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Original Article

In Silico Analysis of Pinostrobin Derivatives from *Boesenbergia pandurata* on ErbB4 Kinase Target and QSPR Linear Models to Predict Drug Clearance for Searching Anti-Breast Cancer Drug Candidates

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ABSTRACT

Background: ErbB4 is a member of ErbB family of receptor tyrosine kinases (RTKs) and plays an important role in resistance to ErbB2 inhibitors. **Objective:** This study aimed to design a pinostrobin derivative with activity as an ErbB4 inhibitor and to establish a quantitative structure-property relationship (QSPR) of pinostrobin and its derivatives to predict drug clearance. **Materials and Methods:** In this research, an in silico study was conducted on pinostrobin and its derivatives by predicting the prediction of activity spectra for substances (PASS) with PASS online, followed by molecular docking using the AutoDockTools 4.2.6 program on ErbB4 protein kinase and visualizing the docking results using the Discovery Studio Visualizer software. While the study of QSPR pinostrobin and its derivatives was determined using physicochemical parameters with clearance (CL_{tot}) using SPSS. **Results:** From the data obtained, 5-O-2-phenylacetylpinostrobin has a high affinity for ErbB4 protein with a free energy of binding (ΔG) -10.37 kcal/mol and an inhibition constant (Ki) of 26.06 nM. **Conclusion:** Probability "to be active" (Pa) 5-O-2-phenylacetylpinostrobin of 0.595 for kinase inhibitors and 0.666 for apoptosis agonists, thus becoming candidates for breast cancer drugs. The QSPR model can be used to predict the properties of molecules such as CL_{tot}, this will be useful in the drug design process. The best QSPR regression equation for pinostrobin and its derivatives is Log ($1/CL_{tot}$) = 0.705 Log S + 0.035 MR + 0.375. This equation can be used as a reference in predicting CL_{tot}.

Key words: 5-O-acylpinostrobin, Molecular docking, PASS, Pharmacokinetic, Physicochemical properties.

INTRODUCTION

ErbB4 (HER4) is a member of the epidermal growth factor (EGF)/ErbB family of receptor tyrosine kinases (RTKs)[1] and other members are EGFR (ErbB1/HER1), ErbB2 (HER2/ Neu), ErbB3 (HER3).[2] ErbB2 overexpression occurs in about 20% of breast cancers and is associated with poorer overall survival.[3] Treatment with ErbB2-targeted inhibitors, trastuzumab, and lapatinib provide considerable clinical benefit in HER2-positive breast cancer patients, but most show resistance to ErbB2-targeted inhibitors[4,5] due to activation of c-Src tyrosine kinase[6], ErbB3 upregulation[7], and ErbB4 activation.[8,9] ErbB4 activation plays a key role in the survival of cancer cells that have developed resistance to ErbB2 inhibitors. ErbB4 knockdown causes a decrease in AKT phosphorylation and activates the PI3K/AKT pathway in lapatinib-resistant cells, thereby triggering apoptosis.[9] Therefore, it is necessary to develop a new drug that has a better activity and more selective as an ErbB4 inhibitor.[9]

Pinostrobin is a flavanone contained in *Boesenbergia pandurata* and is a marker compound of the plant.[10] In recent years, several studies have been conducted on the development of pinostrobin as an anticancer agent such as in silico, in vitro, and in vivo.[11-13] Although encouraging, the development of pinostrobin for breast cancer is still slow. The breast anticancer activity of pinostrobin is still lower than drugs on the market. So that in this study, an in silico was conducted to determine the activity of pinostrobin and its derivatives as ErbB4 inhibitors.

QSPR is not only used to establish quantitative relationships between structural properties and property parameters of new compounds but provides a better explanation of the factors that influence the pharmacokinetic fate of drugs.[14] The CL_{tot} value of a drug is an important pharmacokinetic parameter because it is directly related to the bioavailability and elimination of the drug and can be used to determine the dosing rate and steady-state concentration.[15] Therefore, it is important to predict the value of CL_{tot} during drug discovery so that compounds with acceptable metabolic stability can be identified and compounds with poor bioavailability can be eliminated.[14]

MATERIALS AND METHODS

Hardware

The specification of the computer that is used: Intel® Core™ i7 8565U@ 1.80 GHz processor (CPU), Nvidia® GeForce MX230 graphics processing unit (GPU), and 8 GB Random Access Memory (RAM) with Windows 10.

