundaries were placed in a cubic simulation box (minimum 10 Å) for the solvation process using the Transferable Intermolecular Potentials 3-Point (TIP3P) water model. Next, the system was minimized using Particle Mesh Ewald Molecular Dynamics (PMEMD) in Amber. The system temperature was increased at constant volume (NVT) from 0 K to 310 K. Isotropic position scaling was used to periodically modify the constant pressure (NPT) at 1 bar to equilibrate the molecules in the system (100 ps NVT, 100 ps NPT).



The molecular dynamics production was carried out for 100 ns, and 1000 snapshots were taken at 100 ps intervals using cpptraj in AMBER20 for trajectory analyses, such as RMSD and Root Mean Square Fluctuation (RMSF) (Kumar et al., 2020).

ADMET prediction

The pharmacokinetic and toxicological predictions of pinostrobin and 5-*O*-acylpinostrobin derivatives were examined using the freely available ADMETlab 2.0 server (<https://admetlab3.scbdd.com/>), without registration. In addition, the physicochemical properties were predicted with the same site (Xiong et al., 2021).

Statistical analysis

The docking results were repeated three times and reported as mean $\pm$ standard deviation (SD) using SPSS Statistics 25. Analysis of Variance (ANOVA) with Tukey post-hoc test was conducted, and $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Ligand and receptor preparation

Pharmacophore groups are the key structural features responsible for a molecule's biological activity. Having at least one pharmacophore group identical to the native ligand is an important element in designing effective drugs that bind to the same receptor target (Sahdev et al., 2023).

The grid representation in Fig. 3 aimed to detect potential binding pockets-solely based on the 3D structure of the macromolecules (protein and nucleic acid chains) and split them into sub-pockets. The predicted binding sites on the protein surface were processed using Protoss (a hydrogen prediction tool for protein-ligand complexes), DoGSite3 (a grid-based method), and GeoMine (Graef et al., 2023; Guo et al., 2025). In addition, we defined a pharmacophore as the essential chemical features, such as hydrogen-bond donor/acceptor and hydrophobic groups, that enable optimal interactions between the ligand and receptor (Krivák &

Hoksza, 2018). According to the results (Fig. 3), the pharmacophore group in the progesterone receptor-native ligand complexes was the carbonyl group, which binds to the amino acid residues Gln725 and Arg766. Meanwhile, the pharmacophore groups on the EGFR-HER2 receptor-native ligand complexes were the hydroxyl group, which binds to the amino acid residue Asp863. This pharmacophore group was added to the test ligand.

Validation of the docking method

Root mean square deviation (RMSD) was used to analyse the docking method's validity. The validation of the docking method showed the RMSD of progesterone (1E3K) and EGFR-HER2 (3PP0) receptors were 0.141 and 0.441, respectively (Table 1). These values were lower than the RMSD acceptance limit of 2 Å. Additionally, the ligand-receptor interaction proved to be quite stable, as evidenced by the free binding energy

values of progesterone (1E3K) and EGFR-HER2 (3PP0) receptors, which were -9.174 kcal/mol and -11.445 kcal/mol, respectively.

Furthermore, the native ligand overlays visualization of re-docking with the native ligand from both receptor crystal structures (Fig. 4) shows that there were no significant changes in the molecular geometry during the re-docking process. Therefore, the docking method was valid and could continue molecular docking.

Molecular docking

The most stable ligand-receptor interaction was predicted based on free binding energy and the percentage similarity to the native ligand, as determined by molecular docking. The molecular docking results (Table 2) were compared with pinostrobin as the lead compound.

Table 1. Validation of the docking method result.

PDB ID	Native ligand	RMSD $\pm$ SD (Å)	S $\pm$ SD (kcal/mol)
1E3K	R18	0.141 $\pm$ 0.006	-9.174 $\pm$ 0.052
3PP0	O3Q	0.441 $\pm$ 0.038	-11.445 $\pm$ 0.184

S: free binding energy value; SD: Standard deviation.

