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Molecular Docking and QSAR Study of 5-*O*-acylpinostrobin Derivatives as Topoisomerase IIα Inhibitors

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Abstract

Background: *Cancer is one of the top causes of death worldwide. A wide range of illnesses known as cancer can start in almost any organ or tissue in the body when abnormal cells multiply uncontrollably. Cancer patients have higher levels of the Topo IIα protein in their cells, this protein has been proposed as a relevant target for anticancer treatment development.* ***Objective****: This study aims to predict the anticancer activity of pinostrobin and 5-O-acylpinostrobin derivatives against topoisomerase IIα by docking molecular and QSAR study.* ***Methods****: In silico analysis was performed using the structure of the topoisomerase IIα (PDB: 5GWK)) as templates. Molecular docking analysis was performed with AutoDock Vina.* ***Result****: All 5-O-acyl pinostrobin derivatives, showed lower ΔG values than the parent pinostrobin. The 5-O-acetyl pinostrobin compound showed the highest score, namely -9.14 kcal/mol. 5-O-acetyl pinostrobin is predicted as the most powerful inhibitor that can cause inhibition of topoisomerase IIα.* ***Conclution****: The results of the best QSAR equation obtained can be used as a reference for predicting the activity of the new pinostrobin derivatives to be synthesized by inserting the electronic (E_{tot}) parameter values of the compounds into the equation.*

Keywords*: modification, pinostrobin, QSAR, topoisomerase IIα*

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INTRODUCTION

Cancer is a broad category of disorders that can originate in nearly any organ or tissue in the body when aberrant cells proliferate out of control, cross normal boundaries to infect other body parts, or spread to other organs. Roughly 10 million deaths, or roughly one in six deaths, globally will be attributable to cancer in 2020 (Martel *et al.,* 2020). The Global Burden of Cancer Study (Globocan) from the World Health Organization (WHO) recorded that total cancer cases in Indonesia in 2020 reached 396,914 cases and 234,511 deaths (Sung *et al.,* 2021).

Cancer treatment can currently be done in several ways, such as chemotherapy, surgery and radiation therapy, which depends on the stage of the cervical cancer. In chemotherapy treatment therapy, most cancer drugs are designed to destroy and prevent the growth of cancer cells by triggering apoptosis (Wong, 2011). The selective initiation of apoptosis is a process used in cancer treatment, as it stimulates cancer cells to undergo self-destruction in a precise manner, without affecting healthy cells or creating inflammation (Nagata, 1997). Apoptosis is initiated when topoisomerase IIα (Topo IIα) inhibition induces DNA damage. The occurrence of DNA damage triggers the activation of p53, which controls the progression of the cell cycle and initiates programmed cell death (Sheng *et al.*, 2006). Topo IIα is a crucial regulator of DNA topology since it controls the wrapping and unwinding of DNA strands during transcription or DNA replication. Topo IIα is more prevalent in cancer cells compared to normal cells, making it a prime target for the development of anticancer drugs (Delgado *et al.,* 2018).

For the treatment of cancer, doxorubicin is one of the chemotherapy treatments. Doxorubicin is an antineoplastic drug that functions as a Topo IIα inhibitor (Mastrangelo *et al.,* 2022). This medicine has been established as the primary choice for chemotherapy in treating different forms of cancer. Recent studies have shown that doxorubicin can cause cardiotoxicity in humans (Zhao *et al.,* 2018). The ideal cancer drug is a drug that has a specific target, high selectivity and is abundant in nature (Pal *et al.,* 2020; Sher *et al.,* 2018).

