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FULL PAPER

Molecular docking and QSPR of 5-*O*-acetylpinostrobin derivatives that inhibit ERα as breast cancer drug candidates

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The development of new breast cancer drugs is carried out through Computer-Aided Drug Design. Molecular docking and the Quantitative-Structure Properties Relationship (QSPR) as a step to obtain more effective compounds, selective, and the most influential physicochemical parameters through structural modification. Structural modification through the addition of acetyl groups caused changes in the biological activity of the compound. The research aimed to discover breast cancer drug prediction and its relationship with QSPR 5-*O*-acetylpinostrobin derivatives. The anti-breast cancer prediction used AutoDock Tools with the ERα type (PDB: 6V87). The selected parameters include free energy binding and inhibition constants. The physicochemical properties and excretion parameters were determined via online pkCSM and SwissADME. The relationship between physicochemical properties and total clearance was determined based on the QSPR equation with SPSS. The results of molecular docking showed five compounds with free energy binding and minimum inhibition constant values, namely P1, P2, P3, P4, and P5, with free energy binding values of -7.86, -7.77, -7.57, -7.31, and -6.96 kcal/mol and inhibition constant values of 1.73, 2.02, 2.82, 4.37, and 7.88 mM, respectively. The best QSPR equation was (1/CLtot) = 0.130*nRB - 0.034*MR + 0.366*Log P + 1.534 (n = 20, r = 0.761, SE = 0.579, F = 7.331, .sig = 0.003). An increase in nRB and Log P values and a decrease in MR values affect the increase in total clearance. Based on the results of the study, the five 5-O-acetylpinostrobin derivative compounds have the potential to be synthesized and tested further in vitro.

KEYWORDS

5-*O*-acetylpinostrobin; breast cancer; estrogen alpha; *in silico*.

Introduction

Worldwide, breast cancer cases account for 11.7% of new cases and 6.9% of cancer-based deaths. Indonesia ranked second for new cases of breast cancer by 11.5% and fifth for cancer-based death tolls by 6.6% [1-2]. Most breast cancer development occurs in the breast tissue, especially the ducts or lobules that supply milk into the ducts [3]. Approximately 70-75% of all breast cancers express hormone-positive receptors (estrogen receptor α (ERα)) by 75%, and progesterone receptor (PgR), or both [4,5]. Estrogen bonds with ERα to create an active receptor complex and affect gene transcription that regulates cell proliferation. The most widely used cancer breast drug is Tamoxifen, i.e. a *Selective Estrogen Receptor*

Modulator (SERM) that competes with estrogen to bind ERα to inhibit gene expression [6]. However, there are side effects of tamoxifen, including an increase in Bond Mineral Density (BMD) in postmenopausal women, negative effects on bone protection in premenopausal women, an increased risk of endometrial hyperplasia and uterine cancer, vaginal estrogenic effects including dyspareunia, vaginal discharge, and vaginal dryness. Other adverse effects include cardiovascular and venous thromboembolism and vasomotor symptoms [6,7]. Therefore, there is an objective to obtain anti-breast cancer compounds that have better effectiveness and selectivity [8].

Pinostrobin is a marker substance from the *Boesenbergia pandurata* rhizome that has been examined for its activities, e.g., anticancer, antifungal, antibacterial, anti-inflammatory, antioxidant, anti-parasitic, antiviral, and antiplatelet. Although pinostrobin has been proven to have anti-breast cancer activity, its potential remains lower than that of other drugs currently available on the market [9]. Therefore, it is essential to develop structural modifications of the lead compound that affect physicochemical properties and specific pharmacological effects [10-11]. Structure modification on the hydroxyl group of pinostrobin was synthesized, and five 5-*O*-acylpinostrobin derivatives were obtained as analgesics [8]. Another study on the breast anticancer activity of 5-*O*-acylpinostrobin derivatives *in silico* indicated that the compound had an affinity for the ErbB4 protein in breast cancer cells [13].