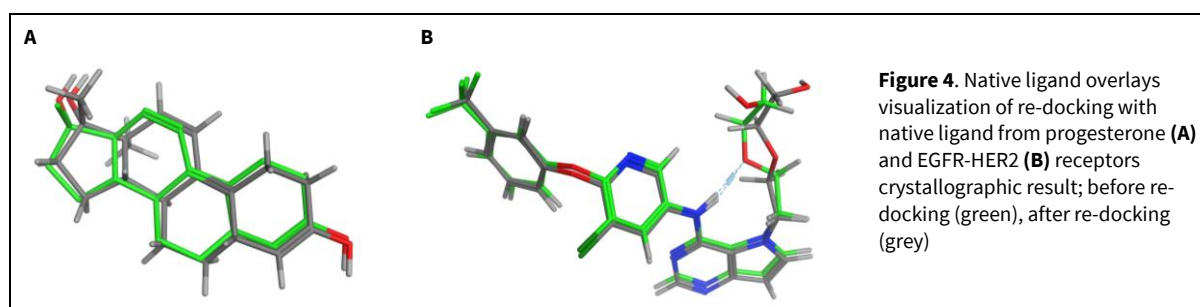
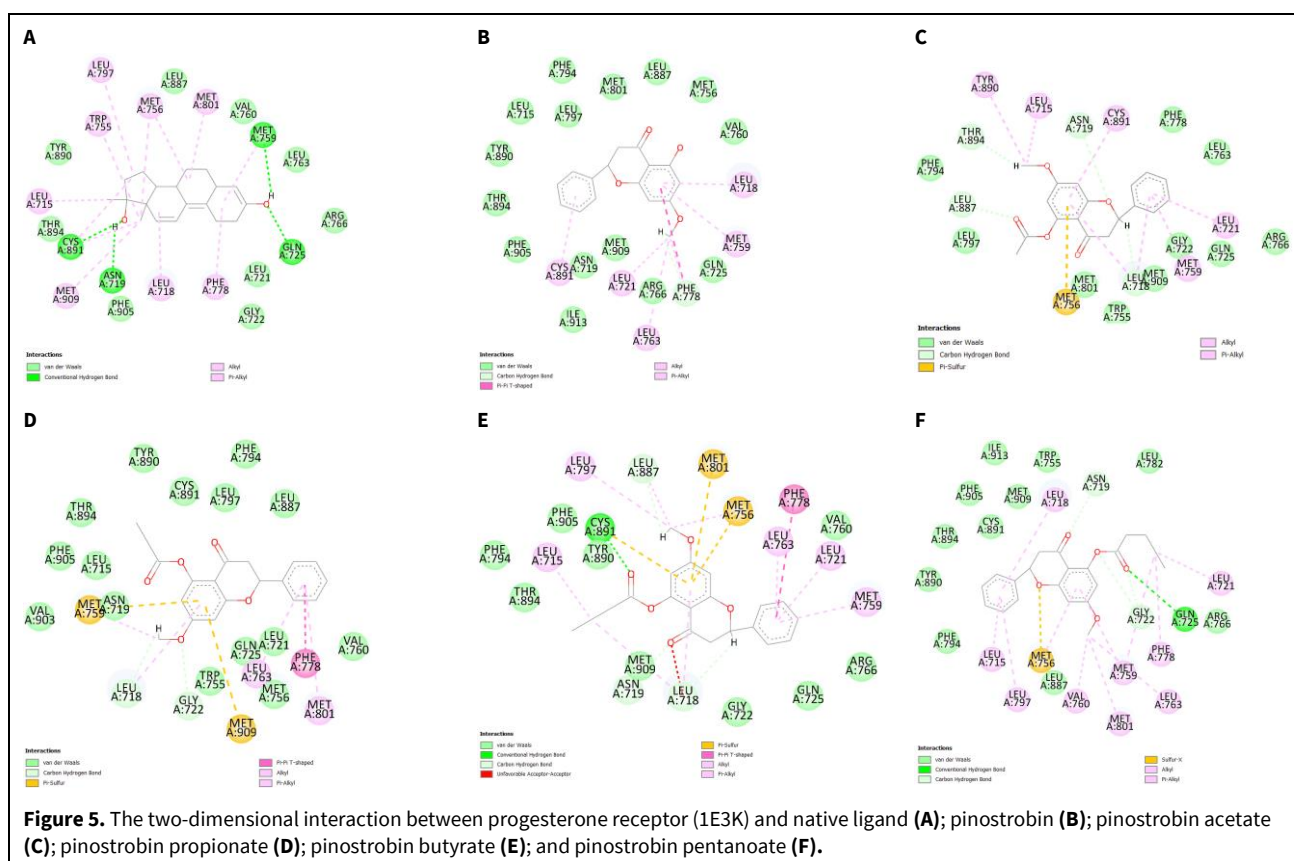