Research on natural ingredients has been proposed as a safer alternative therapy for cancer. The rhizome of *Boesenbergia pandurata* (Roxb.) Schlecht is reported to contain active anti-cancer compounds. Ethanol extract of *B. pandurata* had more significant cytotoxic activity against HeLa cells (IC_{50} of 60 µg/mL) than Vero cells (IC_{50} of 125 µg/mL) (Listyawati *et al.,* 2016). So it was concluded that the ethanolic extract of *B. pandurata* has selective toxicity against cancer cells. According to Pratama *et al.,* (2022), the flavonoids found in *B. pandurata* have demonstrated potential as an anti-cancer agent by effectively suppressing ER-α and HER2 in silico. One of the compounds containing flavonoids and is a marker compound from these plants is pinostrobin. Pinostrobin has cytotoxic activity against carcinogen-induced fibrosarcoma in mice (Sukardiman *et al.,* 2014). Pinostrobin has cytotoxic activity in vitro against cervical cancer cells HeLa with IC_{50} of 50 µM, breast cancer cell T47D with IC_{50} of 2,93 mM, and no cytotoxic effect on normal HEK293 cells (Jaudan *et al.,* 2018; Widiandani *et al.,* 2023). Even though it has good activity against cancer cells, anti-cancer activity of pinostrobin is still lower than currently available drugs.

One effort to increase the anticancer activity of pinostrobin is by adding a group to its basic structure or known as a structural modification. Structure modification on the hydroxyl group of pinostrobin was synthesized, and five 5-*O*-acylpinostrobin derivatives were obtained as analgesics (Siswandono *et al*., 2020; Suryadi *et al*., 2021). 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 (Praditapuspa *et al*., 2021). Pinostrobin structure modification by acyl groups in producing 5-*O*-acylpinostrobin 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 (Siswandono, 2016). Computational approaches are currently crucial in expediting the drug development process and are vital in uncovering novel pharmaceuticals. One of the computational strategies for drug discovery is simulation with molecular docking and quantitative structure-activity relationships (QSAR) (Meng *et al*., 2012).

Molecular docking aims to understand and predict molecular recognition, study drug-receptor interactions, and predict candidate ligands' binding affinity or energy match to target proteins (Meng *et al.,* 2012). The QSAR was used to determine the quantitative relationship between descriptors and inhibitory activity (Daoui *et al.,* 2021). In this study, descriptors represent the most important physical and chemical properties of the molecular structure of pinostrobin and its derivatives. In silico anticancer activity was obtained from the molecular docking of pinostrobin compounds and their derivatives against inhibition at Topo IIα.

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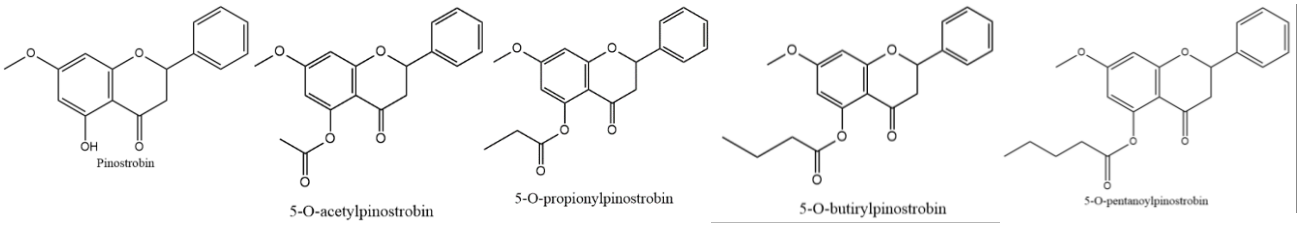

Figure 1. Structure of pinostrobin and four 5-O-acylpinostrobin derivatives

MATERIALS AND METHODS

Materials

The material used in this research were pinostrobin and four 5-O-acylpinostrobin derivative compounds. The structure of the compound was drawn using the ChemDraw 20.0 application (PerkinElmer). The results can be seen in Figure 1. The three-dimensional structure of Topo IIα which forms a complex with DNA and antagonist ligands (PDB ID: 5GWK) was downloaded in .pdb format from the RCSB PDB site https://www.rcsb.org/structure/5GWK has a resolution of 3.15 Å. The 5GWK protein code that binds to the etoposide ligand (with the code EVP).

