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RESEARCH ARTICLE

5-*O*-acetylpinostrobin derivatives inhibit oestrogen alpha and progesterone receptors through a molecular docking approach

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Keywords
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Abstract

Background: Among all cancers, breast cancer accounts for 11.7% of new cases and 6.9% of deaths worldwide. This is driven by increased estrogen receptor alpha (ERα) and progesterone receptor (PgR) expression. Many breast cancer drugs cause various side effects. Modifying the structure of pinostrobin by adding acyl groups to obtain 5-*O*-acetylpinostrobin derivatives can increase its activity and selectivity. **Objective:** This study aimed to predict the interaction of 5-*O*-acetylpinostrobin derivatives with ERα and PgR. **Method:** A molecular docking approach using AutodockTool. The Protein Data Bank (PDB) was used to obtain ID 3ERT (ERα) and 2W8Y (PgR). **Result:** The analysis showed the value of free energy binding (ΔG) to ERα with a range of -8.58 to -5.76 kcal/mol and an inhibition concentration (Ki) of 0.51 to 59.91 µM. PgR had ΔG values of -12.37 to -8.30 kcal/mol and Ki of 0.86 to 830.64 nM. **Conclusion:** The study showed that 5-*O*-4-(dimethylamino)benzoylpinostrobin, 5-*O*-cyclohexancarbonylpinostrobin, 5-*O*-2-phenylacetylpinostrobin, 5-*O*-3-phenylpropanoylpinostrobin, and 5-*O*-cyclobutanecarbonylpinostrobin have the potential to be synthesised and serve as the basis for the development of new anticancer compounds that inhibit ERα and PgR in breast cancer.

Introduction

Breast cancer is a malignancy that affects women (Acharya *et al.*, 2019). Breast cancer ranks first in new cases and fourth in deaths attributed to cancer, according to World Health Organization (WHO) data from 2020. Regarding breast cancer, the percentages of new cases and deaths were 11.7% and 6.7%, respectively (IARC, 2022). A potential risk factor is the increased synthesis of oestrogen receptor (ER) and progesterone receptor (PgR) in the mammary glands during puberty or post-menopause (Mehmood *et al.*, 2021). Between 70–75% of all breast cancers express hormone-positive receptors [oestrogen receptor α (75%; ERα), 65–75% PgR, or both] (Ongwisespaiboon & Jiraungkoorskul, 2017; Lashen *et al.*, 2023). ERα activation is responsible for most of the effects of estrogen on normal breast tissue and breast cancer (Feng *et al.*, 2018). However, in other cases, PgR-positive status influences the incidence of breast cancer (TilakVijay *et al.*, 2019; Lie *et al.*, 2022).

Treatments for breast cancer include medication, surgery, radiation, and chemotherapy. Drug administration depends on the type of breast cancer. For example, tamoxifen, doxorubicin, mifepristone, and trastuzumab are mostly used as the main biomolecular targets of breast cancer cells (Mani *et al.*, 2023). One of the drugs used to inhibit ERα is tamoxifen, and mifepristone inhibits PgR. These drugs are not able to treat breast cancer but can only control the disease (Hilton *et al.*, 2018). However, they have various side effects that can harm the patient's health. To address this issue, bioactive compounds from herbal plants are being developed as a potential solution.

Pinostrobin, a biomarker of *Boesenbergia pandurata* rhizome, has various anticancer, antifungal, antibacterial, anti-inflammatory, antioxidant, antiparasitic, antiviral, and antiplatelet activities (Patel *et al.*, 2016). Previous studies have shown that pinostrobin induces apoptosis and inhibits malignant breast cancer cell motility in the T47D cell line (Sukardiman *et al.*, 2014; Jones & Gehler, 2020). However, because the effectiveness of pinostrobin is low, structure modification has been performed to improve activity and selectivity.

Structural modifications of pinostrobin that have been carried out include adding prenyl groups as anti-breast cancer agents in the MCF-7 cell line (Poerwono *et al.*, 2010). In addition, the modification of the hydroxyl group has been used to obtain 5-*O*-acylpinostrobin derivatives, which have demonstrated analgesic activity (Siswandono *et al.*, 2020). Meanwhile, several 5-*O*-acylpinostrobin derivatives have shown anti-breast cancer activity *in silico* via targeting the ErbB4 protein (Praditapuspa *et al.*, 2022). However, there has been no research on the effects of 5-*O*-acetylpinostrobin derivatives that can inhibit ERα and PgR in breast cancer cells, even though the increased expression of ERα and PgR causes breast cancer. Therefore, we aimed to predict the interaction between 5-*O*-acetylpinostrobin derivatives and ERα and PgR through molecular docking studies.