Pinostrobin structure modification by acyl groups in producing 5-*O*-acetylpinostrobin derivatives is highly rational to be developed. Acyl group addition can be determined through the Topliss model for aliphatic substances. The addition of acyl groups improves lipophilic (π), electronic (δ*), and steric (Es) properties, hence increasing pharmacological activity [14]. Thus, a beneficial synthesis pathway is explored. In this research, 5-*O*-acetylpinostrobin derivatives were selected to be developed as breast cancer drugs using Computer-Aided Drug Design (CADD).

CADD benefits include high productivity, open access, affordability, and clinical trial reduction [15,16]. Target-based drug design (molecular docking) and ligand-based drug design (Quantitative-Structure Properties Relationship (QSPR)) are both parts of CADD [17-18]. Molecular docking aims to analyze the conformation of ligands on the active side of the target macromolecule to predict biological activities [19,20]. The macromolecule of the target protein with PDB: 6V87 showed a bond with the 4-hydroxytamoxifen (4-OHT) native ligand with ERα. Free energy binding (ΔG), inhibition constant (Ki), and amino acid residue similarity are among the variables that have been analyzed for their ability to predict biological activities.

QSPR was employed to discover the mathematical relationship between physicochemical properties and one of the pharmacokinetic parameters using linear regression [21,22]. The significant pharmacokinetic parameter was total clearance (CL_{tot}), which plays an essential role in the drug excretion process in the body. The drug excretion process is essential in determining the average dose and steady-state level [23,24]. Furthermore, QSPR could determine the most influential physicochemical parameter in the excretion process. Therefore, the researchers employed CADD to determine the substance that could potentially be synthesized and developed as a breast cancer drug.

Experimental

System requirements and the online website

A Fujitsu AH544 computer with an Intel®Core(TM) i7-4702MQ, @ 2,20GHz, Nvidia® GeForce, Windows 10 64-bit

operating system, 16 GB RAM, ChemBio Draw 2D and 3D v.20.1.1, AutoDock Tools v.1.5.6, BIOVIA Discovery Studio v.21, and SPSS v.26 were utilized as the study's hardware and software. Online SMILES Translator (https://cactus.nci.nih.gov/translate/), pkCSM (https://biosig.lab.uq.edu.au/pkcsm/prediction), and Protein Data Bank (https://www.rcsb.org/) were the online resources used.

Ligand preparation

ChemDraw 2D was used to build the two-dimensional (2D) structures of 5-*O*-acetylpinostrobin derivatives. The three-dimensional (3D) structures were then created using the ChemDraw 3D tool, and the MMFF94 method was used to perform energy minimization. Ligands were saved in the .sdf and .pdb file types. The .sdf format was translated into .smile format by the Online SMILES Translator (https://cactus.nci.nih.gov/translate/).

Drug-likeness and drug clearance

Determination molecular weight (MW), Log P, number of hydrogen bond donors (nHBD), number of hydrogen bond acceptors (nHBA), number of rotational bonds (nRB), molar refractivity (MR), and topological polar surface area (TPSA) were all drug-likeness parameters. All ligands in .smile format were uploaded to the pkCSM and SwissADME online websites. Parameters determined with pkCSM include MW, Log P, nHBD, nHBA, and CL_{tot} while MR and TPSA were determined with SwissADME. All results were downloaded and saved in a .csv file.

Target protein preparation

The ERα (PDB ID: 6V87) containing the native ligand 4-OHT was downloaded in 3D from the RSCB Protein Data Bank. Using the X-ray diffraction technique, the macrocrystal was chosen because of its excellent crystal structural resolution (2.40 Å). There were two chains, i.e. A and B, totaling 262 amino acids. The protein was downloaded in the .pdb format.

Docking validation

Re-docking aimed to validate the native ligand docking with the AutoDock Tools program [25]. The molecular docking validation protocol was performed by docking ligand cocrystals with ERα receptor. The ligand co-crystal was extracted, and the polar hydrogen, Kollman charges, torsion, and rotational bonds were added. File saved in .pdbqt format. Redocking was performed on a grid box of size 12 x 26 x 34 with grid box center x: -6.212, y: -17.199, and z: 14.539. The re-docking ligand cocrystal was saved in a .pdbqt format. The Root Mean Square Deviation (RMSD), whose value is less than 2 Å, was used to determine the docking validation [26].

