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RESEARCH ARTICLE

In Silico Study of N-Pyrazoline Derivate Compounds as Anticancer Through Inhibition of PI3K and PR Expression

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ABSTRACT

Breast cancer treatment has many options directed at therapeutic targets, but some remain incurable, so new therapies are needed. Pyrazoline has shown various biological activities, one of which is anticancer effectiveness. The purpose of this study was to conduct an in silico analysis of Pyrazoline inhibition of PI3K and PR proteins using docking and MD simulation methods. Predictions of toxicity and pharmacokinetics, including absorption, distribution, metabolism, excretion, and toxicity, were also conducted computationally. The analysis showed that the Pyrazoline compound had interactions with ligands of PI3K proteins and PR proteins. Pharmacokinetic predictions showed that the compound in the human intestine was poorly absorbed, could not cross the blood-brain barrier, and had the potential to be a substrate or inhibitor of CYP, had good plasma protein binding, low clearance, slow excretion rate, short half-life, risk of hepatotoxicity, carcinogenicity, and mutagenicity. LD_{50} is predicted to be 1000 mg/Kg and is included in category IV. These results can guide its development, but further testing is needed to confirm.

Keywords: ADMET prediction, Breast cancer, Pyrazolines, Molecular docking, MD simulation

Introduction

Breast cancer is a prevalent form of cancer that is responsible for causing death in women and is ranked as the fifth most common globally. [1] In 2022, there were 2.3 million women who received a diagnosis of breast cancer. [2] Several factors can contribute to the development of breast cancer, such as reproductive history, insufficient physical activity, free radicals, gene alterations, and exposure to radiation. [3,4] Several therapeutic targets have been identified for breast cancer treatment, but there are still some forms of the disease that cannot be cured. Therefore, the development of novel medicines is necessary. [5–7]

Pyrazoline is a compound derived from N-phenyl Pyrazoline and is a nitrogen chemical compound classified as a heterocyclic compound. These compounds show various biological activities, including anticancer effectiveness against breast cancer, hepatocellular carcinoma, lung cancer, and breast cancer

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cells.[8–10] Pyrazoline derivatives have been studied in many cancer cell lines and have shown the ability to inhibit cell proliferation and induce programmed cell death.[11] Our previous studies found that Pyrazoline can inhibit HER-2 expression through docking simulations.[12] Synthetically produced N-phenyl Pyrazoline has anticancer characteristics that target cells associated with breast and colorectal cancer.[13–15]

This research included conducting a docking analysis to examine the inhibitory effects of Pyrazoline on PI3K and PR (progesterone receptor) proteins. The activation of the PI3K pathway contributes to tumor development, making it an attractive therapeutic direction and target for cancer treatment. Inhibition of PI3K signalling is effective in treating several types of cancer.[16] Meanwhile, PR is also one of the prognostic biomarkers in breast cancer, particularly in hormone-positive. PR-negative breast luminal epithelial cells can undergo intrinsic proliferation when exposed to PR through autocrine activation via the RANKL pathway and subsequent activation of the downstream target cyclin D1.[17,18] We also performed LD_{50} (lethal dose) and pharmacokinetics (absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction analysis. ADMET of a drug plays a critical role in determining which potential candidates to prioritize. In silico approaches are becoming increasingly popular in improving the drug discovery process by illuminating ADMET properties early in drug development. This analysis is essential as a guideline for the safety and efficacy of the compound so that it can be used as a guide for further testing.[19,20]

Materials and methods

3D ligand preparation

The compounds to be tested (Pyrazoline A, Pyrazoline B, Pyrazoline C, Pyrazoline D, and Pyrazoline M) were drawn in 2D structures using the ChemDraw 18.1 application. Then, the 2D structure was converted into a 3D structure using the chem3D 18.1 application by performing energy minimization (MMFF94 minimization) and saved in SDF format.[21]

Docking analysis

The 3D structures of PI3K (PDB ID: 6XRM) and PR (PDB ID: 2OVM) proteins were selected from the RSCB PDB database (https://www.rcsb.org/). Then, the control ligand was downloaded through the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Re-docking was carried out using the specific docking method using the MolDock algorithm integrated into Molegro Virtual Docker 5.0.[22] The grid box size used refers to the control ligand (native ligand) that has been docked to the PDB protein. If the RMSD re-docking results are below 2Å, then the grid box is valid for use for molecular docking.