Compound Test Preparation

Pinostrobin compounds and their derivatives are the results of structural modifications by adding

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a substituted acyl group at the position of the benzene ring of the pinostrobin compound as shown in Table 1. The test compounds were made in 2D and 3D models, then optimized by the MMFF94 method on Chem3D 20.0. And then, the structure is translated to SMILES format using Online SMILES Translator (https://cactus.nci.nih.gov/translate/).

PASS prediction

To validate compounds as suitable drug candidates, prediction of activity spectra for substances (PASS) (http://www.pharmaexpert.ru/passonline/) is used to predict the possible pharmacological effects of a compound based on structural information by looking at the Pa score (probability " to be active") and Pi (probability "to be inactive") by entering the SMILES format.[16]

Molecular docking

The structure of the ErbB4 kinase target receptor (PDB ID: 3BBT) obtained from the Protein Data Bank (https://www.rcsb.org/) and containing the native ligand lapatinib that is shown in Figure 1.

Molecular docking is done using AutoDockTools 4.2.6 program. Starting with the validation process, the redocking method uses the extracted cocrystal ligand from the receptor as the test ligand and the location of the cocrystal ligand as the binding site.[17] The validation results are indicated by the Root Mean Square Deviation (RMSD) value.[18] Center the grid box using a grid box (40 × 40 × 40). The binding site coordinates are x = -36,287; y = 53,585; z = -11962 with spacing per unit 0.375 angstrom. AutoDockTools 4.2.6 program run with the specified parameters: number generation algorithm 27,000, calculate 2,500,000 times (Medium), population 150, and the implementation of running GA as much as 10 times. Visualization analysis of protein-ligand interactions was performed with Discovery Studio Visualizer v.19.1.0.18287 from BIOVIA.

QSPR studies

The QSPR study of pinostrobin and its derivatives was determined using physicochemical parameters with CL_{tot} property. The physicochemical parameters consisted of lipophilic parameters (log P and log S), electronic parameters (E_{tot}, E_{HOMO}, E_{LUMO}), and steric parameters (MW and MR). Properties are indicated by CL_{tot} or log ($1/CL_{tot}$) obtained from prediction results using pkCSM online (http://biosig.unimelb.edu.au/pkcsm/prediction). Physicochemical parameters such as log P, MW, and MR were obtained by the DruLiTo program, while the log S was obtained from the ChemDraw 20.0 program. E_{tot}, E_{HOMO}, E_{LUMO} obtained from Chem3D 20.0. In addition, to determine the QSPR, the SPSS program is used.[19-21]

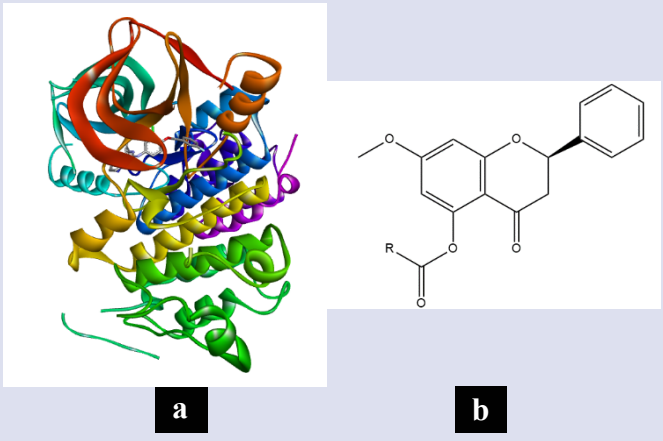

Figure 1: Structure of ErbB4 kinase (a) and pinostrobin derivatives (b).