Molecular docking study

Twenty 5-*O*-acetylpinostrobin derivatives were docked using AutoDock Tools. Gasteiger, torsion, and rotation bonds were added to the ligand, and then it was stored in the .pdbqt format. All ligands were docked with the same grid box position as docking validation and saved in the .pdb format. The parameters evaluated from the docking results included ΔG, Ki, and amino acid residues. The most effective ligand as a breast cancer drug was chosen based on the lowest ΔG and Ki values and the amino acid residue similarity to the native ligand [26].

Visualization

2D and 3D structures of the protein-ligand interaction were visualized using the BIOVIA Discovery Studio Visualizer program.

QSPR models

The QSPR study used *drug-likeness* parameters (MW, log P, nHBA, MR, and RB)

and total clearance parameters (CL_{tot}) as properties. The relationship between the drug-likeness parameter and the log ($1/CL_{tot}$) was determined by QSPR. The SPSS evaluation result produced the best QSPR equation based on the correlation coefficient value (*r*) close to 1, the smallest standard error of estimation (*SE*), the largest *F*-value, and significance (*.sig*) < 0.05 [27].

Results and discussion

Drug-likeness is used to qualitatively assess the bioavailability of oral drug candidates through their physicochemical properties. The advantages of drug similarity development are quickness and affordability [27]. In this study, drug similarity was based on Lipinski's Rule 5 (Ro5), Veber's rule, and Ghose's rule determined through online pkCSM. Orally active substances, according to Ro5, must have MW ≤ 500 Da, log P ≤ 5, nHBD ≤ 5, and nHBA ≤ 10. TPSA, according to Veber's rule, is ≤ 140 [$Å^2$] and nRB ≤ 10. MR-value, according to Ghose's rule, is 40–140 [cm^3mol^{-1}] [28,29].

Table 1 presents all substances with MW values in the range of 298.29-417.46 Da, Log P had a range of 2.94-4.94, nHBA had a range of 5-7, and nHBD had 0. All 5-*O*-acetylpinostrobin derivatives conformed to Lipinski Ro5. The TPSA value of all 5-*O*-acetylpinostrobin derivatives was 61.83–104.35 [$Å^2$]. All compounds had nRBs in the range 3-6. All 5-*O*-acetylpinostrobin derivatives complied with Veber's rules. All substances had an MR of 79.05–117.60 [cm^3mol^{-1}], which complies with Ghose's rule. Therefore, all compounds had good bioavailability to be developed as oral drugs [30-32].

Docking validation results were obtained by redocking the ligand separated from the ERα (PDB: 6V87) using AutoDock Tools. Re-docking between the ligand and ERα obtained a ΔG of -10.05 kcal/mol, a Ki of 42.62 nM, and a RMSD of 0.966 Å. Molecular docking predicts the biological activity of a substance that will be developed as a drug. The lowest ΔG and Ki values, as well as the highest similarity of amino acid residues, were used to predict biological activity. The results of molecular docking of the twenty 5-*O*-acetylpinostrobin derivatives and 4-OHT as standard ligands obtained ΔG values of -7.86 to -5.36 kcal/mol, Ki of 1.73 to 118.93 nM, and similarity percentages of amino acid residues of 40-80% in the ERα receptor (PDB ID: 6V87), as listed in Table 2.

The ΔG values of all 5-*O*-acetylpinostrobin derivatives were lower than pinostrobin but higher than 4-hydroxytamoxifen. The Ki-values of all 5-*O*-acetylpinostrobin derivatives were lower than those of pinostrobin and 4-OHT. There were five ligands with the smallest ΔG and Ki values, including P1, P2, P3, P4, and P5. Based on Table 3, the amino acid residues of P1 and P2 like Leu 525, Thr 347, Ala 350, Glu 353, Leu 387, Leu 346, Leu 391, and Met 421, P3 like Leu 525, Thr 347, Ala 350, Glu 353, Leu 387, Leu 346, and Met 421, P4 like Leu 525, Thr 347, Ala 350, Leu 387, Leu 346, and Met 421, P5 like Leu 525, Ala 350, Leu 387, Leu 391, and Phe 404 were similar with 4-hydroxytamoxifen. The similarities between the amino acid residues were considered to have the same activity.