Methods

Tools and materials

The tools and software provided for research included a Fujitsu AH544 computer with specifications Core i7, CPU @ 2.20 GHz, Nvidia, 16 GB RAM, ChemBio Draw 2D and 3D software ver. 20.1.1, and the AutoDockTools software ver. 1.5.6. The *in silico* study materials included twenty compounds of 5-*O*-acetylpinostrobin derivatives, ERα (PDB ID:3ERT), and PgR (PDB ID:2W8Y).

Ligand preparation

Two-dimensional (2D) structures of the 5-*O*-acetylpinostrobin derivatives were created using ChemDraw 2D software. The 2D structure was copied into ChemDraw 3D, which was used to create the three-dimensional (3D) structure, and the MMFF94 method was used to minimise the energy consumption. The ligands were saved in .mol2 file. All ligands were entered into the AutoDockTools software, and non-polar hydrogen and Gasteiger charges were added. A torsion tree was added, and the ligands were saved in .pdbqt format (Praditapuspa *et al*., 2021).

Receptor preparation

PDB ID 3ERT and 2W8Y were downloaded from www.rcsb.org in pdb format. Water was removed, and missing atoms were repaired using AutoDockTools software. The native ligand binding to the receptor was deleted, and the atoms were repaired. Polar hydrogen atoms and Kollman charges were also added. The file was saved in .pdbqt format (Praditapuspa *et al*., 2021).

Validation of the docking method

Preparation of .gpf and .dpf files was performed by setting up a grid box. Polar hydrogen groups and Kollman charges were also added. The grid box, coordinates, and distance per unit were determined as the ligand locations. The redocked native ligands were stored in pdbqt format. The method was validated before docking to determine the root mean square deviation (RMSD) (Praditapuspa *et al*., 2021).

Docking of compound tests and standard

AutoDockTools software was used to dock twenty 5-O-acetylpinostrobin derivatives and native ligands. Gasteiger bonds, torsion, and rotation were introduced to the ligands. These files were saved in .pdbqt format. All ligands were docked using the same grid box position for validation and saved in .pdb format. The most effective ligand as a potential breast cancer drug was selected based on the lowest ΔG and Ki values.

Visualisation of amino acid residues

The protein-ligand interactions were displayed in 2D and 3D using the BIOVIA Discovery Studio Visualizer tool.

Results

The 2D structures of 5-*O*-acetylpinostrobin derivatives (Figure 1), where R is a substituent in the form of aliphatic compounds, are shown in Table I. The study revealed an ERα target protein with PDB ID: 3ERT. Criteria for 3ERT include: derived from Homo sapiens organisms, X-ray diffraction patterns at 1.90 Å resolution, chain A (261 residues), and 4-hydroxytamoxifen as a native ligand. The target protein, PgR, had a PDB ID of 2W8Y. 2W8Y criteria include: derived from *Homo sapiens* organism, X-ray diffraction pattern, resolution 1.80 Å, chain A and B (260 residues), and (14beta,17alpha)-17-ethynyl-17-hydroxyestr-4-en-3-one (mifepristone) as a native ligand. 4-hydroxytamoxifen is an estrogen alpha inhibitor drug, and mifepristone is a progesterone inhibitor drug that has been on the market (TilakVijay *et al.*, 2019; Lashen *et al.*, 2023).