RESULTS

PASS prediction

The prediction results of the Pa and Pi scores of pinostrobin derivatives are shown in Table 1.

Molecular docking

The results of docking validation are indicated by the RMSD value of 1.008Å, so it can be concluded that the docking protocol can be declared valid because the RMSD value is < 2Å. Based on the docking results, all pinostrobin derivatives obtained more negative ΔG scores than pinostrobin compounds (Table 2). The more negative the ΔG score and the smaller the Ki value, it indicates a very strong complex formed between the ligand and standard. While the visualization of ligands and comparisons can be seen in Figure 2 and Table 3.

QSPR studies

The physicochemical parameter values of the substituted substituents can be seen in Table 4. While the linear regression equation is shown in Table 5.

DISCUSSION

Modification structure can increase the potency and selectivity of compound. In designing a potent and selective compound, several methods can be used, one of the methods is in silico. The advantage of using this method is to optimize activity, geometry, and reactivity before the compound is synthesized experimentally. This can reduce the synthesis step of a compound that requires time and expensive costs, but the resulting compound does not have the activity as expected. In developing pinostrobin as a new breast cancer drug, to increase the anticancer activity of the breast, modification of the structure of pinostrobin was carried out by adding an acyl group. The selection of these substituents is based on changes in lipophilic, electronic, and steric properties. In this study, several initial stages in the development of new drugs have been carried out by the principles of rational drug discovery and development.

The Pa value is the possibility of a compound being active in carrying out biological activities in laboratory experiments, while the Pi value is the opposite. If a compound has a value of Pa > Pi, then the compound has the potential to have this activity. In Table 1, pinostrobin has strong potential on a laboratory scale because the Pa value > 0.7, while its derivatives have moderate activity because the Pa value is 0.5<Pa<0.7.[22] Because these compounds have not been studied on a laboratory scale, further research is needed.

Molecular docking is computational modeling research that aims to detect the interaction of ligands with receptors. Bond energy is influenced by Gibbs free energy (ΔG), a reaction that takes place spontaneously will have a negative Gibbs free energy at temperature and constant temperature. Bond energy is affected by several components which are expressed by the following equation: ⟦ΔG⟧ _Hatanic = ⟦ΔG⟧ _Gauss + ⟦ΔG⟧ _Repulsion + ⟦ΔG⟧ _HBond + ⟦ΔG⟧ _Hydrophobic + ⟦ΔG⟧ _Torsion. The more energy components contribute, the smaller the "G" value (becomes negative), the bond impact will be stronger and cause high affinity.[23] From the results of the study [Table 2], it is known that 5-O-2-phenylacetylpinostrobin has a stronger inhibitory activity than lapatinib, marked by ΔG of -10.37 kcal/mol and lapatinib -10.30 kcal/mol. So that ΔG is very negative, it can be ascertained that the reaction will be proceed spontaneously and lead to high affinity. The Ki values of these compounds are 26.06 and 28.11 nM. The Ki value is not only used to indicate the affinity of a ligand, it is also used to predict in vitro analysis processes. In this study, the presence of the 2-phenylacetyl substituent had a significant effect on the affinity of the pinostrobin derivative for the ErbB4 kinase receptor target. Thus,

