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6-aminomethylpinostrobin Derivatives as Anti-breast Cancer: *In Silico* Insight

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Abstract

Pinostrobin, a flavanone isolated from various medicinal plants, is known to have various potential pharmacological activities, one of which is anti-breast cancer. Derivatization of pinostrobin to increase its activity has been reported previously but has never been carried out for aminomethyl derivatives. This study aims to determine the 6-aminomethylpinostrobin derivative with the best potential as anti-breast cancer through *in silico* studies. The method used was molecular docking using AutoDock Vina, with 10 6-aminomethylpinostrobin derivatives as test ligands and five receptors related to breast cancer. The docking results showed that 6-aminomethylpinostrobin derivatives showed the best potential against HER2 and EGFR receptors among the five receptors. Meanwhile, the derivatives with the best potential are 6-(*N*-dicyclohexylamine)methylpinostrobin and 6-(*N*-diphenylamine)methylpinostrobin, with potential affinity exceeding lapatinib on HER2. In conclusion, 6-aminomethylpinostrobin derivatives show promising potential as anti-breast cancer through HER2 inhibition and need to be proven in further studies both *in vitro* and *in vivo*.

Keywords: 6-aminomethylpinostrobin ; breast cancer ; EGFR ; HER2 ; molecular docking

1. Introduction

As aprominent molecule that has attracted the interest of many researchers in developing it, pinostrobin (5-hydroxy-7-methoxyflavanone) is a hot topic, especially in terms of developingits derivative compounds[1]. The amount is abundant enough to be isolated directly from various sources such as *Pinus strobus*[2], *Boesenbergiapandurata*[3], *Artocarpusodoratissimus*[4], *RenealmiaAlpinia* [5], and other sources. In addition, total synthesis of pinostrobin is also possible enantioselectively by rhodium-catalyzed reaction[6].Various types of modifications of pinostrobin have been reported previously, such as by prenylation[7],[8], acylation[9][10], benzoylation[11][12], or in the form of a cyclodextrin complex[13]. Our previous bibliometric studies have found patterns of derivatization that indicate a growing trend regarding pinostrobin derivatization, especially in Southeast Asian countries[14].

Pinostrobin is reported to exhibit various activities, one of the most interesting being anticancer[15]. Pinostrobin and various derivatives that have been reported are known to show various anticancer activities, and one of the most frequently studied is breast cancer [16]. Several types of derivatives, such as various variants of 5-*O*-prenylpinostrobin, 6-prenylpinostrobin, 8-prenylpinostrobin[7], 5-*O*-acylpinostrobin[10], and 5-

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O-benzoylpinostrobin[12] show better cytotoxic activity on various breast cancer cells than pinostrobin, both *in vitro* as well as *in silico*.In general, pinostrobin derivatization shows an excellent opportunity to increase its potential as an anti-breast cancer, and the determination of the type of derivative is a critical point in its development.

Among the many groups often used as benchmarks for the derivatization of lead compounds as anti-breast cancer agents, one widely reported is aminomethyl derivatives. Several studies reported aminomethyl derivatives of various chemical compounds, such as 4-methyl-2-prenylphenol[17], curcumin mono-carbonyl[18], pyridine chalcone[19], and eugenol[20], with increased cytotoxic activity in various cell lines, indicating the potential of these aminomethyl derivatives to increase their anticancer activity.Synthesis of aminomethyl derivatives is possible by the addition of a secondary amine (Mannich base)[21], and our previous preliminary studies with pinostrobin demonstrated that aminomethylpinostrobin derivatives can be made to form 6-aminomethylpinostrobinas well as several variants of its substituents.This derivative has never been reported before and has enormous novelty potential to be developed as an anti-breast cancer agent.

Therefore, this study aims to determine the 6-aminomethylpinostrobin derivative with the best potential as an anti-breast cancer through *in silico* studies on various relevant receptors. The approach used is the molecular docking method, with the test receptors used covering various breast cancer-related receptors such as human estrogen receptor α (ERα), human epidermal growth factor receptor 2 (HER2), human progesterone receptor (PR)[12], and epidermal growth factor receptor (EGFR), both wild-type and mutant[22].

2. Experimental

2.1. Hardware and software

The *in silico* study was performed with the same hardware and software reported in our previous studies [23][24], using the Toshiba Portege Z30-C series Ultrabook with an Intel™ Core i7-6600U@2.6 GHz and Windows 10 Pro operating system. The software used was Chem3D for energy minimization of ligands, OpenBabel 3.1.1 for ligands and receptors format conversion, AutoDockTools 1.5.6 for docking protocol configuration, AutoDock Vina 1.2.3 for the docking process, PyMOL 2.4.1 for docking protocol validation, and Discovery Studio Visualizer 20.1.0.19295 for visualization and observation of docking results. All software used has a free license, except for PyMOL, for which the evaluation version (30-day trial) was used.

2.2. Receptors preparation

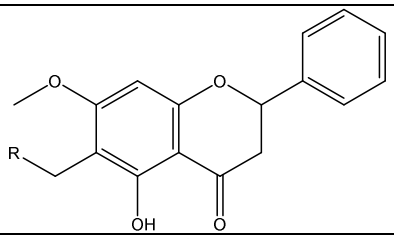
Five receptors were used in the docking process, consisting of ERα(PDB ID 3ERT), HER2 (PDB ID 3RCD), PR (PDB ID 1E3K)[12], and EGFR wild-type (PDB ID 5FED) as well as mutant L858R, T790M, V948R (PDB ID 5HG7)[22], downloaded from the Protein Data Bank website (https://www.rcsb.org/). Parts of unused receptors (e.g., water, solvent, unused chain) were then removed, and polar hydrogen, as well as charges, were added and saved in pdbqt format using AutoDockTools 1.5.6. All co-crystal ligands from the receptors at the binding site were validated by the redocking method on the size and coordinates of each co-crystal ligand[25].