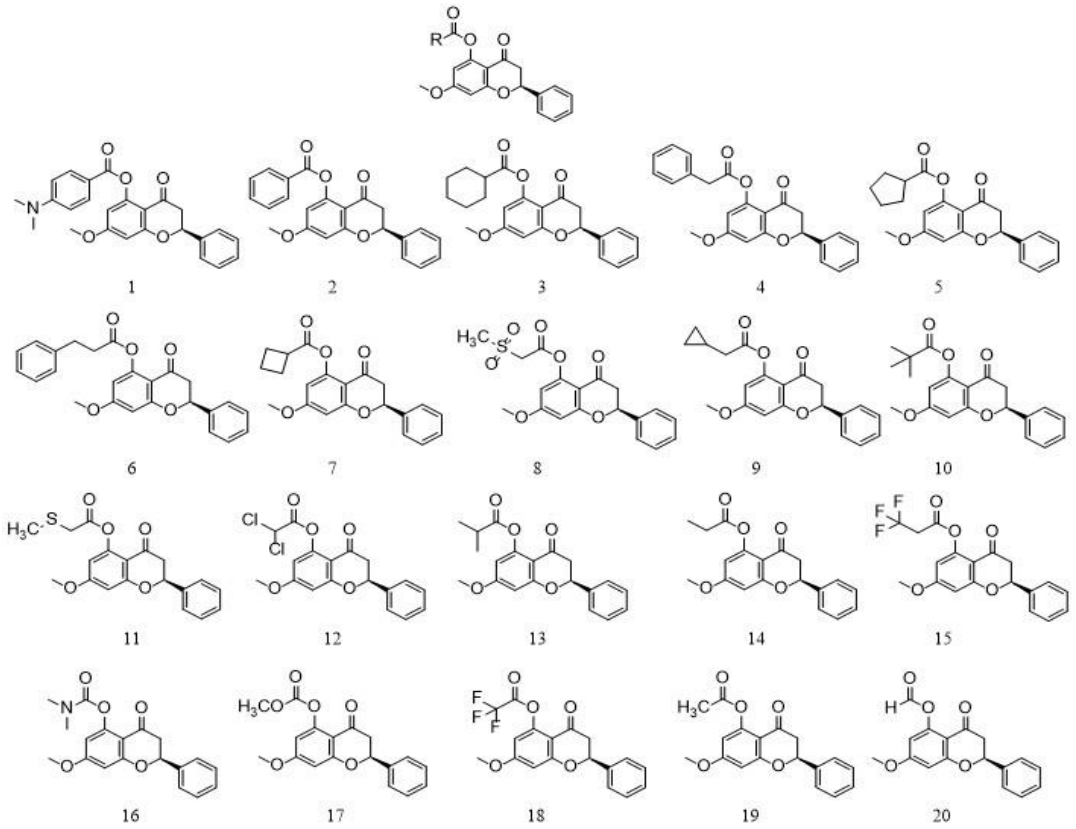


Figure 1: 2D structure of 5-*O*-acetylpinostrobin derivatives

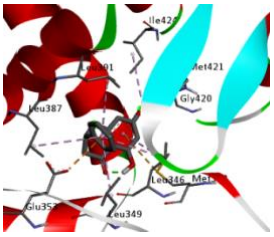
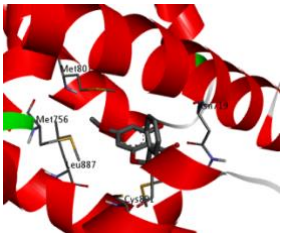
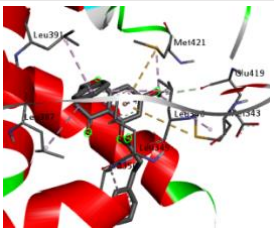
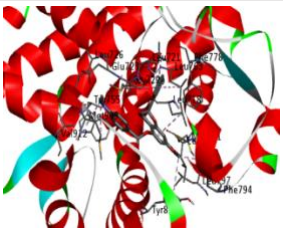
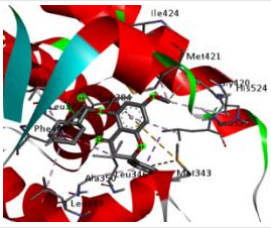
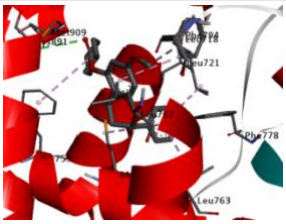
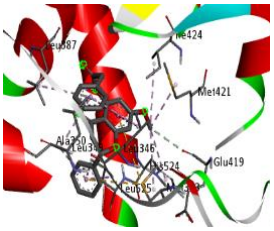
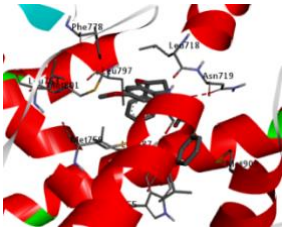
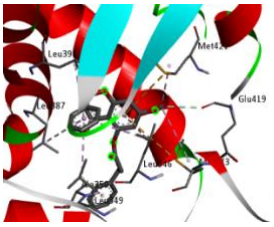
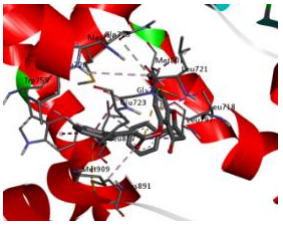
Table I: Molecular docking results of 5-*O*-acetylpinostrobin derivatives against ERα and PgR