Figure 4. Native ligand overlays visualization of re-docking with native ligand from progesterone (A) and EGFR-HER2 (B) receptors crystallographic result; before re-docking (green), after re-docking (grey)

Table 2. Molecular docking results.

Code	S $\pm$ SD (kcal/mol)		Similarity of amino acids with native ligand (%)		Similarity of interaction types with native ligand (%)		Similarity of ligand-receptor interaction (%) ^a	
	1E3K	3PP0	1E3K	3PP0	1E3K	3PP0	1E3K	3PP0
P1	-7.539 $\pm$ 0.229*	-7.291 $\pm$ 0.074*	86	55	38	41	62	48
P2	-8.071 $\pm$ 0.085*	-8.052 $\pm$ 0.128*	86	77	38	59	62	68
P3	-8.386 $\pm$ 0.235*	-8.321 $\pm$ 0.082*	77	82	38	64	58	73
P4	-8.997 $\pm$ 0.187*	-8.548 $\pm$ 0.254*	95	91	48	73	71	82
P5	-9.163 $\pm$ 0.088*	-8.766 $\pm$ 0.163*	90	86	43	64	67	75

P1: Pinostrobin; P2: pinostrobin acetate; P3: pinostrobin propionate; P4: pinostrobin butyrate; P5: pinostrobin pentanoate; S: free binding energy value; SD: Standard deviation; ^a(similarity of amino acid residues + similarity of interaction types)/2. The molecular docking results were shown as mean $\pm$ SD of three replicates, with *p<0.001 indicating the significant differences compared with the lead compound.



As shown in Table 2, all 5-O-acylpinostrobin derivatives displayed lower free binding energy than pinostrobin on each receptor, indicating enhanced binding affinity. This result supports previous findings that the addition of alkyl chains can improve ligand activity (Praditapuspa et al., 2021). Moreover, pinostrobin pentanoate consistently showed the most favorable binding energy across both receptors based on molecular docking.