Tools

The hardware used is the ASUS X409FJ computer with Intel® Core™ i5 8265U @ 1.80 GHz Processor specifications and 4 GB Random Access Memory (RAM). The software used is ChemDraw 20.0 and Chem3D 20.0 to create the structure of the test ligand compounds, AutoDockTools 4.2.6 for the preparation of target macromolecules, AutodockVina in the PyRx 0.8 system and Discovery Studio Visualizer v.19.1.0.18287 for in silico testing, and SPSS Ver. 21 to determine QSAR equation.

Method

Ligan preparation

The structure of the tested compounds were pinostrobin, 5-*O*-acetyl pinostrobin, 5-*O*-propionylpinostrobin, 5-*O*-butiryl pinostrobin, 5-*O*-pentanoylpinostrobin. The native ligand of this receptor is etoposide. The structures were designed using the ChemDraw 20.0 program and then converted into a three-dimensional structure using the Chem3D 20.0 program and optimized to minimize energy. The most stable form is saved in *.mol2 format, then open the compound in PyRx, click Load Molecule, and create a ligand to dock with the target receptor.

Protein Preparation

Protein structure preparation was using AutoDock Tools. Topo IIα used chain D from the crystal model of the Human Topoisomerase IIα in complex with DNA and etoposide. Water molecules and all non-standard residues from the initial structure were removed. Then, all the missing hydrogen and Kollman charges were added to the system, and the prepared protein receptors were saved in *.pdbqt format and immediately placed into the PyRx workspace folder.

Molecular docking

The prepared macromolecules are subjected to preliminary tests and method validation to ensure that the method used is valid in the molecular docking process for the test ligand. Validation of the docking method for the acyl ligand was carried out to look for the conformation of the original ligand. This is done by determining a grid box to determine the coordinates of the active site of the target receptor macromolecule. Validation of the docking method was carried out to look for the 3D conformation of the cocrystal ligand and copy ligand for the target protein using PyMOL software which was expressed in a Root Mean Square Deviation (RMSD) value $\leqslant$ 2Å. The molecular docking test was performed with five repetitions using the same grid box settings.

Quantitative structure-activity relationship (QSAR) of pinostrobin derivatives

The parameters observed in this study were physicochemical parameters, including (1) Lipophilic Parameters (LogP and LogS), (2) Electronic Parameters (E_{tot}, E_{LUMO} and E_{HOMO}), (3) Steric Parameters (WM and MR), and *in silico* activity parameters, namely value of binding affinity (ΔG). The QSAR equation is made to see the relationship between physicochemical properties parameters and activity parameters using IBM SPSS Ver 21.

RESULTS AND DISCUSSION

Moleculer docking validation

Table 1 shows the gridbox settings and RMSD values of the target macromolecules. The RMSD calculation result between the original ligand and the docking results was 1.083 Á, which shows that the method used is valid and can be used for the test ligand.

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Table 1. Gridbox settings and RMSD values of target macromolecules

Makromolecul	Grid Center			Grid Size (Å)	RMSD	Condition
	X	Y	Z			
Topoisomerase IIα (5GWK)	31.3837	-22.6558	-58.1512	25	1.083 Å	< 2 Å

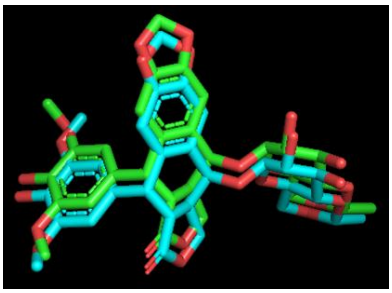

Figure 2. Topo IIα overlay results validate the docking method with PyMOL. Green (crystallography results) and blue (re-docking results)

Table 2. Results of $\Delta G_{binding}$ values and results of interaction of amino acid residues between pinostrobin and 5-O-acylpinostrobin with Topoisomerase IIα