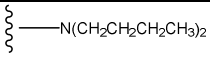
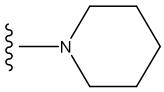
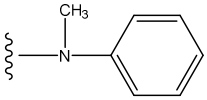
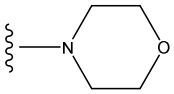
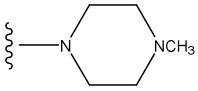
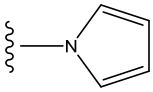
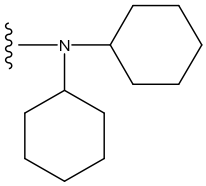
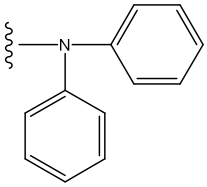
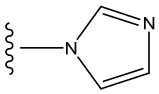
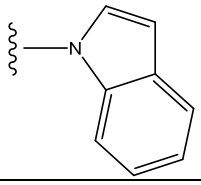
2.3. Receptors preparation

Ten 6-aminomethylpinostrobin derivatives were used as test ligands, with 2D structures presented in **Table 1**. As a comparison, the co-crystal ligands from each receptor include 4-hydroxytamoxifen (3ERT), metribolone (1E3K), nazartinib (5FED), and PF-06459988 (5HG7). For the 3RCD receptor, the comparison ligand used was lapatinib, a tyrosine kinase inhibitor for HER2[26]. The two-dimensional structure of all ligands was obtained from PubChem in SDF format, and then energy minimization was performed with Chem3D using MMFF94 force field [27].

Table 1

The two-dimensional structure of6-aminomethylpinostrobin derivatives



Compound number	R	Group	Name
1	Di-*n*-butylamine		6-(*N*-di-*n*-butylamine)methylpinostrobin
2	Piperidine		6-(*N*-piperidine)methylpinostrobin
3	*N*-methylaniline		6-(*N*-methylaniline)methylpinostrobin
4	Morpholine		6-(*N*-morpholine)methylpinostrobin
5	1-methylpiperazine		6-(*N*-methylpiperazine)methylpinostrobin
6	Pyrrole		6-(*N*-pyrrole)methylpinostrobin
7	Dicyclohexylamine		6-(*N*-dicyclohexylamine)methylpinostrobin
8	Diphenylamine		6-(*N*-diphenylamine)methylpinostrobin
9	Imidazole		6-(*N*-imidazole)methylpinostrobin
10	Indole		6-(*N*-indole)methylpinostrobin

2.4. Validation of docking protocol

The docking protocol validation was carried out using the redocking method reported by our previous researchusing co-crystal ligands from each receptor [23]. The observed parameter was a root-mean-square deviation (RMSD), with the maximum limit required not more than 2 Å to conclude that the protocol used was valid and could be used for the

docking process. The docking process was repeated three times, and then the free energy of binding (ΔG; kcal/mol) value obtained was calculated using the average value and deviation.

2.5. Molecular docking

Docking for all test ligands was performed the same way as the validation process, with similar sizes and positions of the grid box for each receptor. The results were grouped into two parameters: ΔG and ligand-receptor interactions, in which ligand-receptor interactions were obtained from the average percentage of the similarity of interactions of the amino acids that interacted and the types of interactions that occurred. As in the validation process, the docking process was repeated thrice. The two parameters of each test ligand were compared for their similarity with each comparison ligand, then made in a two-dimensional graph as exemplified in our previous report[28].The docking protocols used for each receptor are presented in **Table 2**.

Table 2

Docking protocol of each receptor

Parameters	**Values**				
PDB ID	3ERT	3RCD	1E3K	5FED	5HG7
Co-crystal ligand	4-hydroxytamoxifen	TAK-285	Metribolone	Nazartinib	PF-06459988
Grid box size (Å)	38 x 28 x 30	30 x 32 x 22	10 x 18 x 28	30 x 30 x 36	28 x 36 x 36
Grid box coordinates (x; y; z)	30.010	12.480	28.454	-2.124	-13.489
	-1.913	2.964	-8.011	51.583	15.359
	24.207	27.995	8.752	-20.44	-25.336
Energy range	3	3	3	3	3
Exhaustive-ness	18	18	18	18	18
Number of modes	8	8	8	8	8

3. Results and discussion

The validation results of all receptors showed RMSD values between 0.619 and 1.817 Å. This value is lower than the RMSD consensus limit in the valid category, which is not more than 2 Å[29]. Therefore, the docking protocol is valid and can be used for the test ligand. The validation results from all receptors provide information that the hardware, software, and configuration used can provide valid results. Thus, the same protocol can be applied to test ligands to obtain valid results.The visualization of ligand overlays from redocking with the reference ligands from all receptors' crystallographic results is presented in **Figure 1**.

The docking of all the test ligands showed varying results, in which no single ligand dominated all the test receptors. Therefore, the best test ligand was determined by considering two test parameters: the difference in the ΔG value and the percentage of ligand-receptor interaction similarity to the reference ligand. The values of these two parameters for all the test ligands were then plotted on a two-dimensional graph for easier observation, as shown in **Figure 2**.