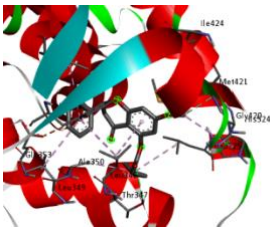
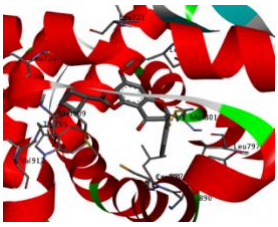
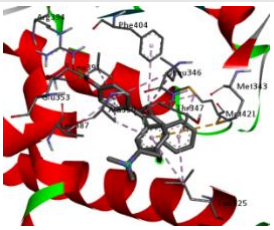
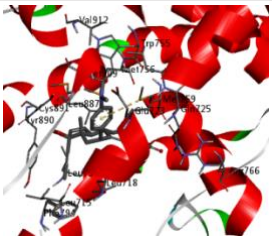
No. of compound	R	Compound	PDB: 3ERT		PDB: 2W8Y	
			ΔG (kcal/mol)	Ki (μM)	ΔG (kcal/mol)	Ki (nM)
1.	-4-N$(CH_3)_2C_6H_5$	5-*O*-4-(dimethylamino)benzoylpinostrobin	-8.58	0.51	-11.85	2.07
2.	-C_6H_5	5-*O*-benzoylpinostrobin	-8.55	0.54	-11.26	5.53
3.	-cyclo-C_6H_{11}	5-*O*-cyclohexanecarbonylpinostrobin	-8.54	0.55	-11.45	4.04
4.	-$CH_2C_6H_5$	5-*O*-2-phenylacetylylpinostrobin	-8.45	0.63	-11.96	1.70
5.	-cyclo-C_5H_9	5-*O*-cyclopentanecarbonylpinostrobin	-8.40	0.69	-11.02	8.33
6.	-$(CH_2)_2C_6H_5$	5-*O*-3-phenylpropanoylpinostrobin	-8.39	0.70	-12.37	0.86
7.	-cyclo-C_4H_7	5-*O*-cyclobutanecarbonylpinostrobin	-8.29	0.83	-11.02	8.40
8.	-$CH_2SO_2CH_3$	5-*O*-2-(methylsulfonyl)acetylpinostrobin	-8.09	1.17	-10.70	14.23
9.	-CH_2-cyclo-C_3H_5	5-*O*-cyclopropanecarbonylpinostrobin	-7.77	2.00	-10.82	11.76
10.	-t-C_4H_9	5-*O*-pivalylpinostrobin	-7.61	2.66	-10.10	39.32
11.	-CH_2SCH_3	5-*O*-2-(methylthio)acetylpinostrobin	-7.38	3.91	-10.07	41.53
12.	-$CHCl_2$	5-*O*-2,2-dichloroacetylpinostrobin	-7.20	5.26	-9.66	83.40
13.	-i-C_3H_7	5-*O*-isobutonylpinostrobin	-6.97	7.79	-9.92	53.66
14.	-CH_2CH_3	5-*O*-propionylpinostrobin	-6.92	8.42	-9.41	125.76
15.	-CH_2CF_3	5-*O*-3,3,3-trifluoropropanoylpinostrobin	-6.84	9.67	-9.46	116.26
16.	-$N(CH_3)_2$	5-*O*-dimethylcarbamylpinostrobin	-6.55	15.86	-9.33	145.82
17.	-OCH_3	5-*O*-methoxyformylpinostrobin	-6.54	16.06	-9.09	215.56
18.	-CF_3	5-*O*-2,2,2-trifluoroacetylpinostrobin	-6.28	24.79	-8.90	299.18
19.	-CH_3	5-*O*-acetylpinostrobin	-6.22	27.39	-8.72	406.02
20.	-H	5-*O*-formylpinostrobin	-5.76	59.91	-8.30	830.64
21.	P	Pinostrobin	-4.97	228.18	-7.76	2050.00

No. of compound	R	Compound	PDB: 3ERT		PDB: 2W8Y	
			ΔG (kcal/mol)	Ki (μM)	ΔG (kcal/mol)	Ki (nM)
22.	4-OHT	4-hiydroxytamoxifen	-10.57	0.017	-	-
23.	MFP	Mifepristone	-	-	-14.75	0.02

The docking method's validation results using 3ERT and 2W8Y showed RMSD values of 0.951 Å and 0.308 Å, respectively. The molecular docking result in Table II showed the ΔG value to ERα with a range of -8.58 to -5.76 kcal/mol and Ki value with a range of 0.51 to 59.91 μM. PgR had ΔG values of -12.37 to -8.30 kcal/mol and Ki values of 0.86 to 830.64 nM. The amino acid residues of the selected compounds are listed in Table II.