Pharmacokinetic prediction

Prediction of pharmacokinetic properties of Pyrazoline was performed using Web ADMETlab 2.0 by following Lipinski's rule of five (RoF) (https://admetmesh.scbdd.com/service/evaluation/cal). The SMILEs required in ADMET analysis were obtained from PubChem (http://pubchem.ncbi.nlm.nih.gov).

LD_{50} toxicity prediction

Toxicity prediction was evaluated using the Protox II database (https://tox-new.charite.de/protox_II/index.php?site$ = $compound_input)

Results and discussion

3D ligand structure

Molecular docking can identify a new compound for therapeutic interest, predict the interaction between target proteins and ligands at the molecular level and describe the relationship between structure-activity. The use of molecular docking studies reduces costs and increases the opportunity to find new desired drug candidates to discover new drugs more efficiently. In this study, in silico testing was carried out, it required the 3D structure of the test compound to describe the experiments carried out with the help of a computer. In many drug discovery applications, docking is carried out between small molecules and macromolecules (protein-ligand docking).

Docking is also applied to predict the binding mode between two macromolecules (protein-protein docking).[23] The 3D structures of the compounds Pyrazoline A, Pyrazoline B, Pyrazoline C, Pyrazoline D, and Pyrazoline M) that have been drawn are shown in Fig. 1.

PI3K protein docking analysis results

The control RMSD results shown in Table 1. are less than 2 Åby the standard so that it can be continued to molecular docking with test compounds.[24]

The results of molecular docking of PI3K protein (ID: 6XRM) with the test compounds in Table 2. show that no Pyrazoline compound has a more substantial

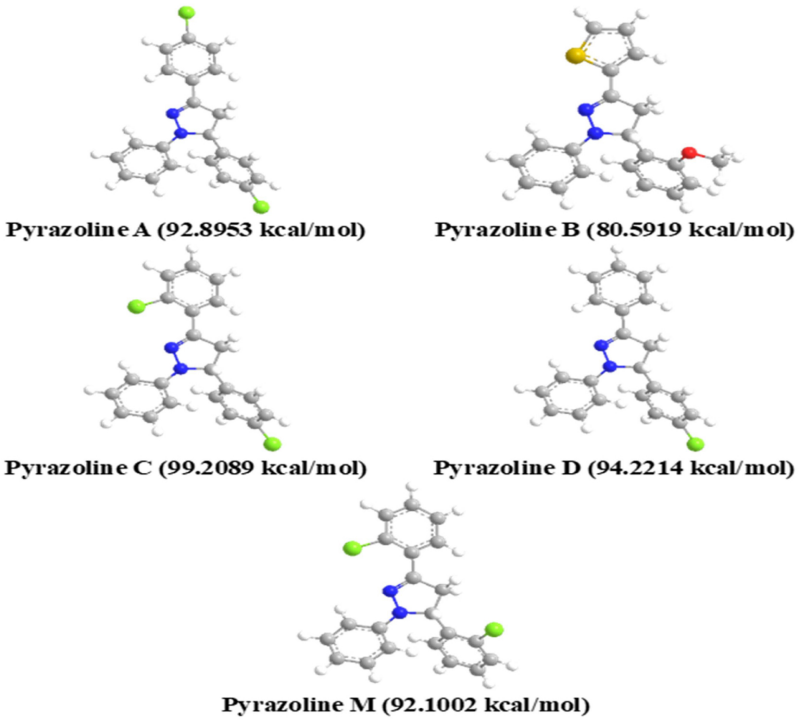

Fig. 1. 3D structure of Pyrazoline ligands.

Table 1. Gridbox settings used.