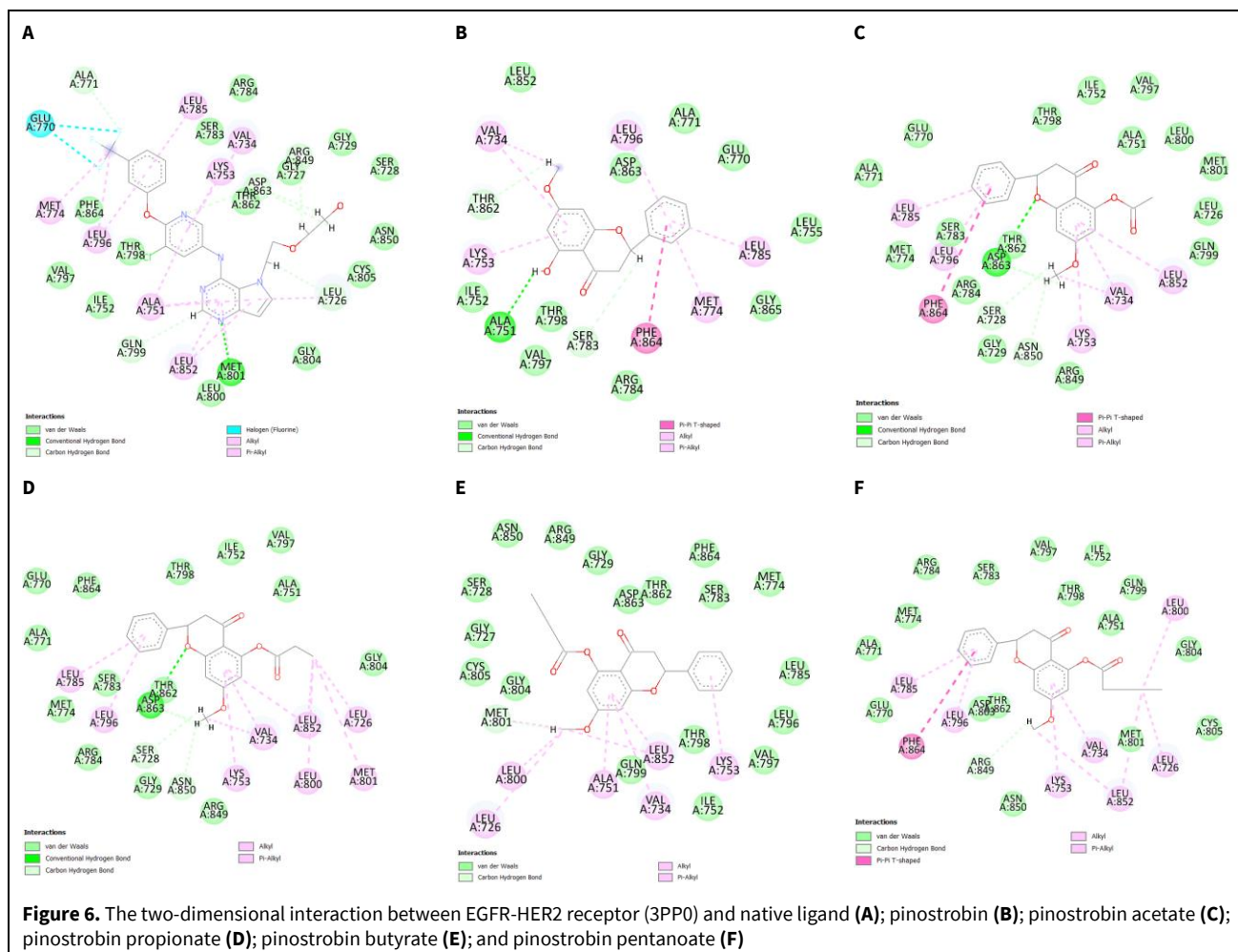
Furthermore, ligand-receptor bonds were used to analyze the percentage similarity to the native ligand. The more comparable the amino acid residues are, the greater the possibility of similar activity with the native ligand (Neshich et al., 2015; Pratama et al., 2019). A hydrogen bond can affect a compound's affinity for the protein. Moreover, hydrophobic bonds contributed to the biological activity. It can improve the stability of ligand-receptor interaction by minimising interactions between non-polar residues and water (Susilawati et al., 2024; Widiandani et al., 2025).

As shown in Fig. 5 and Table 2, pinostrobin butyrate achieved the highest similarity to the progesterone receptor's native ligand (R18), with 71% overall similarity and particularly strong amino acid overlap (95%). Other derivatives, such as pinostrobin acetate (62%), pinostrobin propionate (58%), and pinostrobin pentanoate (67%), showed intermediate values, while

pinostrobin showed greater similarity to pinostrobin acetate.

A similar examination was observed in the EGFR-HER2 receptor (Fig. 6, Table 2). Pinostrobin butyrate again demonstrated the highest similarity to the native ligand (O3Q), with 82% overall similarity, 91% amino acid similarity, and 73% interaction type similarity. In contrast, pinostrobin showed only 48% overall similarity, while pinostrobin acetate (68%), pinostrobin propionate (73%), pinostrobin pentanoate (75%) derivatives displayed intermediate values.

These findings support the superior interaction profile of pinostrobin butyrate compared to both the lead compound and other derivatives. The progressive elongation of the alkyl chain from the pinostrobin acetate to pinostrobin butyrate derivatives appeared to strengthen hydrophobic interactions between the ligand and nonpolar residues within the binding cavity. Pinostrobin butyrate substituent likely offers an optimal chain length that enhances van der Waals interactions while minimizing steric interference. Hence, these structural may contribute to the binding affinity and stability observed for pinostrobin butyrate, implying that moderate alkyl chain addition can favorably influence the biological potential of pinostrobin derivatives.



Most of observed interactions with progesterone and EGFR/HER2 receptors were dominated by van der Waals bonds, predicting preferential binding within hydrophobic areas. This is supported by the lower Gibbs free energy (S) values of the 5-O-acylpinostrobin derivatives compared to pinostrobin, further indicating stronger and more stable receptor interactions.