Of the five tested receptors, the majority of the tested ligands showed a ΔG value that was not too far away (<2 kcal/mol) from the difference with the reference ligand in each receptor, except for PR in which even the best ligand had a much larger ΔG value than that (>3.5 kcal/mol).This value is even greater than that of the tested ligands on other receptors, with the largest difference in ΔG value from the comparison (2.48 kcal/mol), with a difference of more than 1 kcal/mol.On the other hand, the average receptor also showed ligand-receptor similarity for each of the tested ligands in the majority range of 40-75%, except for ERα, which, apart from **Compound 3**, showed low similarity (<30%).

These results show that the 6-aminomethylpinostrobin derivative has more potential as an anti-breast cancer agent by inhibiting the HER2 and EGFR receptors (both wild-type and mutant).This is interesting because HER2 is part of the EGFR receptor family, often called EGFR2 or ERBB2[30]. In other words, 6-aminomethylpinostrobin derivatives are more suitable as inhibitors of this receptor family than hormonal receptors such as ERα and PR.

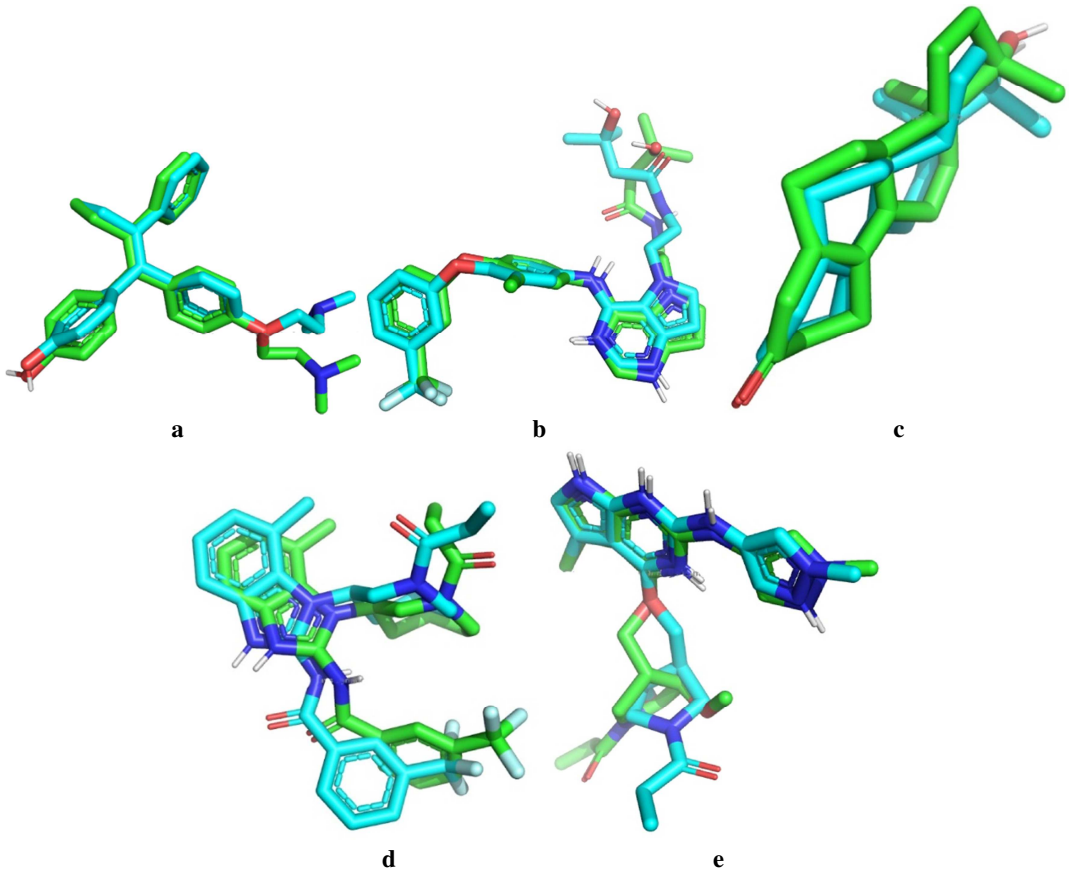


Fig. 1. Overlays of redocking ligands (**blue**) with reference ligands from crystallography data (**green**) at (**a**) receptors 3ERT with RMSD 1.691 Å, (**b**) 3RCD with 1.251 Å,(**c**) 1E3K with 0.869 Å, (**d**) 5FED with 1.817 Å, and (**e**) 5HG7 with 0.619 Å.

Further analysis of the EGFR receptor revealed subtle differences in the tested ligands between wild-type and mutant receptors. Several test ligands (**Compounds1**, **3**, **4**, **7**, **8**, and **10**) showed minor differences in ΔG values (<1 kcal/mol) but higher similarity in the wild-type form compared to the mutant. This is undesirable, considering breast cancer occurs more frequently in receptor mutations[31], implying that the test ligand is not selective for the receptor of interest. There are also test ligands (**Compounds 2** and **5**) that have a similarity that is not much different (<5%), and the difference in ΔG value is slight (<1 kcal/mol), indicating no selectivity of these compounds for receptor mutations, thus, is not desirable in development. Ideal results were shown by **Compounds 6** and **9**, which showed that both had higher similarity and lower ΔG values in the mutant receptor, although the difference was not too significant. Thus, **Compounds 6** and **9** (which also have a similar structure, differing by one N group) have the greatest potential as anti-breast cancer agents by inhibiting the EGFR receptor.

The ideal results were shown for the HER2 receptor, of which of the ten tested ligands, there were two tested ligands with lower ΔG values than the reference compound available on the market (lapatinib). The two ligands (**Compounds7** and **8**) also showed a moderate level of similarity (>50%), indicating a moderate probability compared to lapatinib. Uniquely, these two compounds show the largest ΔG values at the PR, even positive values, indicating that the two compounds experience steric hindrance at the receptor[32]. Structurally, the two compounds are also similar in steric parameters (differences in lipophilic parameters due to differences in the cyclohexane and phenyl groups[33]), thus allowing variations in both the cyclohexane and phenyl groups, especially by adding new substituents to explore their electronic parameters.