Protein	X	Y	Z	Radius	RMSD Re-docking	Binding affinity (kcal/mol)
6XRM	–24.30	13.02	–21.92	10	0.61	–150.517
2OVM	–29.60	50.91	44.21	10	0.74	–129.488

Table 2. Binding affinity between PI3K protein and test compounds.

Compounds	Binding Affinity (kcal/mol)	RMSD (Å)
V81 (native ligand)	–157.513	0.61
Pyrazoline A	–91.091	0
Pyrazoline B	–93.508	0.04
Pyrazoline C	–94.865	0
Pyrazoline D	–93.401	0.04
Pyrazoline M	–96.313	0
Sorafenib	–102.684	0.04

binding affinity value than the native ligand in the form of V81 or 5-[2-amino-3-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-5-yl]-2-[(1S)-1-cyclopropylethyl]-7-(trifluoromethyl)-2,3-dihydro-1H-isoindol-1-one [1] or sorafenib as a commercial drug.[25]

Table 3. shows the interactions between each ligand and the PI3K protein. Based on the type of bond produced, van der Waals and hydrophobic bonds are the most dominant bonds. Residues marked (*) are amino acid residues from the control retained by the sample. The analysis results show that the Pyrazoline A sample retains the most active site residues from the control, namely 13. Meanwhile, Pyrazoline B, C, D, and M each form 6, 7, 11, and 8 amino acids that are the same as the control, while Sorafenib forms nine amino acids that are the same as the control.

Additionally, displaying the surface hydrophobicity map, Fig. 2 displays the 3D visualization results of the PI3K protein complex with the native ligand, the commercial medication sorafenib, and five Pyrazoline compounds. The color of the protein surface determines hydrophobicity; brown indicates hydrophobicity toward white (intermediate) to blue hydrophilic). The complex form obtains higher stability if the resulting interaction is more hydrophobic.[26]

Results of PR protein docking analysis

The RMSD results of the control, shown in Table 4, are by the standard (<2 Å).[26] PR protein (ID: 2OVM) with the test compounds showed that the five Pyrazoline test compounds did not have a stronger binding affinity compared to the native ligand in the form of AS0 or 4-[(11beta,17beta)-17-Methoxy-17-(Methoxymethyl) -3-Oxoestra-4,9-Dien-

Table 3. Interaction of amino acid residues produced in the PI3K protein with test compounds.

Ligand	Interaction					
	Van der Waals	Conventional Hydrogen	Hydrogen Carbon	Hydrophobic	Other	Unfavorable
V81 (native ligand)	A:MET842 A:ASP841 A:LEU845 A:ASP964 A:THR887 A:TRP812	A:LYS833 A:VAL882 A:ALA885	A:GLU880 A:TYR867	A:TYR867 A:PHE961 A:CYS869 A:PRO810 A:LEU838 A:MET804 A:PHE965 A:ILE831 A:ILE879 A:ILE963 A:MET953 A:MET804 A:ILE881 A:VAL882		
Pyrazoline A	A:LEU838 A:ASP841* A:LEU845* A:PHE965 A:HIS834 A:MET804 A:TRP812* A:GLU880		A:PRO810 A:ILE963	A:TYR867* A:ALA885 A:ILE831* A:ILE879* A:ILE963* A:LYS808 A:PRO810* A:LYS833 A:ILE881* A:VAL882* A:MET953* A:PHE961* A:CYS869*	A:LYS833	
Pyrazoline B	A:LEU838 A:PHE961 A:VAL882 A:ILE881 A:GLU880 A:ASN951 A:LYS808 A:ASP964 A:HIS834 A:HIS962 A:PHE965 A:LEU845* A:CYS869 A:ASP841*		A:ILE963	A:ILE831* A:ILE879* A:ILE963* A:PRO810* A:LYS833	A:LYS833 A:TYR867	
Pyrazoline C	A:HIS962 A:PHE965 A:ASP964* A:LEU845* A:ASP841 A:CYS869 A:LEU838 A:HIS834 A:ILE831 A:MET953 A:ILE881 A:VAL882 A:GLU880		A:PRO810 A:ILE963A: LYS833	A:TYR867* A:PHE961* A:LYS808 A:PRO810* A:LYS833 A:ILE963* A:ILE879*		

(Continued)

Table 3. Continued.