The QSPR test was conducted to determine the quantitative relationship between physicochemical parameters and log ($1/CL_{tot}$) through statistical linear regression analysis with SPSS. The linear regression equations were obtained from 39 equations. The best equations were assessed based on the values of *r*, *SE*, *F*, and *.sig*. Based on the assessment criteria, the best equation is obtained as follows:

$(1/CL_{tot}) = 0.130*nRB - 0.034*MR + 0.366*Log P + 1.534$

(n = 20, r = 0.761, SE = 0.579, F = 7.331, sig. = 0.003)

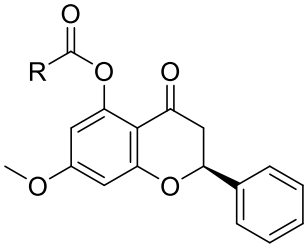


TABLE 1 Drug likeness and physicochemical properties of 5-*O*-acetylpinostrobin derivatives

Code	R	Ro5 Lipinski				Veber Rule		Ghose Rule	CL_{tot}
		MW	Log P	nHBA	nHBD	TPSA	nRB	MR	
P	Pinostrobin	270.28	3.11	4	1	55.76	2	74.02	0.21
P1	-4-N$(CH_3)_2C_6H_5$	417.46	4.69	6	0	65.07	5	117.60	0.65
P2	-$CH_2C_6H_5$	388.42	4.55	5	0	61.83	5	107.98	0.33
P3	-$(CH_2)_2C_6H_5$	402.45	4.94	5	0	61.83	6	112.79	0.41
P4	-cyclo-C_6H_{11}	380.44	4.89	5	0	61.83	4	105.41	1.05
P5	-cyclo-C_4H_7	352.39	4.11	5	0	61.83	4	95.80	0.24
P6	-$CH_2SO_2CH_3$	390.41	2.35	7	0	104.35	5	97.26	0.60
P7	-CH_2-cyclo-C_3H_5	352.39	4.11	5	0	61.83	5	95.80	0.32
P8	-cyclo-C_5H_9	366.41	4.50	5	0	61.83	4	100.61	0.25
P9	-C_6H_5	374.39	4.62	5	0	61.83	4	103.39	0.57
P10	-*t*-C_4H_9	354.40	4.35	5	0	61.83	3	97.65	0.24
P11	-CH_2SCH_3	358.42	3.67	6	0	87.13	5	95.89	0.50
P12	-$CHCl_2$	381.21	4.11	5	0	61.83	4	93.08	0.34
P13	-CH_2CH_3	326.35	3.72	5	0	61.83	4	88.30	0.41
P14	-OCH_3	328.32	3.55	6	0	71.06	3	84.97	0.30
P15	-CH_2CF_3	380.32	4.26	5	0	61.83	4	88.49	0.14
P16	-i-C_3H_7	340.38	3.96	5	0	61.83	4	93.11	0.31
P17	-CH_3	312.32	3.33	5	0	61.83	3	83.49	0.39
P18	-$N(CH_3)_2$	341.36	3.46	5	0	65.07	3	91.58	0.51
P19	-CF_3	366.29	3.87	5	0	61.83	3	83.68	0.10
P20	-H	298.29	2.94	5	0	61.83	4	79.07	0.19