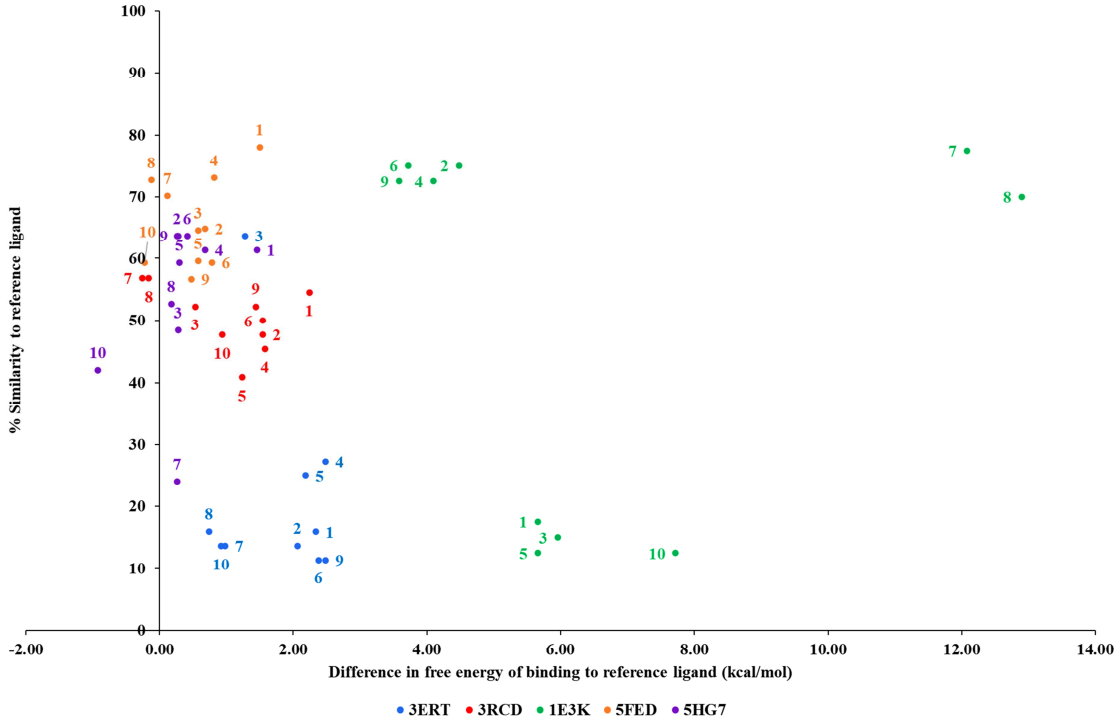


Fig. 2. The two-dimensional graph between the difference in the value of free energy of binding and the percentage of similarity of ligand-receptor interactions compared to the reference ligands on the 3ERT (**blue**), 3RCD (**red**), 1E3K (**green**), 5FED (**orange**), and 5HG7 (**violet**) receptors.

Further analysis per ligand showed implied patterns for each receptor but no absolute relationship overall. **Compound 1**, for example, shows a difference in ΔG values of >1.5 kcal/mol across all receptors (even >5.5 kcal/mol in PR). However, in some receptors, the similarity shown was relatively high (>50%), especially in wild-type EGFR, which reached >78% (**Figure 3**), even though ERα and PR were <20%.Interestingly, even though the similarity is the highest, the butyl substituent gives an unfavorable bump to lysine 745, indicating that sterically, this compound is not the most ideal for EGFR wild-type.

The pattern in **Compound 1**is almost identical to **Compound 10**, although with a lower overall similarity level. However, **Compound 10** showed the lowest ΔG value to the reference ligand of all the tested ligands on the EGFR mutant, which reached more than -0.9 kcal/mol.In this compound, the indole substituent plays a major role [34][35]by being involved in forming two alkyl/pi-alkyl interactions at phenylalanine 723 and 856, and also forming a hydrogen bond with serine 720 (**Figure 4**).Although ideal in terms of affinity, the indole substituent showed little interaction similarity to the mutant EGFR, with a similarity of only around 42%, compared to the wild-type EGFR with more than 59%. This condition is influenced by the absence of interaction with the 790 amino acid mutation from threonine to methionine, initially shown in wild-type EGFR[36].

As previously mentioned, **Compounds 7** and **8** show superiority over the other compounds in affinity and interaction at the HER2 and EGFR wild-type receptors,especially in EGFR wild-type, which shows very similar interactions, as shown in **Figures 5** and **6**. Interestingly, both compounds show the presence of an unfavorable bump by the substituent's cyclohexane and phenyl, which both occur in threonine 790 (as well as lysine 745). These bumps were not shown for the EGFR mutant, which did not even show any interaction with methionine 790 (**Figures 7** and **8**). In other words, the mutation at position 790 plays an essential role in the interaction similarity of **Compounds 7** and **8** but not for the affinity (the difference of ΔG values in the wild-type

and mutant EGFR of **Compounds 7** and **8** is less than 0.2 and 0.3, respectively). This means that even with the same affinity, it is highly likely that **Compounds 7** and **8**will trigger different interactions and reactions in wild-type and mutant EGFR [37].