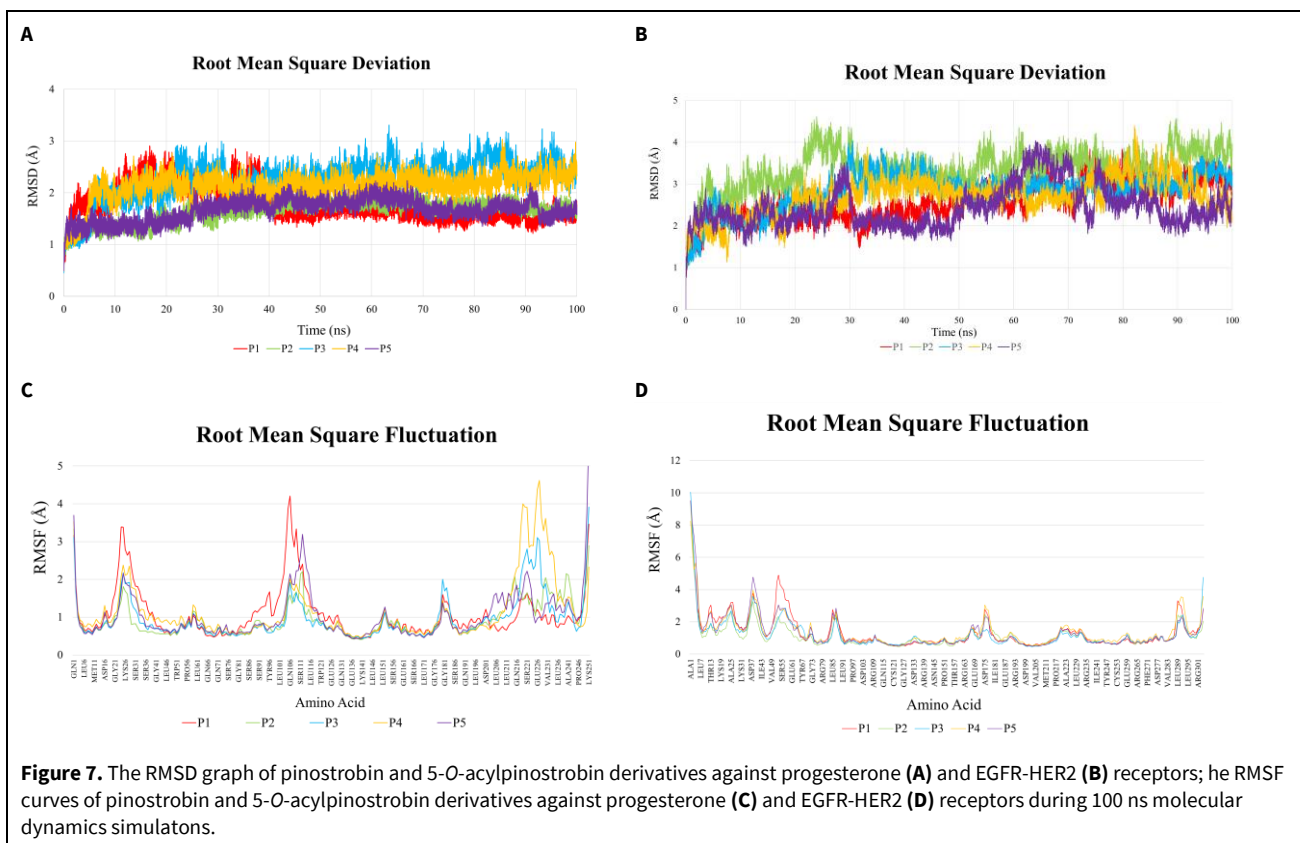
To further validate these docking results, molecular dynamics simulations were performed to examine the stability of ligand-receptor complexes over time.

Molecular dynamics simulations

Molecular dynamics simulations can examine protein enzyme stability, conformational changes, protein folding, and ion transport. The parameters that were examined in this study were root mean square deviation (RMSD) and root mean square fluctuation (RMSF). RMSD can predict the time required for a ligand to reach a stable conformation within the receptor's active site (Santos et al., 2019). RMSF can analyze the fluctuations to predict the amino acid flexibility during

simulations. Low fluctuations indicate low flexibility, suggesting a stable bonding interaction at the ligand-receptor binding active site (Renadi et al., 2023).