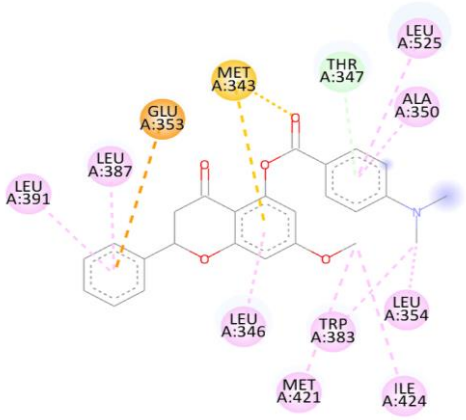
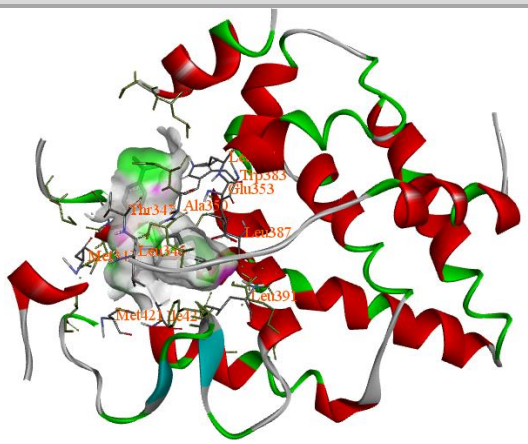
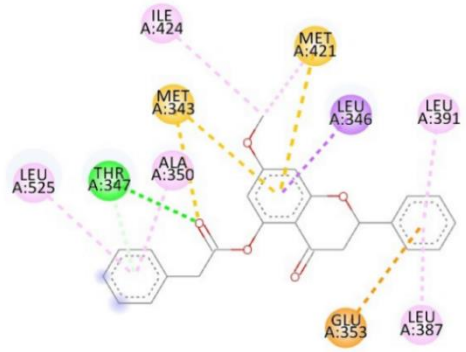
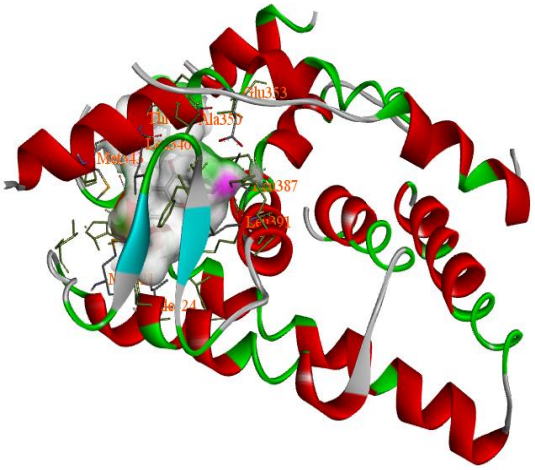
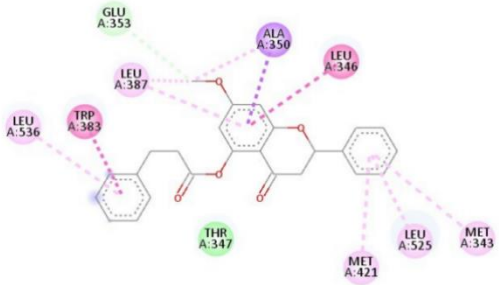
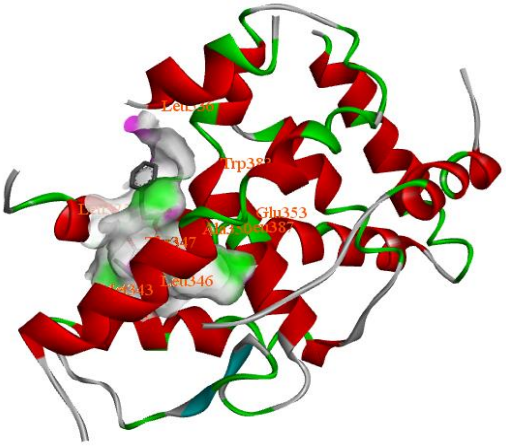
MW: Molecular Weigh (Da), Log P: Partition coefficient, nHBA: number of Hydrogen Bond Acceptors, (nHBD): number of Hydrogen Bond Donors, nRB: number of Rotational Bonds, MR: Molar Refractivity (cm^3mol^{-1}), TPSA: Topological Polar Surface Area ($Å^2$), and CL_{tot}: Clearance total (log mL/minute/kg).