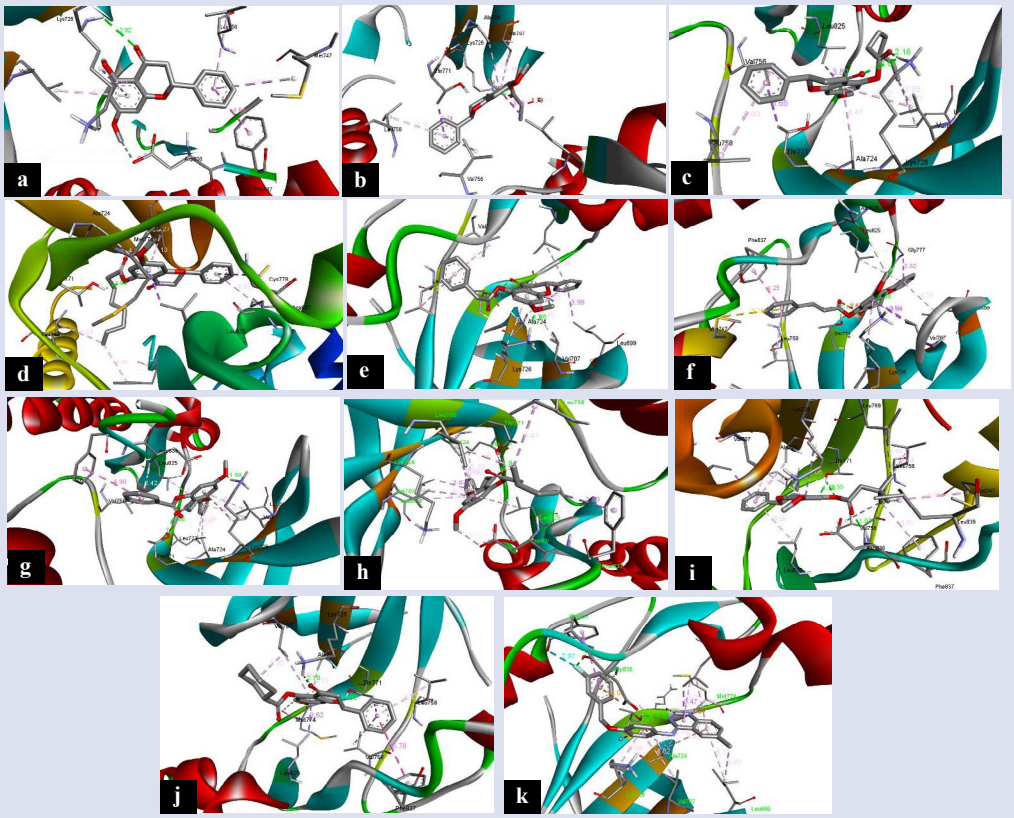

Figure 2: Visualization of pinostrobin (a), 5-O-2-cloropropionylpinostrobin (b), 5-O-heptanoylpinostrobin (c), 5-O-octanoylpinostrobin (d), 5-O-2-phenylacetylpinostrobin (e), 5-O-3-phenylpropionylpinostrobin (f), 5-O-benzoylpinostrobin (g), 5-O-3-methylpentanoylpinostrobin (h), 5-O-3,3-dimethylbutyrylpinostrobin (i), 5-O-cyclohexanecarbonylpinostrobin (j), lapatinib (k) bound to the active sites of ErbB4 kinase.

Table 1: The pinostrobin derivatives test compound and PASS result.

Code	R	Compound Name	Kinase inhibitor		Apoptosis agonist	
			Pa	Pi	Pa	Pi
P	H	Pinostrobin	0.805	0.005	0.730	0.012
P1	$Cl\text{-}CH_2\text{-}CH_2$	5-O-2-cloropropionylpinostrobin	0.566	0.024	0.475	0.045
P2	C_6H_{13}	5-O-heptanoylpinostrobin	0.546	0.027	0.666	0.019
P3	C_7H_{15}	5-O-octanoylpinostrobin	0.546	0.027	0.584	0.025
P4	$C_6H_5\text{-}CH_2$	5-O-2-phenylacetylpinostrobin	0.595	0.021	0.666	0.019
P5	$C_6H_5\text{-}CH_2\text{-}CH_2$	5-O-3-phenylpropionylpinostrobin	0.544	0.027	0.593	0.027
P6	C_6H_5	5-O-benzoylpinostrobin	0.667	0.015	0.672	0.018
P7	$CH_3\text{-}CH_2\text{-}CH(CH_3)\text{-}CH_2$	5-O-3-methylpentanoylpinostrobin	0.544	0.035	0.603	0.026
P8	$(CH_3)_3CH\text{-}CH_2$	5-O-3,3-dimethylbutyrylpinostrobin	0.546	0.027	0.594	0.027
P9	$C_6H_{11}CO$	5-O-cyclohexanecarbonylpinostrobin	0.650	0.016	0.614	0.025

Table 2: Molecular docking binding affinity of pinostrobin derivatives, ranked by the lowest free energy of binding (ΔG) and inhibition constant (Ki).