Ligand	Interaction					
	Van der Waals	Conventional Hydrogen	Hydrogen Carbon	Hydrophobic	Other	Unfavorable
Pyrazoline D	A:HIS962 A:PHE965 A:LEU845* A:ASP841 A:LEU838 A:HIS834 A:ASP964* A:TRP812* A:ILE881 A:GLU880		A:PRO810 A:ILE963A: LYS833	A:PHE961* A:TYR867* A:ILE831* A:ILE879* A:ILE963* A:LYS808 A:PRO810* A:LYS833 A:VAL882* A:CYS869*		
Pyrazoline M	A:HIS962 A:LEU845* A:PHE965 A:ASP841* A:CYS869 A:LEU838 A:ASP964* A:LYS808 A:HIS834 A:MET953 A:PHE961 A:ILE881 A:VAL882 A:GLU880			A:TYR867* A:ILE963* A:PRO810* A:ILE831* A:LYS833 A:ILE879*		
Sorafenib	A:THR887* A:ALA805 A:ASP964* A:GLU880 A:PHE961 A:LYS883 A:MET953	A:LYS833 A:VAL882 A:ASN951 A:ILE963	A:SER806 A:ALA885 A:VAL882	A:TYR867* A:ILE881* A:TRP812 A:MET804* A:PRO810* A:ILE831* A:ILE879* A:ILE963* A:VAL882	A:ASP950 A:VAL882	

*: Amino acid residues from the retained control sample.

11-Yl]Benzaldehyde Oxime.[27] However, the five pyrazoline test compounds had a stronger binding affinity than the drug norethisterone.

Table 5. shows the interactions formed between each ligand and the PR protein. Based on the type of bond produced, van der Waals and hydrophobic bonds are the most dominant bonds. Residues marked with (*) are retained amino acid residues from the control sample. The analysis results show that the Pyrazoline M sample retains the most active site residues from the control, which is 14. Meanwhile, Pyrazoline A, B, C, and D each form 11, 12, 12, and 11 amino acids that are the same as the control. As a commercial drug, Norethisterone forms the least amino acid bonds, the same as the control, which is ten residues. Therefore, the binding affinity of Norethisterone is the weakest compared to other test compounds.[28]

Fig. 3 shows the results of 3D visualization of PR protein complexes with control ligands, commercial norethisterone drugs, and five Pyrazoline compounds. Surface hydrophobicity is displayed based on the color of the protein surface. Brown color indicates hydrophobicity towards white (intermediate) to blue (hydrophilic).[29]

Pharmacokinetic prediction results

The SMILE search was obtained from PubChem of Pyrazoline compounds A, B, C, D, and M, as shown in Table 6. Furthermore, Lipinski's Rule of Five (RoF) analysis was used to evaluate drug similarity or determine whether a chemical compound with a specific pharmacological or biological activity has chemical and physical properties that have the potential to be a drug candidate. This rule plays a vital role in drug development. It is used to estimate the solubility and permeability of compounds and predict qualifications as drug candidates, whether the compound is orally active or not. The assessment depends on the