On the other hand, both **Compounds 7** and **8** also showed dominance compared to other compounds at the HER2 receptor. Interestingly, both also showed superior affinity compared to lapatinib, although the difference was only 0.16 to 0.26. The strong interactions of lapatinib, such as halogen bonds on lysine 796 and glycine 865 and hydrogen bonds on glutamine 799 and threonine 862[38] (**Figure 9**) are not reproduced by **Compounds 7** and **8**, and weak interactions replace the interactions at these positions, such as van der Waals or at least alkyl/pi-alkyl interactions (**Figures 10** and **11**).

Albeit the phenyl group in **Compound 8** allows the formation of pi-sigma interactions in leucine 785, which should contribute to increasing the affinity and interaction of the compound, this interaction does not affect anything. Even though it is small, the affinity of **Compound 7** is slightly better than **Compound 8** (a difference of 0.1 kcal/mol), which means that interactions influenced by electronic parameters do not play an essential role in the overall interaction [39]. What should be observed is that compared to other test ligands, the test ligand with the affinity and interaction parameters closest to **Compounds 7** and **8** is **Compound 3**, which also has tertiary amines with alkyl branches containing phenyl groups. In other words, **Compound 3** shows the closest similarity in steric (and lipophilic) parameters to **Compounds 7** and **8**, one of which is characterized by the alkyl/pi-alkyl interaction in leucine 796 (**Figure 12**), which is not found in any of the other tested ligands.

Lapatinib also demonstrated this interaction, which indirectly confirmed that the 6-aminomethylpinostrobin derivative must exhibit an alkyl/pi-alkyl interaction on leucine 796 to show potential as an anti-breast cancer through HER2 inhibition[40]. Thus, further development of 6-aminomethylpinostrobin derivatives needs to be carried out by considering the existence of these interactions to obtain optimal results.

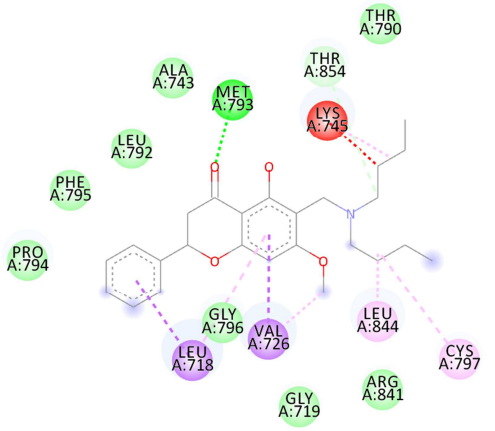


Fig. 3. Two-dimensional interaction of **Compound** 1 in EGFR wild-type.

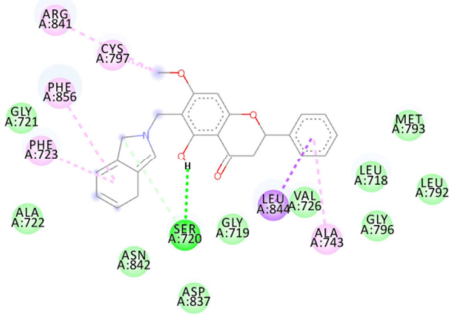


Fig. 4. Two-dimensional interaction of **Compound** 10 in EGFR mutant.

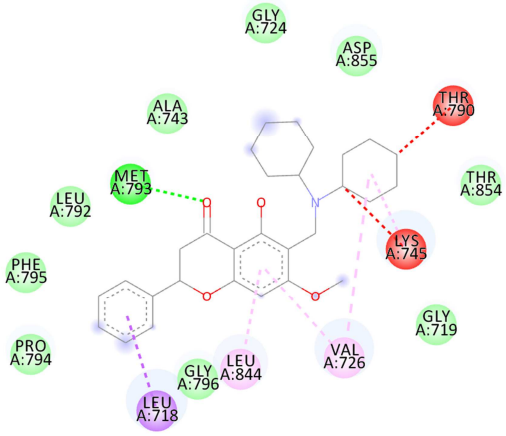


Fig. 5. Two-dimensional interaction of **Compound7** in EGFR wild-type.

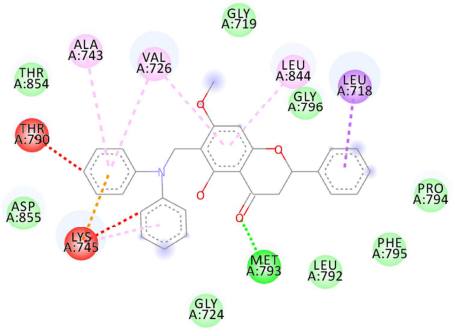


Fig. 6. Two-dimensional interaction of **Compound8** in EGFR wild-type.

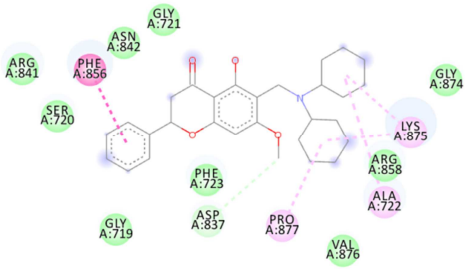


Fig. 7. Two-dimensional interaction of **Compound7** in EGFR mutant.

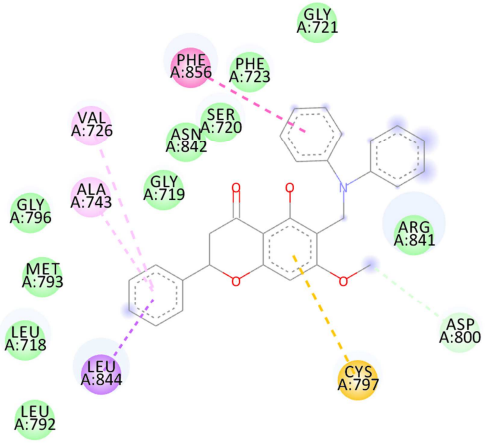


Fig. 8. Two-dimensional interaction of **Compound8** in EGFR mutant.