Code	Compound name	ΔG (kcal/mol)	Ki (nM)
P4	5-O-2-phenylacetylpinostrobin	-10.37	26.06
L	Lapatinib	-10.30	28.11
P5	5-O-3-phenylpropionylpinostrobin	-10.23	31.93
P3	5-O-octanoylpinostrobin	-9.85	60.67
P7	5-O-3-methylpentanoylpinostrobin	-9.53	102.69
P2	5-O-heptanoylpinostrobin	-9.39	131.65
P8	5-O-3,3-dimethylbutyrylpinostrobin	-9.37	134.77
P6	5-O-benzoylpinostrobin	-9.14	200.71
P9	5-O-cyclohexanecarbonylpinostrobin	-9.08	219.20
P1	5-O-2-cloropropionylpinostrobin	-8.60	495.35
P	Pinostrobin	-7.18	5470

Table 3: Interaction of ligands and amino acid residues. The hydrogen bond distance is given, the hydrophobic interactions are indicated by a tick (✓).

Code	Leu699	Val707	Ala724	Lys726	Met747	Val756	Leu758	Thr771	Gln772	Leu773	Met774	Leu825	Asp836	Phe837
L	✓	✓	✓	✓	-	-	-	2.92 Å	✓	-	✓	✓	✓	✓
P	-	✓	-	2.92 Å	✓	-	✓	-	-	-	-	-	✓	✓
P1	-	✓	✓	2.29 Å 2.73 Å	-	✓	✓	-	-	-	-	✓	-	-
P2	✓	✓	✓	2.18 Å 2.65 Å	-	✓	✓	✓	-	-	-	✓	-	-
P3	-	✓	✓	-	-	-	✓	2.03 Å	-	-	✓	✓	-	✓
P4	-	✓	✓	1.86 Å	-	-	✓	1.75 Å	-	✓	-	✓	-	-
P5	✓	✓	-	1.88 Å	-	-	✓	2.09 Å 2.16 Å	-	-	-	✓	-	✓
P6	✓	✓	✓	1.98 Å	-	✓	-	1.68 Å	-	✓	-	✓	-	✓
P7	✓	✓	✓	✓	-	-	✓	1.94 Å 2.20 Å	-	-	-	✓	-	✓
P8	✓	✓	✓	✓	-	✓	✓	1.78 Å 2.55 Å	-	✓	✓	✓	1.93 Å	✓
P9	-	✓	✓	2.70 Å	-	✓	✓	1.92 Å	-	-		✓	-	✓

L: Lapatinib, P: Pinostrobin, P1: 5-O-2-cloropropionylpinostrobin, P2: 5-O-heptanoylpinostrobin, P3: 5-O-octanoylpinostrobin, P4: 5-O-2-phenylacetylpinostrobin, P5: 5-O-3-phenylpropionylpinostrobin, P6: 5-O-benzoylpinostrobin, P7: 5-O-3-methylpentanoylpinostrobin, P8: 5-O-3,3-dimethylbutyrylpinostrobin, P9: 5-O-cyclohexanecarbonylpinostrobin.

Table 4: Physicochemical parameters and CL_{tot}.