Compound	$\Delta G_{binding}$ (kkal/mol)*	Residues	
		Hydrogen Bond	Non-Hydrogen Bond
Native Ligand	-12.82 ± 0.04	**Arg487**, **Gly462**, **Asp463**, **DT9**	Gly488, **DG13**, **Met766**, Pro803
Doxorubicin	-11.78 ± 0.04	Gly488, **Asp463**, **Gly462**, DC8	Glu461, **Arg487**, DA12, **DG13**
Pinostrobin	-8.5 ± 0.00	DC8	**DG13**, **Arg487**, Met762
5-O-acetyl pinostrobin	-9.14 ± 0.05	DC8, **Arg487**, **DT9**	**DG13**, Met762
5-O-propionylpinostrobin	-8.94 ± 0.05	**Arg487**, **DT9**	DC8, Met762, **DG13**
5-O-butiryl pinostrobin	-8.86 ± 0.05	**Arg487**, **DT9**	**DC13**, Met762, DC8
5-O-pentanoylpinostrobin	-8.88 ± 0.04	DC8, **Arg478**	**DG13**, Tyr805

Note: *average results of 5 replications. Bold print represents the similarity of amino acids to the original ligand.

In addition to the RMSD value, the similarity of the interaction of the redocked ligand and the original ligand is crystallographic to the amino acid residues in the active site of the target protein. The overlay results between the original ligand and the crystallographic ligand can be seen in Figure 2.

Moleculer docking

Molecular docking of the test ligand is carried out in the same way as the validation process using the same size and position of the grid box. The parameters observed to determine the affinity of a ligand for a receptor are binding free energy (ΔG), amino acid residues, and the number of hydrogen bonds (Kontoyianni *et al*., 2004). The binding affinity score (ΔG) is a parameter of conformational stability between ligand and macromolecule. Molecular docking results are ranked based on the value of binding affinity score from the smallest to the largest. The lowest binding affinity score indicates that the conformation formed is stable. So the lowest binding affinity, more potent the macromolecular-ligand complex (Daoui *et al*., 2021).

There are 2 types of topoisomerase, namely topoisomerase I and topoisomerase II (Topo IIα and Topo IIβ) (Vejpongsa and Yeh, 2014). Topoisomerase IIα was chosen as the inhibitory target because Topo IIα is overexpressed in cancer cells while Topo IIβ is expressed in normal cells (Florkemeier *et al*., 2021). So suppressing Topo IIα activity using potential inhibitors is very important to inhibit DNA replication. Therefore, this research was carried out to predict the Topo IIα inhibitory activity of pinostrobin derivative compounds using the molecular docking method. The selected Topo IIα macromolecule has a cocrystal ligand and X-Ray crystallography results with the PDB ID code 5GWK. The parameters observed are the affinity of the ligand for the receptor which is expressed in the form of binding free energy values (ΔG), residue interactions and hydrogen bonds of 5-*O*-acylpinostrobin derivative compounds. The results of molecular docking studies on macromolecular targets with Autodock Vina. Analysis of the ΔG value and amino acid residues of molecular docking results on Topo IIα can be seen in table 2. The results of native ligand redocking obtained a ΔG value of -12.82 kcal/mol interacting with the 5GWK binding site. Doxorubicin as a positive control obtained a ΔG value of -11.78 kcal/mol. The 5-*O*-acylpinostrobin