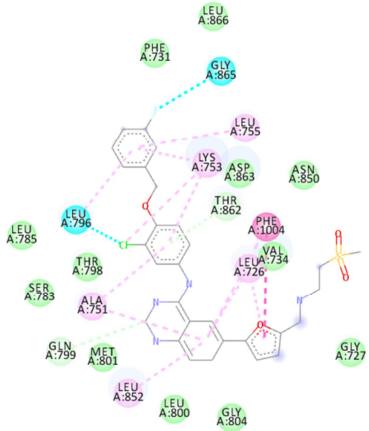


Fig. 9. Two-dimensional interaction of lapatinib in HER2.

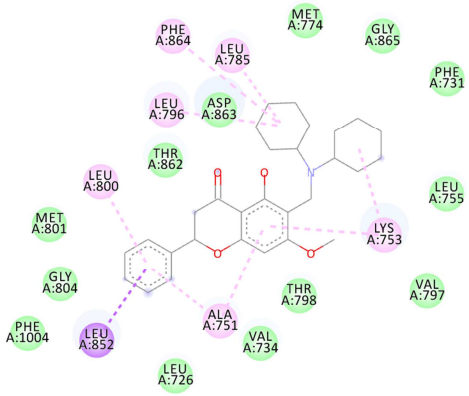


Fig. 10. Two-dimensional interaction of **Compound 7** in HER2.

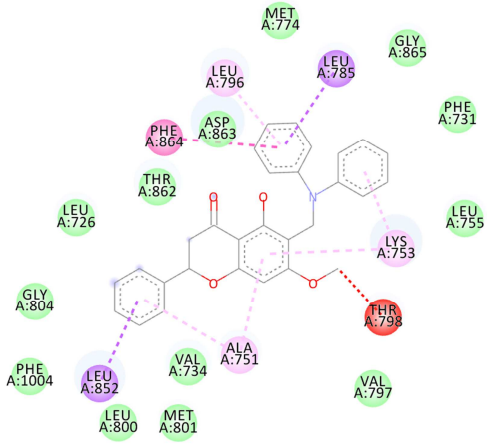


Fig. 11. Two-dimensional interaction of **Compound 8** in HER2.

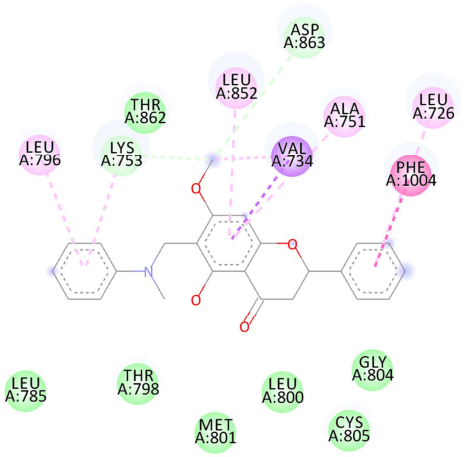


Fig. 12. Two-dimensional interaction of **Compound 3** in HER2.

4. Conclusions

6-aminomethylpinostrobin derivatives show potential as anti-breast cancer through inhibition of HER2 as well as EGFR wild-type and mutants. Among the derivatives, 6-(*N*-dicyclohexylamine)methylpinostrobin and 6-(*N*-diphenylamine)methylpinostrobin showed the highest potency, primarily through HER2 inhibition comparable to lapatinib. Further evaluation through *in vitro* and *in vivo* studies must be carried out to confirm the potential of these compounds.

5. Conflicts of interest

There are no conflicts to declare.

6. Formatting of funding sources

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8. References

[1] Patel, N. K.; Jaiswal, G.; Bhutani, K. K. A review on biological sources, chemistry and pharmacological activities of pinostrobin. Natural Product Research 2016, 30 (18), 2017-2027. https://doi.org/10.1080/14786419.2015.1107556

[2] Erdtman, H. The phenolic constituent of pineheartwood. Svensk Kemisk Tidskrift 1944, 56, 26.

[3] Eng-Chong, T.; Yean-Kee, L.; Chin-Fei, C.; Choon-Han, H.; Sher-Ming, W.; Li-Ping, C. T.; Gen-Teck, F.; Khalid, N.; Rahman, N. A.; Karsani, S. A.; Othman, S.; Yusof, R. Boesenbergia rotunda: From Ethnomedicine to Drug Discovery. Evidence-Based Complementary and Alternative Medicine 2012, 2012, 473637. https://doi.org/10.1155/2012/473637

[4] Nyokat, N.; Yen, K. H.; Hamzah, A. S.; Lim, I. F.; Saaidin, A. S. Isolation and Synthesis of Pinocembrin and Pinostrobinfrom Artocarpus odoratissimus. Malaysian Journal of Analytical Sciences 2017, 21 (5), 1156-1161. https://doi.org/10.17576/mjas-2017-2105-19

[5] Gómez-Betancur,I; Pereañez,J. A.; Patiño,A. C.; Benjumea, D. Inhibitory effect of pinostrobin from Renealmia alpinia, on the enzymatic and biological activities of a PLA2. International Journal of Biological Macromolecules 2016, 89, 35-42. https://doi.org/10.1016/j.ijbiomac.2016.04.042