Code	Log P	Log S	E_{tot}	E_{HOMO}	E_{LUMO}	MW	MR	CL_{tot}	Log (1/CL_{tot})
P	1.825	-3.433	46.2483	-11.207	-3.449	255.98	81.96	0.136	0.8664
P1	2.537	-4.501	75.4066	-10.968	-3.569	360.08	100.81	0.358	0.4461
P2	4.545	-5.824	54.9488	-11.306	-3.573	382.18	108.07	1.258	-0.0996
P3	5.114	-6.242	56.0354	-11.308	-3.572	396.19	110.98	1.283	-0.1082
P4	3.349	-5.646	91.0089	-11.295	-3.519	388.13	120.26	0.238	0.6234
P5	3.729	-5.814	72.3604	-11.313	-3.542	402.15	125.12	0.312	0.5058
P6	3.078	-5.813	109.8573	-11.381	-3.720	374.12	115.71	0.471	0.3269
P7	3.915	-5.214	60.5646	-11.315	-3.592	368.16	107.87	0.348	0.4584
P8	3.952	-4.973	69.2658	-11.301	-3.520	368.16	109.65	0.164	0.7851
P9	3.929	-5.690	70.8073	-11.370	-3.612	390.16	107.23	1.038	-0.0162

Log P: Partition coefficient, Log S: Solubility, E_{tot}: Minimum energy, E_{HOMO}: Highest occupied molecular orbital, E_{LUMO}: Lowest unoccupied molecular orbital, MW: Molecular weight, MR: Molar refractivity, CL_{tot}: Clearance total.

Table 5: Linear regression equation.

No.	Linear regression equation	n	r	SE	F	Sig.
One Physicochemical Parameter						
1	Log (1/CL_{tot}) = – 0.258 Log P – 1.309	10	0.699	0.2669	7.640	0.025
2	Log (1/CL_{tot}) = 0.298 Log S + 1.960	10	0.702	0.2659	7.759	0.024
3	Log (1/CL_{tot}) = 0.002 E_{tot} + 0.271	10	0.081	0.3720	0.053	0.824
4	Log (1/CL_{tot}) = 0.832 E_{HOMO} + 9.765	10	0.279	0.3584	0.676	0.435
5	Log (1/CL_{tot}) = 2.666 E_{LUMO} + 9.886	10	0.537	0.3149	3.237	0.110
6	Log (1/CL_{tot}) = – 0.005 MW + 2.148	10	0.570	0.3066	3.849	0.085
7	Log (1/CL_{tot}) = – 0.007 MR + 1.163	10	0.240	0.3622	0.490	0.504
Two Physicochemical Parameter						
8	Log (1/CL_{tot}) = – 0.261 Log P – 0.001 E_{tot} + 1.373	10	0.700	0.2849	3.365	0.095
9	Log (1/CL_{tot}) = – 0.28 Log P – 0.34 E_{HOMO} + 2.444	10	0.706	0.2827	3.472	0.090
10	Log (1/CL_{tot}) = – 0.222 Log P + 1.90 E_{LUMO} + 7.956	10	0.791	0.2442	5.840	0.032
11	Log (1/CL_{tot}) = – 0.228 Log P – 0.001 MW + 1.540	10	0.730	0.2838	3.414	0.092
12	Log (1/CL_{tot}) = – 0.296 Log P + 0.006 MR + 0.828	10	0.717	0.2782	3.698	0.080
13	Log (1/CL_{tot}) = 0.354 Log S + 0.007 E_{tot} + 1.759	10	0.785	0.2473	5.605	0.035
14	Log (1/CL_{tot}) = 0.352 Log S – 0.644 E_{HOMO} – 5.014	10	0.723	0.2757	3.829	0.075
15	Log (1/CL_{tot}) = 0.249 Log S + 0.095 E_{LUMO} + 5.181	10	0.720	0.2770	3.761	0.078
16	Log (1/CL_{tot}) = 0.471 Log S + 0.004 MW + 1.494	10	0.724	0.2750	3.865	0.074
17	Log (1/CL_{tot}) = 0.705 Log S + 0.035 MR + 0.375	10	0.944	0.1318	28.566	0.000

pinostrobin derivatives have greater activity against target receptors than pinostrobin.