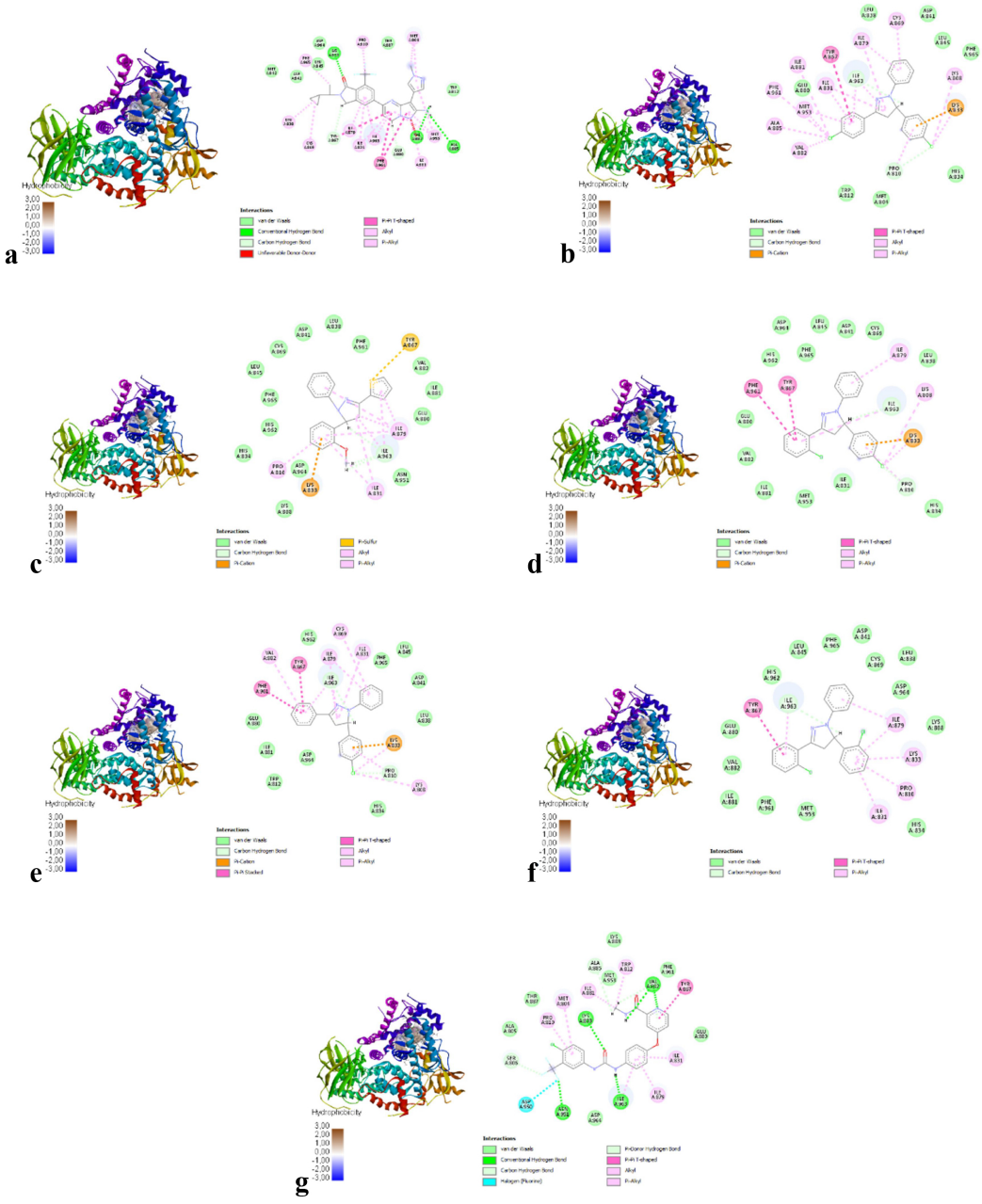

Fig. 2. Visualization of docking results of binding with PI3K protein, a) native ligand, b) Pyrazoline A, c) Pyrazoline B, d) Pyrazoline C, e) Pyrazoline D, f) Pyrazoline M, g) sorafenib. The left section displays 3D visualization, while the right section displays the bond generated between the ligand-protein.

Table 4. Binding affinity between PR protein and test compounds.

Compounds	Binding Affinity (kcal/mol)	RMSD (Å)
AS0 (native ligand)	–130.543	0.02
Pyrazoline A	–96.966	0.00
Pyrazoline B	–98.229	0.01
Pyrazoline C	–98.732	0.41
Pyrazoline D	–94.131	0.05
Pyrazoline M	–95.020	0.00
Norethisterone	–83.763	0.00

Table 5. Interaction of amino acid residues produced in the PR protein with test compounds.