The stability interaction using a 100 ns molecular dynamics simulation by the RMSD and RMSF (Fig. 7) analyses revealed some differences compared with the docking method. Based on RMSD values, pinostrobin butyrate exhibited greater stability than pinostrobin and other 5-O-acylpinostrobin derivatives to both progesterone and EGFR-HER2 receptors. RMSF analysis identified key amino acid residues with low fluctuations on the 1E3K receptors, including Lys141, Met140, Phe137, Leu138, and Cys139, as well as Ile124 and Tyr203 on EGFR-HER2. These stable residues suggest favourable binding interactions, as indicated by molecular dynamics results. Pinostrobin butyrate is more stable when interacting with the progesterone receptor than the EGFR-HER2 receptor. To further strengthen these findings, future studies may extend the simulation time to 200 ns or longer, thereby providing greater confidence in the stability of the complexes.



ADMET prediction

The physicochemical properties were predicted and evaluated for oral bioavailability using the drug scan based on the drug-like soft principle (Song et al., 2020). The drug-like soft rule consists of molecular weight (MW) 100-600, log of octanol/water partition coefficient (logP) 3 to 6, number of hydrogen bond acceptors (nHA) ≤ 12 , number of hydrogen bond donors (nHD) ≤ 7 , topological polar surface area (tPSA) ≤ 180 , number of rotatable bonds (nRot) ≤ 11 , rigidBonds (nRig) ≤ 30 , number of rings (nRing) ≤ 6 , number of atoms in the biggest ring (MaxRing) ≤ 18 , number of heteroatoms (nHet) 1-15, formal charge (fChar) ≤ 4 .

The green color (lower limit) and the blue color (upper limit) on the radar view indicate the drug-like soft rule. Meanwhile, the yellow color indicates the compound properties result. Based on the result (Fig. 8) shows that pinostrobin and 5-O-acylpinostrobin derivative properties were completely between the lower and upper limits of the drug-like soft rule. Therefore, it can be predicted that all test ligands have a high oral bioavailability potential. The ADMET prediction is necessary to fully establish its suitability as a drug candidate. The pharmacokinetic and toxicity prediction result can be seen in Table 3.