TABLE 2 The results of molecular docking

Code	Compound	ΔG (kcal/mol)	Ki (mM)
P	Pinostrobin	-5.00	217.14
P1	5-*O*-4-(dimethylamino)benzoylpinostrobin	-7.86	1.73
P2	5-*O*-2-phenylacetylylpinostrobin	-7.77	2.02
P3	5-*O*-3-phenylpropanoylpinostrobin	-7.57	2.82
P4	5-*O*-cyclohexanecarbonylpinostrobin	-7.31	4.37
P5	5-*O*-cyclobutanecarbonylpinostrobin	-6.96	7.88
P6	5-*O*-2-(methylsulfonyl)acetylpinostrobin	-6.69	12.45
P7	5-*O*-cyclopropanecarbonylpinostrobin	-6.58	14.94
P8	5-*O*-cyclopentanecarbonylpinostrobin	-6.51	16.85
P9	5-*O*-benzoylpinostrobin	-6.43	19.38
P10	5-*O*-pivalylpinostrobin	-6.36	21.68
P11	5-*O*-2-(methylthio)acetylpinostrobin	-6.23	27.27
P12	5-*O*-2,2-dichloroacetylpinostrobin	-6.03	37.82
P13	5-*O*-propionylpinostrobin	-6.00	39.80
P14	5-*O*-methoxyformylpinostrobin	-5.94	44.01

P15	5-*O*-3,3,3-trifluoropropanoylpinostrobin	-5.94	44.13
P16	5-*O*-isobutonylpinostrobin	-5.82	54.47
P17	5-*O*-acetylpinostrobin	-5.60	77.94
P18	5-*O*-dimethylcarbamylpinostrobin	-5.57	82.07
P19	5-*O*-2,2,2-trifluoroacetylpinostrobin	-5.45	101.87
P20	5-*O*-formylpinostrobin	-5.35	118.93
4-OHT	4-hydroxytamoxifen	-9.67	0.08

TABLE 3 The amino acid residues of 5-*O*-acetylpinostrobin derivatives

Code	2-D	3D
P1		
P2		
P3		

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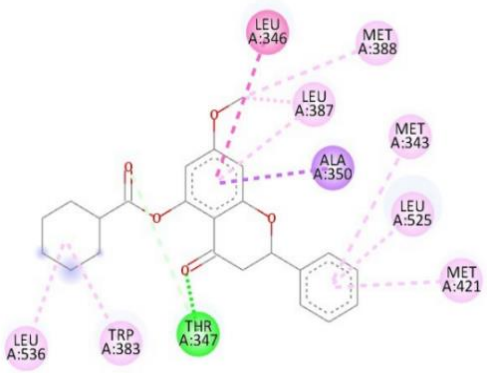