Table II: Amino acid residues of five selected 5-*O*-acetylpinostrobin derivatives with ERα and PgR

No	Compound	PDB: 3ERT		PDB: 2W8Y	
		3D structure	Amino acids	3D structure	Amino acids
1.	Pinostrobin		Carbon hydrogen bond: Leu 387, Alkyl & Pi-Alkyl: Leu 525, Met 421, Leu 384, Leu 346, Leu 391, Ala 350		Alkyl: Met 801, Met 756, Pi-Sigma: Asn 719, Pi-Alkyl: Met 909, Pi-Sulfur: Met 756, Met 801, Cys 891
2.	5-*O*-4-(dimethylamino)benzoylpinostrobin		Conventional hydrogen bond: Thr 347, Carbon hydrogen bond: Glu 419, Pi-anion: Met 343, Pi-Sulfur: Glu 353, Pi-Sigma: Leu 346, Alkyl & Pi-Sigma: Leu 525, His 524, Met 421, Leu 346, Leu 391, Ala 350, Leu 354		Carbon hydrogen bond: Gly 722, Glu 273, Pi-Pi T-Shaped: Phe 778, Alkyl: Leu 718, Leu 715, Leu 797, Met 909, Val 912, Met 759, Pi-Alkyl: Trp 755, Met 759, Leu 763, Leu 721, Phe 794, Tyr, 890, Leu 718
3.	5-*O*-cyclohexanecarbonylpinostrobin		Carbon hydrogen bond: Gly 420, Pi-Sigma: Leu 525, Pi-Sulfur: Met 343, Alkyl & Pi-Alkyl: Leu 391, Leu 387, Leu 346, Phe 404, Ile 424, Met 421, His 524, Ala 350		Conventional hydrogen bond: Cys 891, Pi-Pi T-shaped: Phe 778, Alkyl: Leu 718, Leu 797, Met 909, Pi-Alkyl: Phe 794, Leu 718, Trp 755, Leu 763, Met 759, Trp 755.
4.	5-*O*-2-phenylacetylpinostrobin		Carbon hydrogen bond: Glu 419, Pi-Sigma: Leu 525, Pi-cation: Arg 394, Pi-Sulfur: Met 343, Alkyl & Pi-Alkyl: Ala 350, Leu 391, Leu 387, Leu 346, Met 421, His 524		Carbon hydrogen bond: Gly 722, Pi-Pi T-shaped: Trp 755, Alkyl: Leu 763, Met 759, Pi-Sigma: Leu 797, Leu 718, Pi-Alkyl: Leu 887, Phe 778, Met 909, Leu 726, Pi-Sulfur: Met 801, Unfavoravle Acceptor-Acceptor: Asn 719
5.	5-*O*-3-phenylpropanoylpinostrobin		Carbon hydrogen bond: Glu 419, Pi-Sulfur: Met 421, Alkyl & Pi-Alkyl: Ala 350, Leu 525, Met 343, Leu 346, Leu 387, Leu 391		Carbon hydrogen bond: Gln 725, Pi-Pi T-shaped: Trp 755, Amide-Pi stacked: Gly 722, Alkyl: Met 759, Lys 721, Pi-Sigma: Leu 797, Leu 718, Pi-Alkyl: Leu 887, Cys 891, Pi-Sulfur: Met 809, Met 801

No	Compound	PDB: 3ERT		PDB: 2W8Y	
		3D structure	Amino acids	3D structure	Amino acids
6.	5-*O*-cyclobutanecarbonylpinostrobin		Conventional hydrogen bond: Thr 347, Carbon hydrogen bond: Gly 521, Pi-Sigma: Leu 391, Alkyl & Pi-Alkyl: Met 421, His 524, Leu 525, Ala 350, Leu 346, Leu 387		Conventional hydrogen bond: Cys 891, Pi-Pi T-shaped: Tyr 890, Alkyl: Leu 721, Leu 718, Leu 726, Val 912, Met 909, Pi-Sigma: Leu 797, Pi-Alkyl: Leu718, Cys 891, Leu 887, Trp 755, Pi-Sulfur: Met 801
7.	4-hiydroxytamoxifen		Conventional hydrogen bond: Glu 353, Arg 394, Van der Waals: Thr 347, Pi-Sulfur: Met 343, Amide-Pi-Stacked: Leu 346, Leu 525, Met 421, Alkyl& Pi-Alkyl: Ala 350, Leu 387, Leu 391	-	-
8.	Mifepristone	-	-		Conventional hydrogen bond: Gln 725, Arg 766, Carbon hydrogen bond: Glu 723, Alkyl: Leu 726, Met 909, Val 912, Met 759, Met 756, Leu 887, Leu 797, Leu 718, Leu 715, Cys 891, Pi-Sigma: Trp755, Pi-Alkyl: Met 909, Trp 755, Phe 794, Tyr 890, Pi-Sulfur: Met 759