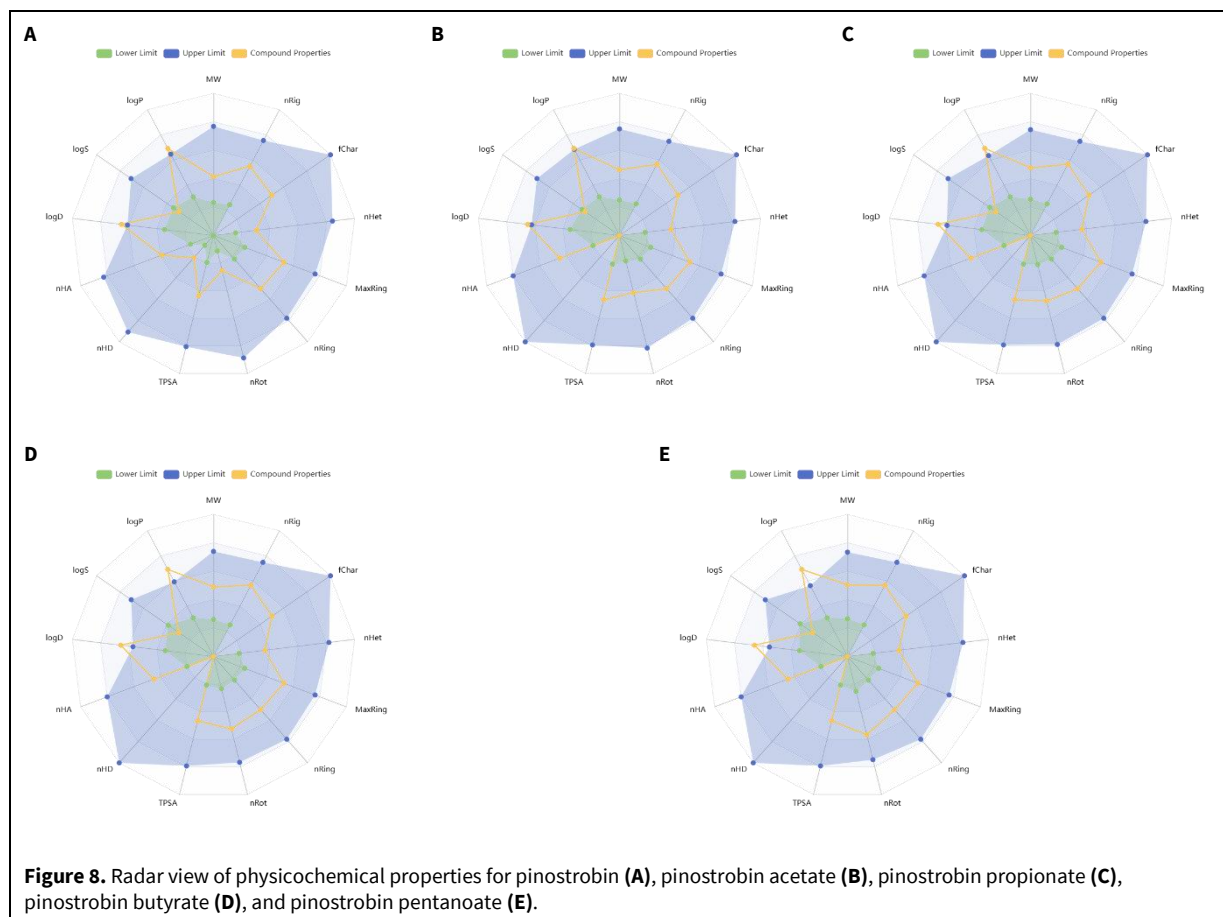
The pharmacokinetic properties consist of absorption, distribution, metabolism, and excretion (ADME) that were evaluated with 2 to 4 parameters on each

property. The parameters on absorption analysis were Caco-2 permeability ($> -5.15 \log \text{ cm/s}$), and human intestinal absorption (HIA) values provide an estimate of oral bioavailability, while the inhibitor of P-glycoprotein (Pgp-inhibitor) and substrate (range of 0 to 0.3) indicate the potential for efflux-mediated drug resistance.

The distribution involves plasma protein binding (PPB $\leq 90\%$), which indicated an adequate fraction of the compounds remains pharmacologically active, while the volume of distribution at steady state (VDss) in the range of 0.04-20 L/kg suggested sufficient tissue penetration. Blood-brain barrier (BBB) penetration (range of 0 to 0.3) limits potential central nervous system side effects, and the fraction unbound in plasma ($F_u \geq 5\%$) indicated excellent F_u .

The metabolism can be analysed using CYP2C19 and CYP3A4 substrate/inhibitor activity (range of 0 to 0.3), which suggests a reduced risk of drug-drug interactions and supports metabolic stability. The excretion involves plasma clearance ($CL < 5$), which indicates excellent clearance, and a half-life ($T_{1/2} > 8$ hours), which indicates a long half-life.

The toxicity prediction was analysed in the human hepatotoxicity (H-HT) range of 0 to 0.3, representing hepatic safety, and AMES toxicity, ranging from 0 to 0.3, was predicted to be non-mutagenic.



Meanwhile, rat oral acute toxicity and carcinogenicity (range of 0 to 0.3) require further *in vivo* validation.

According to the result (Table 3), pinostrobin and 5-*O*-acypinostrobin derivatives demonstrated several favourable pharmacokinetic properties. A previous study exhibited that, for the pharmacokinetic and toxicity prediction of pinostrobin and its derivatives against human estrogen receptor alpha, 2-parameter pKCSM models showed good results (Susilawati et al., 2024). In this study, we included several parameters to increase the variety of data collected and can be used for additional data in future study. Meanwhile, the toxicity prediction indicated potential carcinogenicity and acute oral toxicity in rats. However, all the compounds were predicted to be non-mutagenic in the AMES toxicity test and non-hepatotoxic, which are favourable indicators of genetic and hepatic safety. This research should be continued for further preclinical development.