Ligand	Interaction					
	Van der waals	Conventional hydrogen	Hydrogen carbon	Hydrophobic	Other	Unfavorable
AS0 (native ligand)	A:LEU721 A:PHE778 A:LEU763 A:VAL760 A:MET801 A:LEU887 A:MET756 A:TYR890 A:THR894 A:LEU718 A:TRP755 A:ASN719 A:LEU715 A:GLU723 A:LEU726	A:GLN725 A:ARG766	A:CYS891	A:PHE794 A:LEU797 A:CYS891	A:MET759	
Pyrazoline A	A:LEU721* A:GLN725 A:VAL760* A:LEU726* A:TRP755 A:GLU723* A:MET756* A:ASN719* A:THR894* A:LEU715*			A:PHE778 A:GLY722* A:GLU723* A:MET759* A:LEU763 A:LEU718		A:ARG766
Pyrazoline B	A:TYR890 A:MET801* A:VAL760* A:ARG766 A:PHE778* A:GLN725 A:TRP755* A:ASN719* A:LEU726* A:GLU723*		A:LEU718	A:GLY722* A:GLU723* A:LEU718 A:LEU721 A:MET759 A:LEU763 A:MET756 A:LEU797* A:LEU887 A:CYS891*	A:MET756 A:MET759*	
Pyrazoline C	A:LEU715* A:THR894* A:ASN719* A:MET756* A:GLU723* A:LEU726* A:TRP755* A:VAL760* A:ARG766 A:LEU721*		A:GLN725	A:PHE778 A:GLY722* A:GLU723* A:MET759 A:LEU763 A:LEU718 A:CYS891*		
Pyrazoline D	A:LEU721* A:LEU715* A:THR894* A:ASN719* A:MET756* A:GLU723* A:LEU726* A:TRP755* A:VAL760* A:GLN725 A:ARG766			A:PHE778 A:GLY722 A:GLU723 A:MET759* A:LEU763 A:LEU718 A:CYS891*		

(Continued)

Table 5. Continued.

Ligand	Interaction					
	Van der waals	Conventional hydrogen	Hydrogen carbon	Hydrophobic	Other	Unfavorable
Pyrazoline M	A:TRP755* A:LEU718* A:GLU723* A:ASN719* A:MET756* A:GLY722 A:LEU715* A:THR894* A:TYR890* A:LEU797 A:LEU887* A:LEU721* A:MET801* A:ARG766 A:VAL760*		A:GLN725	A:PHE778 A:MET759* A:LEU763 A:CYS891*		
Norethisterone	A:LEU721* A:GLN725 A:GLY722 A:TRP755* A:LEU715* A:TYR890* A:LEU763* A:PHE778	A:ARG766*	A:CYS891*	A:MET756 A:MET759 A:VAL760 A:LEU797* A:MET801 A:LEU887 A:CYS891* A:LEU718 A:PHE794*		

* Amino acid residues from the control sample were retained.

molecular properties, namely molecular weight ≤ 500, high lipophilicity (logP) ≤ 5, hydrogen bond acceptor ≤10, and hydrogen bond donor ≤5. A compound or drug is said to fulfill Lipinski's RoF if there are no more than two rules that are not in accordance.[30] Table 6 shows that the Pyrazoline B compound fulfills Lipinski's RoF. At the same time, other compounds do not meet the lipophilicity requirements (logP >5).

Furthermore, ADMET analysis was performed; the results are shown in Table 7. Pyrazoline absorption in the human intestine and Caco-2 permeability as an indicator of the rate of oral drug absorption showed that the observed compound was poorly absorbed (ideal value> -5.15 cm/s).[31,32] The observed compound has an ideal value (<90%) in plasma protein binding. Plasma protein binding is related to how much the drug binds to proteins in the bloodstream. Drugs with fewer bonds show higher efficiency.[33,34] Based on the Blood-Brain Barrier (BBB) parameters, this compound is predicted to not pass through the BBB (ranging from 0.7-1.0). Drugs that work in the central nervous system must pass through the BBB to reach their molecular targets. However, drugs that target the periphery do not need to penetrate the blood-brain barrier to prevent potential side effects on the central nervous system.[35] Furthermore, these compounds can potentially be substrates or inhibitors of CYP. Only a few CYPs are neither substrates nor inhibitors. CYP enzymes are essential for drug metabolism. The value is the probability of being a substrate/inhibitor in the range of 0 to 1.[36]