Discussion

In cases of breast cancer, there is an overproduction of the hormone progesterone and oestrogen (Mehmood *et al.*, 2021). There are 23 furanocoumarin chemicals that could have anti-cancer. Xanthotoxol inhibited ERα and PgR (Acharya *et al.*, 2019). Another study showed that 2,4,6 tris-methylphenylamino1,3,5-triazine (MPAT) was shown to have activity as an ERα and PgR inhibitor in vivo (Mehmood *et al.*, 2021).

Molecular docking plays a significant role in drug development by predicting the binding between ligands and the active side of target receptors (Mani *et al.*, 2023). This study selected target receptors that influence breast cancer, namely ERα and PgR, as ligands. These receptors interact with 5-O-acetylpinostobin derivatives. This becomes the basis for selecting five compounds from 5-*O*-acetylpinostobin derivatives that have the potential to be synthesised in the future so that their anti-breast cancer activity can be determined with specific targets on ERα and PgR.

The molecular docking process involves method validation to ensure the suitability of the method before docking, as seen from the RMSD value (<2 Å) (Norhayati *et al.*, 2023). The RMSD values on both receptors were <2 Å, which indicated that the docking method was accurate and appropriate. The ΔG and Ki values in Table I are arranged according to the smallest values. A smaller ΔG value reveals high conformational stability between the ligand complex and the target receptor (Norhayati *et al.*, 2023). All derivatives of 5-*O*-acetylpinostobin have smaller ΔG values than pinostrobin in both receptors, suggesting that all compounds have better potential than pinostrobin. The compound called 5-*O*-4-(dimethylamino) benzoylpinostrobin was docked with ERα receptor, having the smallest ΔG value of -8.58 kcal/mol. In contrast, 5-*O*-3-phenylpropanoylpinostrobin had the smallest ΔG value of -12.37 kcal/mol docked with PgR. This indicates that both compounds have the greatest potential compared with the other derivatives. Smaller Ki values indicate stronger inhibition of the compound against the receptor. 5-*O*-4-(dimethylamino)benzoylpinostrobin and 5-*O*-3-phenylpropanoylpinostrobin had the smallest Ki, indicating stronger inhibition of 5-*O*-4-(dimethylamino)benzoylpinostrobin against ERα as well as 5-*O*-3-phenylpropanoylpinostrobin against PgR.

Based on the smallest ΔG and Ki values, five potential compounds were synthesised and tested for *in vitro* activity: 5-*O*-4-(dimethylamino)benzoylpinostrobin, 5-

O-cyclohexancarbonylpinostrobin, 5-*O*-2-phenylacetylpinostrobin, 5-*O*-3-phenylpropanoylpinostrobin, and 5-*O*-cyclobutanecarbonylpinostrobin. The five selected compounds were visually inspected for amino acid residue interactions between the ligand and target receptor. The addition of conventional hydrogen bonds can result in greater strength than that of carbon-hydrogen bonds. Adding hydrophobic interactions can increase hydrophilicity, increasing the stability of ligand-receptor interactions (Siswandono *et al.*, 2020).

This study has limitations because it discusses only the predicted activity of two mechanisms that affect the incidence of breast cancer. Therefore, further research is needed to provide laboratory evidence of these mechanisms' activity in vitro and in vivo.

Conclusion

This study showed that 5-*O*-4-(dimethylamino)benzoylpinostrobin, 5-*O*-cyclohexancarbonylpinostrobin, 5-*O*-2-phenylacetylpinostrobin, 5-*O*-3-phenylpropanoylpinostrobin, and 5-*O*-cyclobutanecarbonylpinostrobin have the potential to be synthesised and serve as the basis for the development of new anticancer compounds that inhibit ERα and PgR.

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