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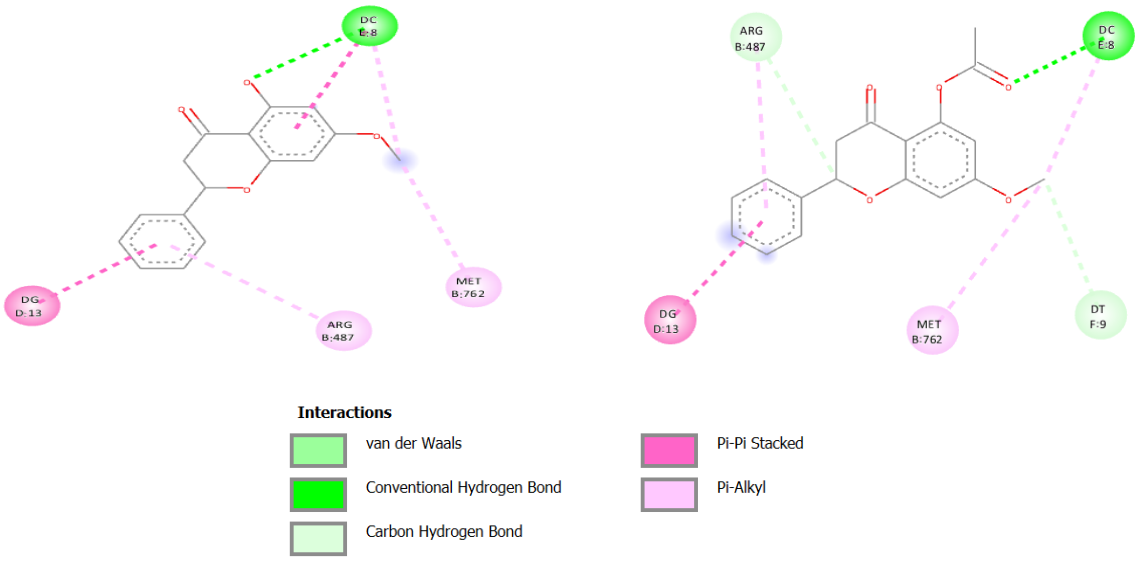
derivative obtained a ΔG value of -8.88 to -9.14 kcal/mol, while pinostrobin obtained a ΔG value of -8.5 kcal/mol. The results of this study showed that 5-*O*-acylpinostrobin derivatives obtained lower ΔG values than pinostrobin.

The best 5-*O*-acylpinostrobin derivative is 5-*O*-acetylpinostrobin where this compound shows stronger inhibitory activity than other 5-*O*-acylpinostrobin derivatives, because the ΔG value of 5-*O*-acetylpinostrobin is the most negative, namely -9.14 kcal/mol. The increase in the ΔG value in the 5-*O*-pentanoylpinostrobin compound occurs due to the formation of hydrogen bonds with residues Arg487, DT9 and DG13. Interactions at the same residue as the positive control are predicted to inhibit DNA strand unwinding so that replication does not occur, which then causes anticancer activity. According to a study conducted by Agustin *et al.*, (2022) and Widiyana *et al.*, (2023), pinostrobin derivatives exhibited stronger anti-cancer effects on the HER-2 and Erα receptor in silico compared to pinostrobin. According to Praditapuspa *et al.*, (2021), acetyl pinostrobin derivatives can be used as possible anticancer drugs because they have stronger apoptosis activator mechanisms than pinostrobin. Pinostrobin derivative compounds exhibit enhanced efficacy and selectivity in vitro compared to pinostrobin, making them highly promising for advancing as potential anticancer agents (Widiandani *et al.*, 2023). Based on research conducted by Sukardiman *et al.* (2000), pinostrobin isolate from B. pandurata has inhibitory activity against topoisomerase in vitro. Pinostrobin can interfere with the DNA strand unwinding reaction mediated by topoisomerase, thereby inhibiting cancer cell replication and transcription and inducing apoptosis in T47D breast cancer cells. This indicates that the 5-*O*-pentanoylpinostrobin derivative compound has the potential to be better than pinostrobin for development as an anticancer drug.

QSAR is an important stage of drug development so as to obtain equations that can later be used for further drug development. The QSAR technique has the concept that similar structures have the same properties and the more differences there are between molecules, the more difficult it is to relate their physical and chemical properties to biological activity. The physicochemical properties that provide the greatest contribution to activity are lipophilic, electronic and steric properties (Siwandono, 2016). In this stage, we study the quantitative relationship between physicochemical property parameters and the inhibitory activity of the Topo IIα anti-cancer receptor in silico. The physicochemical parameter values (Log P, Log S, E_{tot}, E_{HOMO}, E_{LUMO}, MW and MR) and the results of in silico of binding free energy values (ΔG) of the inhibitory activity of the Topo IIα for pinostrobin and four 5-*O*-acylpinostrobin derivative compounds can be seen in Table 3.