The main objective of the QSPR study is to design drugs by modifying the chemical structure of active drugs pharmacodynamically. The main advantage of QSPR lies that once the association is confirmed with a sufficient level of statistical confidence, it can be a valuable aid in the prognosis of the behavior of new molecules, even before the synthesis is done.[24] The results of statistical analysis [Table 5], proposed the best equation: Log $(1/CL_{tot})$ = 0.705 Log S + 0.035 MR + 0.375 (n=10; sig.=0.000; r=0.944; F=28.566; and SE=0.1318). The equation was chosen because it has the largest correlation coefficient (r=0.944) and the smallest significance that is 0.000. From the selected equation, it can be explained that the physicochemical properties affect CL_{tot} pinostrobin and its derivatives are lipophilic (log S) and steric (MR) properties. This equation can be used as a reference in predicting the CL_{tot} of pinostrobin-derived compounds with different substituents by including the log S and MR parameters in the equation.

CONCLUSION

Based on the research, 5-O-2-phenylacetylpinostrobin has a high affinity for ErbB4 protein with ΔG-10.37 kcal/mol and Ki 26.06 nM and Pa score of 5-O-2-phenylacetylpinostrobin of 0.595 for kinase inhibitors and 0.666 for apoptosis agonists and therefore it becomes candidate for breast cancer drugs. The statistical results and the application of the developed model to the test set show that the QSPR model can be used to predict molecular properties such as CL_{tot}, so it will be useful in the drug development process. The best QSPR regression equation of pinostrobin and its derivatives is Log $(1/CL_{tot})$ = 0.705 Log S + 0.035 MR + 0.375.

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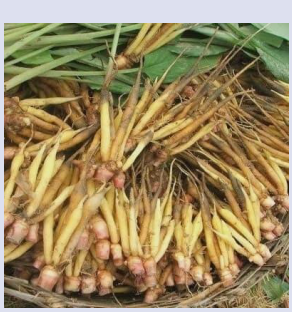
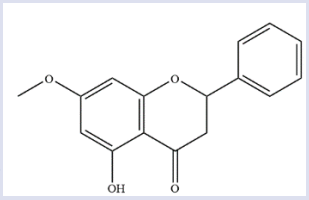
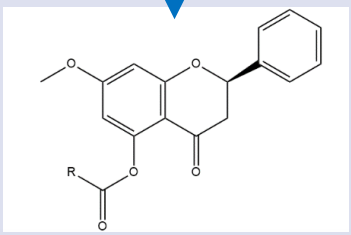
GRAPHICAL ABSTRACT



Boesenbergia pandurata



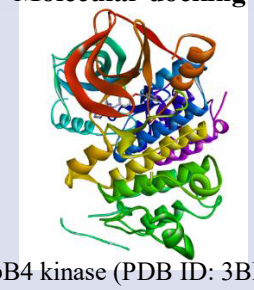
Pinostrobin



Pinostrobin derivatives

Methods

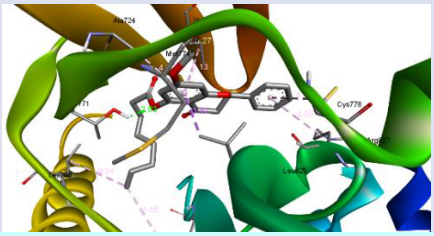
Molecular docking



ErbB4 kinase (PDB ID: 3BBT)

QSPR

PASS online



5-O-2-phenylacetylpinostrobin has a high affinity with Pa score of 0.595 for kinase inhibitors, 0.666 for apoptosis agonists, ΔG -10.37 kcal/mol, and Ki 26.06 nM.

Result prediction

The best QSPR regression equation of pinostrobin and its derivatives is:
$\text{Log } (1/CL_{tot}) = 0.705 \text{ Log S} + 0.035 \text{ MR} + 0.375.$

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Tri Widiandani is a lecturer at Faculty of Pharmacy, Airlangga University. She obtained her bachelor degree in Pharmacy at Faculty of Pharmacy, Airlangga University. She was further persued her Specialist of Hospital Pharmacy and Doctoral degree at Faculty of Pharmacy, Airlangga University. Her main courses is Medicinal Chemistry, Physical Chemistry. Her research is focuses on virtual modeling, synthesis of biologically active compounds especially for cancer targeted.

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