CONCLUSION

In silico analyses demonstrate that 5-*O*-acypinostrobin derivatives exhibit stronger interactions with progesterone and the EGFR-HER2 receptors than the lead compound. Pinostrobin butyrate displays the highest stability in molecular dynamics simulations, suggesting potential as an anti-breast cancer candidate. Favourable pharmacokinetic properties and low predicted hepatotoxicity further support its potential, although carcinogenicity concerns must be evaluated experimentally. Future studies should include *in vitro* and *in vivo* validation to confirm efficacy and safety.

CONFLICT OF INTEREST

The research was conducted entirely free from any involvement in commercial, financial, or personal matters that might be perceived as a possible conflict of interest or that could have influenced the outcomes or interpretation of the study.

Table 3. Pharmacokinetic and toxicity prediction.

Property	Parameter	Predicted value				
		P1	P2	P3	P4	P5
Absorption	Caco-2 permeability (log cm/s)	-4.660	-4.728	-4.771	-4.779	-4.791
	Pgp-inhibitor	+++	+++	+++	+++	+++
	Pgp-substrate	---	---	---	---	---
	HIA	---	---	---	---	---
Distribution	PPB (%)	97.067	97.916	94.814	96.286	97.176
	VDss (L/kg)	0.532	0.570	0.293	0.295	0.283
	BBB penetration	--	---	---	---	---
	Fu (%)	2.165	6.474	1.986	1.552	1.213
Metabolism	CYP2C19 inhibitor	+++	+++	+++	+++	+++
	CYP2C19 substrate	---	++	++	+	+++
	CYP3A4 inhibitor	++	-	+	-	+
	CYP3A4 substrate	---	--	---	--	---
Excretion	CL (mL/min/kg)	5.055	3.661	4.254	4.355	4.183
	T _{1/2}	0.981	0.651	0.610	0.589	0.634
Toxicity	H-HT	--	---	---	---	---
	AMES toxicity	-	-	--	--	--
	Rat oral acute toxicity	-	+	-	+	+
	Carcinogenicity	+	-	-	-	-

HIA: human intestinal absorption; Pgp-inhibitor and substrate: P-glycoprotein inhibitor and substrate; PPB: plasma protein binding; VDss: Volume of distribution at steady state; BBB: Blood-brain Barrier; Fu: Fraction unbound in plasma; CL: clearance; T_{1/2}: the half-life; H-HT: human hepatotoxicity; The prediction probability values are transformed into six symbols: 0-0.1(--), 0.1-0.3(--), 0.3-0.5(-), 0.5-0.7(+), 0.7-0.9(++), and 0.9-1.0(+++).

ACKNOWLEDGMENTS

This research was supported by the Indonesian Ministry of Education, Culture, Research and Technology, under contract number 040/E5/PG.02.00.PL/2024; 1689/B/UN3.LPPM/PT.01.03/2024 (PTM Scheme). The authors would like to thank the Research Group of Drug Development, Faculty of Pharmacy, Universitas Airlangga, for the license of Molecular Operating Environment (MOE) 2022.02 program.

GENERATIVE ARTIFICIAL INTELLIGENCE (AI)

The authors used Quillbot (AI tool) to improve the language and readability of the manuscript. The authors reviewed and edited the content and take full responsibility for its accuracy. No images were generated or manipulated using AI tools.

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AUTHOR CONTRIBUTION:

Contribution	Widiandani T	Susilawati D	Purwanto BT	Siswodihardjo S
Concepts or ideas	x			
Design	x	x	x	x
Definition of intellectual content	x			x
Literature search		x	x	
Experimental studies	x	x	x	x
Data acquisition		x		
Data analysis	x		x	x
Statistical analysis		x		
Manuscript preparation	x	x		
Manuscript editing		x		
Manuscript review	x	x	x	x

Citation Format: Widiandani T, Susilawati D, Purwanto BT, Siswodihardjo S (2026) The potential of 5-O-acylpinostrobin derivatives against progesterone and EGFR-HER2 receptors as anti-breast cancer: Docking, molecular dynamic simulation, and ADMET prediction. J Pharm Pharmacogn Res 14(2): 2472. https://doi.org/10.56499/jppres_14.2.2472

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