Pinostrobin **5-acetylpinostrobin**

Figure 3. Interaction of pinostrobin and 5-Oacetylpinostrobin compounds with Topo IIα

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Table 3. Physicochemical parameters and activity of pinostrobin and four pinostrobin acyl derivatives

Compound	LogP	LogS	E_{tot}	E_{HOMO}	E_{LUMO}	MW	MR	Log (1/ΔG)
Pinostrobin	2,75	-3,84	46,19	-11,21	-3,45	270	74,02	-0.9294
5-*O*-acetil pinostrobin	3,00	-3,64	56,72	-11,31	-3,53	312	83,49	-0.9609
5-*O*-propionyl pinostrobin	3,27	-3,94	55,52	-11,31	-3,58	326	88,30	-0.9513
5-*O*-butiryl pinostrobin	3,43	-4,17	55,31	-11,31	-3,57	340	93,11	-0.9474
5-*O*-pentanoyl pinostrobin	3,72	-4,52	55,11	-11,31	-3,57	354	97,91	-0.9484

Note: Log P = Logarithm of octanol/water partition; Log S = Logarithm of solubility (in water); Etot = Total energy (kcal/mol); EHOMO = Energy Highest Occupied Molecular Orbital (eV); E_{LUMO} = Energy Lowest Unoccupied Molecular Orbital (eV); MR= Molar Refraction (cm3/mol); MW= Molecular Weight (Da)

Table 4. QSAR equation

No.	QSAR Equation	n	r	SE	F	Sig
1	Log (1/ ΔG) = - 0.011 Log P – 0.912	5	0.360	0.199	0.446	0.552
2	Log (1/ ΔG) = - 0.004 Log S – 0.963	5	0.110	0.095	0,037	0.860
3	Log (1/ ΔG) = - 0.003 E_{tot} – 0.812	5	0.942	0.016	23.589	0.017
4	Log (1/ ΔG) = 0.226E_{HOMO} + 1.604	5	0.884	0.041	10.770	0.046
5	Log (1/ ΔG) = 0.144 E_{LUMO} – 0.438	5	0.679	0.141	2.563	0.208
6	Log (1/ ΔG) = 0.000 MW – 0.882	5	0.576	0.178	1.493	0.309
7	Log (1/ ΔG) = - 0.001 MR – 0.895	5	0.481	0.198	0.902	0.412
8	Log (1/ ΔG) = - 0.419 Log P + 0.063 Log P^2 – 0.260	5	0.521	0.250	1.088	0.479
9	Log (1/ ΔG) = - 0.453 Log S - 0.055 Log S^2 – 1.876	5	0.207	0.164	0.260	0.793

CONCLUSION

Based on research, 5-*O*-acetylpinostrobin has a high affinity for topo IIα inhibitors with ΔG -9.14 kcal/mol so it can be a cancer drug candidate. The best QSAR equation results (Log (1/ΔG) = - 0.003 Etot – 0.812) obtained can be used as a reference for predicting the activity of new pinostrobin derivatives that will be synthesized by entering the electronic value (Etot) of the compound into the equation.

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AUTHOR CONTRIBUTIONS

Conceptualization, T.W.; Methodology, T.W., J.E., S.R.; Software, T.W., J.E., S.R., P.A.P..; Validation, T.W., J.E., S.R.; Formal Analysis, T.W., J.E., S.R.; Investigation, S.R., P.A.P.; Resources, T.W.; Data Curation, T.W., J.E., S.R.; Writing - Original Draft, S.R., P.A.P.; Writing - Review & Editing, T.W., J.E.; Visualization, S.R.; Supervision, T.W.; Project Administration, T.W., S.R.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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