[6] Korenaga, T.; Hayashi, K.; Akaki, Y.; Maenishi, R.; Sakai, T. Highly Enantioselective and Efficient Synthesis of Flavanones Including Pinostrobin through the Rhodium-Catalyzed Asymmetric 1,4-Addition. Organic Letters 2011, 13 (8), 2022-2025. https://doi.org/10.1021/ol2004148

[7] Poerwono, H.; Sasaki, S.; Hattori, Y.; Higashiyama, K. Efficient microwave-assisted prenylation of pinostrobin and biologicalevaluation of its derivatives as antitumor agents. Bioorganic and Medicinal Chemistry Letters 2010, 20 (7), 2086-2089. https://doi.org/10.1016/j.bmcl.2010.02.068

[8] Marliyana, S. D.; Mujahidin, D.; Syah, Y. M. Pinostrobin Derivatives from Prenylation Reaction and theirAntibacterial Activity against Clinical Bacteria. IOP Conference Series: Materials Science and Engineering 2018, 349, 012057. https://dx.doi.org/10.1088/1757-899X/349/1/012057

[9] Agustin, S. L.; Widiandani, T.; Hardjono, S.; Purwanto, B. T. QSAR of Acyl pinostrobin derivatives as Anti-breast cancer against HER-2 receptor and their ADMET properties based on in

silico Study. Research Journal of Pharmacy and Technology 2022, 15 (10), 4641-4648. https://doi.org/10.52711/0974-360X.2022.00779
[10] Praditapuspa, E. N.; Siswandono; Widiandani, T. 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. Pharmacognosy Journal 2021, 13 (5), 1143-1149. http://dx.doi.org/10.5530/pj.2021.13.147
[11] Pratama, M. R. F.; Poerwono, H.; Siswodiharjo, S. ADMET properties of novel 5-O-benzoylpinostrobin derivatives. Journal of Basic and Clinical Physiology and Pharmacology 2019, 30 (6), 20190251. https://doi.org/10.1515/jbcpp-2019-0251
[12] Pratama, M. R. F.; Poerwono, H.; Siswandono, S. Design and Molecular Docking of Novel 5-O-benzoylpinostrobin Derivatives as Anti-breast Cancer. Thai Journal of Pharmaceutical Sciences 2019, 43 (4), 201-212.
[13] Kicuntod, J.; Khuntawee, W.; Wolschann, P.; Pongsawasdi, P.; Chavasiri, W.; Kungwan, N.; Rungrotmongkol, T. Inclusion complexation of pinostrobin with various cyclodextrin derivatives. Journal of Molecular Graphics and Modelling 2016, 63, 91-98. https://doi.org/10.1016/j.jmgm.2015.11.005
[14] Pratama, M. R. F.; Praditapuspa, E. N.; Widiyana, A. P.; Kesuma, D.; Poerwono, H.; Widiandani, T.; Rudyanto, M.; Siswodiharjo, S. Bibliometric Analysis of Research on Boesenbergia rotunda, Pinostrobin, and Their Derivatives: Dominance of Southeast Asian Researchers. Revista Cubana de Información en Ciencias de la Salud 2023, 34, e2423.
[15] Jaudan, A.; Sharma, S.; Verma, R.; Dixit, A. Pinostrobin inhibits proliferation and induces apoptosis in cancer stem-like cells through a reactive oxygen species-dependent mechanism. RSC Advances 2019, 9 (21), 12097-12109. https://doi.org/10.1039/c8ra08380k
[16] Widyananda, M. H.; Wicaksono, S. T.; Rahmawati, K.; Puspitarini, S.; Ulfa, S. M.; Jatmiko, Y. D.; Masruri, M.; Widodo, N. A Potential Anticancer Mechanism of Finger Root (Boesenbergia rotunda) Extracts against a Breast Cancer Cell Line.Scientifica 2022, 2022, 913252. https://doi.org/10.1155/2022/9130252
[17] Buravlev, E. V.; Fedorova, I. V.; Shevchenko, O. G.; Kutchin, A. V. Novel Aminomethyl Derivatives of 4-Methyl-2-prenylphenol: Synthesis and Antioxidant Properties. Chemistry and Biodiversity 2019, 16 (3), e1800637. https://doi.org/10.1002/cbdv.201800637
[18] Kurnia, A.; Saputri, F. C.; Hayun. Synthesis and anticancer potential of aminomethyl derivatives of methyl-substituted asymmetrical curcumin mono-carbonyl. Journal of Applied Pharmaceutical Science 2019, 9 (8), 18-24. https://doi.org/10.7324/JAPS.2019.90803
[19] Durgapal, S. D.; Soni, R.; Umar, S.; Suresh, B.; Soman, S. S. 3-Aminomethyl pyridine chalcone derivatives: Design, synthesis, DNA binding and cytotoxic studies. Chemical Biology and Drug Design 2018, 92 (1), 1279-1287. https://doi.org/10.1111/cbdd.13189
[20] Rudyanto, M.; Ekowati, J.; Widiandani, T.; Syahrani, A.In vivo anticancer activity of benzoxazine and aminomethyl compounds derived from eugenol. Journal of Public Health in Africa 2023, 14 (Suppl 1), 2511. https://doi.org/10.4081/jphia.2023.2511
[21] Roman, G. Mannich bases in medicinal chemistry and drug design.European Journal of Medicinal Chemistry 2015, 89, 743-816. https://doi.org/10.1016/j.ejmech.2014.10.076
[22] Pratama, M. R. F.; Poerwono, H.; Siswodihardjo, S. Molecular docking of novel 5-O-benzoylpinostrobin derivatives as wild type and L858R/T790M/V948R mutant EGFR inhibitor. Journal of Basic and Clinical Physiology and Pharmacology 2019, 30 (6), 20190301. https://doi.org/10.1515/jbcpp-2019-0301
[23] Pratama, M. R. F.; Praditapuspa, E. N.; Kesuma, D.; Poerwono, H.; Widiandani, T.; Siswodihardjo, S. Boesenbergia Pandurata as an Anti-Breast Cancer Agent: Molecular Docking and ADMET Study. Letters in Drug Design and Discovery 2022, 19 (7), 606-626. http://dx.doi.org/10.2174/1570180819666211220111245
[24] Zinad, D. S.; Mahal, A.; A-Qader, A. M.; Siswodihardjo, S.; Pratama, M. R. F.; Mohapatra, R. 3D-Molecular Modeling, Antibacterial Activity and Molecular Docking Studies of Some Imidazole Derivatives. Egyptian Journal of Chemistry 2021, 64 (1), 93-105. https://doi.org/10.21608/ejchem.2020.31043.2662
[25] Forli, S.; Huey, R.; Pique, M. E.; Sanner, M. F.; Goodsell, D. S.; Olson, A. J. Computational protein-ligand docking and virtual drug screening with the AutoDock suite. Nature Protocols 2016, 11 (5), 905-919. https://doi.org/10.1038/nprot.2016.051
[26] Schlam, I.; Swain, S. M. HER2-positive breast cancer and tyrosine kinase inhibitors: the time is now. NPJ Breast Cancer 2021, 7 (1), 56. https://doi.org/10.1038/s41523-021-00265-1
[27] Cousins, K. R. Computer review of ChemDraw Ultra 12.0. Journal of the American Chemical Society 2011, 133 (21), 8388. https://doi.org/10.1021/ja204075s
[28] Pratama, M. R. F.; Poerwono, H.; Siswodihardjo, S. Introducing a two-dimensional graph of docking score difference vs. similarity of ligand-receptor interactions. Indonesian Journal of Biotechnology 2021, 26 (1), 54-60. https://doi.org/10.22146/ijbiotech.62194
[29] Dankwa, B.; Broni, E.; Enninful, K. S.; Kwofie, S. K.; Wilson, M. D. Consensus docking and MM-PBSA computations identify putative furin protease inhibitors for developing potential therapeutics against COVID-19. Structural Chemistry 2022, 33 (6), 2221-2241. https://doi.org/10.1007/s11224-022-02056-1
[30] Casalini, P.; Iorio, M. V.; Galmozzi, E.; Ménard, S. Role of HER receptors family in development and differentiation. Journal of Cellular