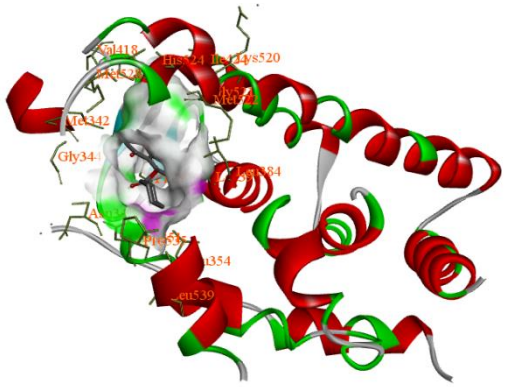

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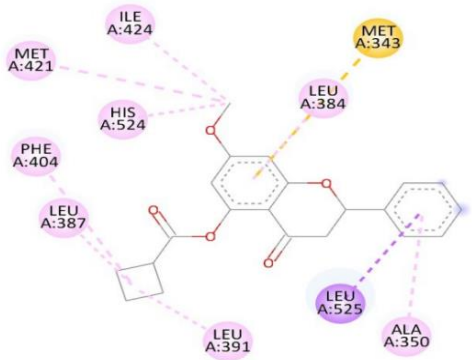
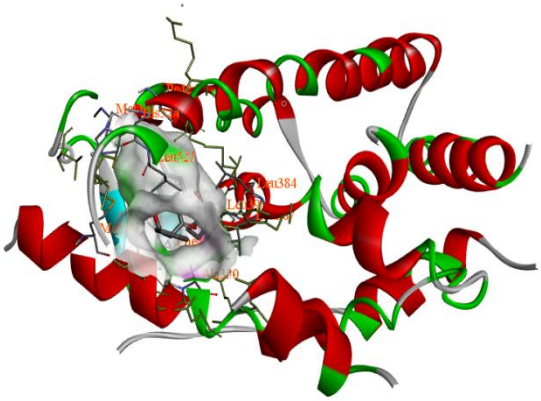
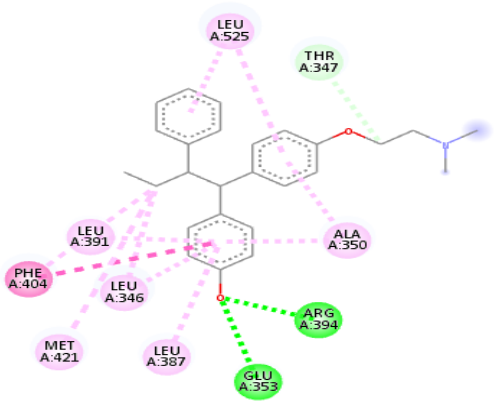
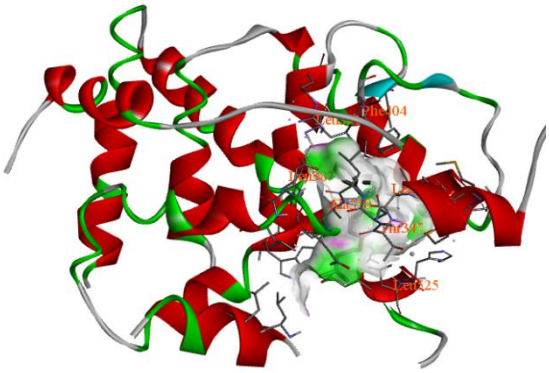




4-OHT





The selected equation had the best *r* value of 0.761 (r_{table} = 0.444; α= 0.05, two-tailed). Hence, there was a strong relationship between the physicochemical parameters and total clearance compared to the other equations. The *SE* was 0.579 and tended to be 0, indicating a small error and high predictive ability. The highest *F*-value was 7.331 (F_{table} = 3.592, α= 0.05) compared to the other equations, which means that the relationship obtained is correct and not due to chance. The smallest *.sig* value was 0.003 (<0.05), meaning that the equation was highly significant. The physicochemical parameters that most influenced the total clearance of the 5-*O*-acetylpinostrobin derivatives were nRB, MR, and Log P. The positive sign of the nRB and Log P indicated that the total clearance would increase with increasing nRB and Log P and also decrease with MR.

Conclusion

This research describes twenty 5-*O*-acetylpinostrobin derivatives that have the activity prediction to inhibit ERα. Five compounds with the minimum free energy binding and inhibition constant were selected,

namely P1, P2, P3, P4, and P5. The free energy binding values were -7.86, -7.77, -7.57, -7.31, and -6.96 kcal/mol, and the inhibition constant values were 1.73, 2.02, 2.82, 4.37, and 7.88 mM, respectively, which have the potential to be developed. In addition, all compounds were based on Lipinski's Rule of 5 to determine drug similarity. QSPR in this study used physicochemical parameters to obtain the best equation and determine the parameters that have the most influence on pharmacokinetics. The best equation was calculated based on statistical criteria, and the three physicochemical parameters that have the most impact on total clearance are nRB, MR, and Log P. The increase of nRB and Log P values and the decrease of MR values affect the increase in total clearance. The five compounds and the three physicochemical parameters impacted were the basis for synthesis and *in vitro* activity tests.

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Authors' contributions

SS, TW, and APW contributed to conception, design, and methodology; APW utilized the software; APW and TW obtained the data; SS, TW, and APW contributed to the data analysis; APW contributed to preparing the draft article; SS, TW, and APW contributed to review and editing; SS supervised the research. The manuscript's published form was approved by all authors.

Conflict of interest

The authors had no competing interests in the process of writing the article.

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