In the excretion parameters, we examined the clearance and half-life, two critical factors in drug excretion. This information is essential for preparing a drug dosage regimen.[37] The average clearance of Pyrazoline compounds is in the low category (<5 mL/min/Kg), indicating a slower excretion rate. The half-life ($T_{1/2}$) of this compound is also predicted to be in the short category (<3 hours), indicating relatively rapid elimination from the body. This compound is also predicted to show a risk of hepatotoxicity and carcinogenicity but has a moderate risk of mutagenicity.[38]

LD_{50} toxicity prediction results

The toxicity of a drug is significant because, in addition to efficacy, the drug must also provide a safe effect.[39] The LD_{50} toxicity prediction results are shown in Table 8. Toxicity is one of the criteria that needs to be considered in selecting drug candidates to ensure their safety. The toxicity parameter used is acute oral toxicity. Acute oral toxicity indicates

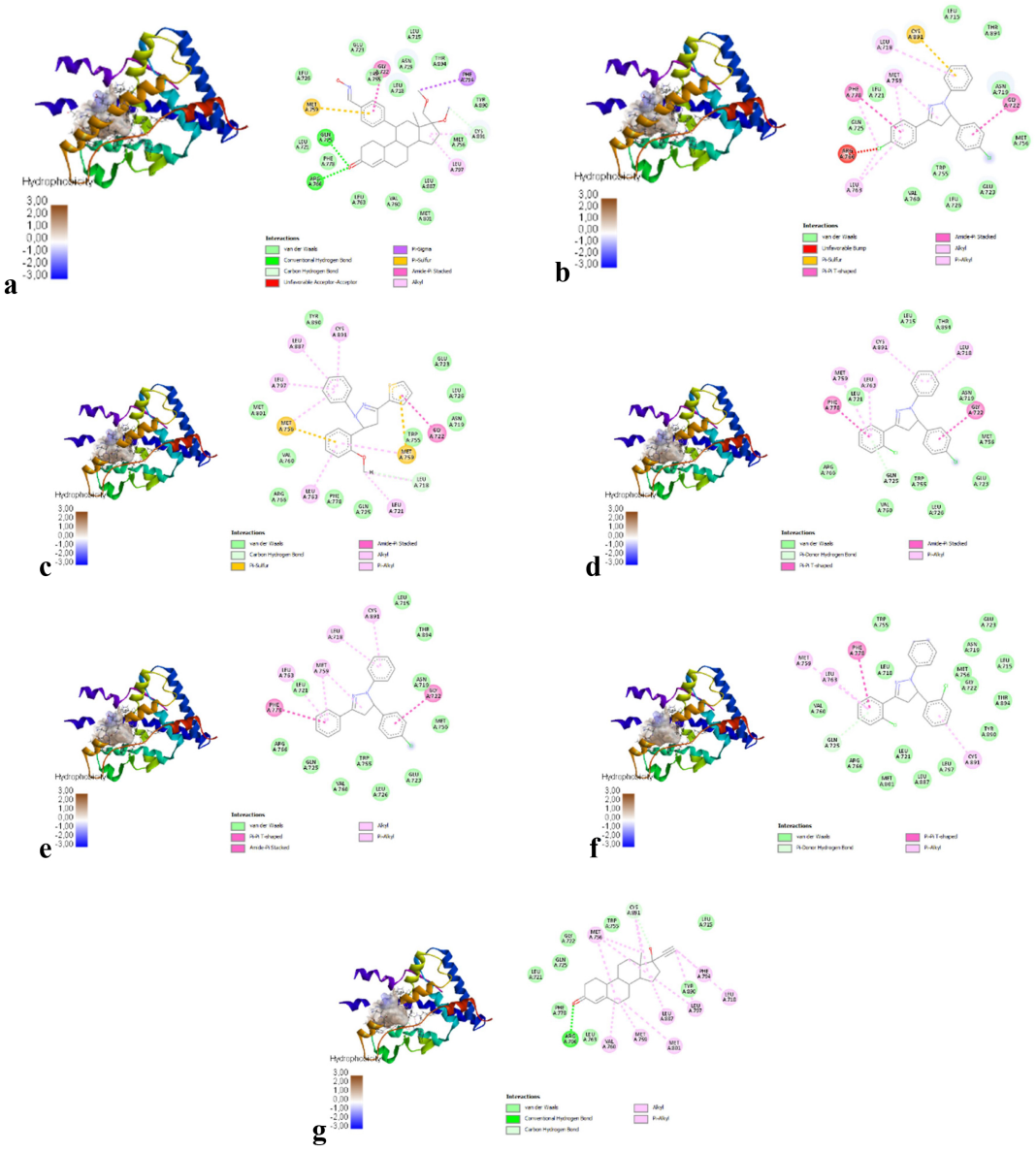

Fig. 3. Visualization of docking results with PR protein, a) native ligand, b) Pyrazoline A, c) Pyrazoline B, d) Pyrazoline C, e) Pyrazoline D, f) Pyrazoline M, g) Norethisterone. The left section displays 3D visualization, while the right section displays the bond generated between the ligand-protein.

Table 6. Lipinski's RoF estimates the value of Pyrazoline.

Compounds	SMILE	Molecular weight (g/mol)	Hacc	Hdon	logP
Pyrazoline A	ClC1=CC=C(C=C1)C1CC(=NN1C1=CC=CC=C1)C1=CC=C(Cl)C=C1	366.07	2	0	5.81*