Physiology 2004, 200 (3), 343-350. https://doi.org/10.1002/jcp.20007
[31] Łukasiewicz,S.; Czeczelewski,M.; Forma,A.; Baj,J.; Sitarz,R.; Stanisławek, A. Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies-An Updated Review. Cancers 2021, 13 (17), 4287. https://doi.org/10.3390/cancers13174287
[32] Zheng, L.; Xia, K.; Mu, Y. Ligand Binding Induces Agonistic-Like Conformational Adaptations in Helix 12 of Progesterone Receptor Ligand Binding Domain. Frontiers in Chemistry 2019, 7, 315. https://doi.org/10.3389/fchem.2019.00315
[33] Redka,M.; Baumgart,S.; Kupczyk,D.; Kosmalski,T.; Studzińska, R. Lipophilic Studies and In Silico ADME Profiling of Biologically Active 2-Aminothiazol-4(5 H)-one Derivatives. International Journal of Molecular Sciences 2023, 24 (15), 12230. https://doi.org/10.3390/ijms241512230
[34] Dhuguru, J.; Skouta, R. Role of Indole Scaffolds as Pharmacophores in the Development of Anti-Lung Cancer Agents. Molecules 2020, 25 (7), 1615. https://doi.org/10.3390/molecules25071615
[35] Gaur, A.; Peerzada, M. N.; Khan, N. S.; Ali, I.; Azam, A. Synthesis and Anticancer Evaluation of Novel Indole Based Arylsulfonylhydrazides against Human Breast Cancer Cells. ACS Omega 2022, 7 (46), 42036-42043. https://doi.org/10.1021/acsomega.2c03908
[36] Tetsu, O.; Hangauer, M. J.; Phuchareon, J.; Eisele, D. W.; McCormick, F. Drug Resistance to EGFR Inhibitors in Lung Cancer. Chemotherapy 2016, 61 (5), 223-235. https://doi.org/10.1159/000443368
[37] Yun, C. H.; Mengwasser, K. E.; Toms, A. V.; Woo, M. S.; Greulich, H.; Wong, K. K.; Meyerson, M.; Eck, M. J. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. Proceedings of the National Academy of Sciences of the United States of America 2008, 105 (6), 2070-2075. https://doi.org/10.1073/pnas.0709662105
[38] Verma,S.; Goyal,S.; Kumari,A.; Singh,A.; Jamal,S.; Grover, A. Structural investigations on mechanism of lapatinib resistance caused by HER-2 mutants. PloS One 2018, 13 (2), e0190942. https://doi.org/10.1371/journal.pone.0190942
[39] Zhang, Y.; Opresko, L.; Shankaran, H.; Chrisler, W. B.; Wiley, H. S.; Resat, H. HER/ErbB receptor interactions and signaling patterns in human mammary epithelial cells. BMC Molecular and Cell Biology 2009, 10, 78. https://doi.org/10.1186/1471-2121-10-78
[40] Sohrab, S. S.; Kamal, M. A. Screening, Docking, and Molecular Dynamics Study of Natural Compounds as an Anti-HER2 for the Management of Breast Cancer. Life 2022, 12 (11), 1729. https://doi.org/10.3390/life12111729