Pyrazoline B	COC1=C(C=CC=C1)C1CC(=NN1C1=CC=CC=C1)C1=CC=CS1	334.11	3	0	4.08
Pyrazoline C	ClC1=CC=C(C=C1)C1CC(=NN1C1=CC=CC=C1)C1=C(Cl)C=CC=C1	366.07	2	0	5.33*
Pyrazoline D	ClC1=CC=C(C=C1)C1CC(=NN1C1=CC=CC=C1)C1=CC=CC=C1	332.11	2	0	5.20*
Pyrazoline M	ClC1=CC=CC=C1C1CC(=NN1C1=CC=CC=C1)C1=C(Cl)C=CC=C1	366.07	2	0	5.14*

Note: logP: Partition coefficient (Lipophilicity), Hacc: Hydrogen bond acceptor, Hdon: Hydrogen bond donor.
*Does not meet Lipinski's RoF.

the acute toxic properties of compounds or drugs administered orally. Acute oral toxicity tests are carried out to measure the degree of toxicity of a compound within 24 hours and are expressed based on LD_{50}. LD_{50} is divided into six categories, namely category I (super toxic $\leq$ 5 mg/kg), category II (extremely toxic

Table 7. ADMET predicted result.

Property	Model Name	Ideal value	Pyrazoline A	B	C	D	M
Absorption	Papp (Caco-2 Permeability)	> **–5.15 cm/s**	–4.41	–4.83	–4.66	–4.41	–4.79
	Human Intestinal Absorption	<**30%**	0	0.0003	0	0	0
Distribution	Plasma Protein Binding	<**90%**	98.86	98.21	98.21	98.53	98.00
	Blood Brains Barrier	• Excellent: 0–0.3 • Medium: 0.3–0.7 • Poor: 0.7–1.0	0.99	0.98	0.99	0.99	0.99
Metabolism	CYP1A2 substrate		0.78 (Yes)	0.15 (No)	0.92 (Yes)	0.45 (No)	0.99 (Yes)
	CYP2C19 substrate		0.97 (Yes)	0.41 (No)	0.98 (Yes)	0.98 (Yes)	0.99 (Yes
	CYP2C9 substrate		0.92 (Yes)	0.40 (No)	0.47 (Yes)	0.15 (No)	0.70 (Yes)
	CYP2D6 substrate		0.04 (No)	0.64 (Yes)	0.10 (No)	0.11 (No)	0.05 (No)
	CYP1A2 inhibitor		0.99 (Yes)	0.99 (Yes)	0.99 (Yes)	0.99 (Yes)	0.99 (Yes)
	CYP2C19 inhibitor		0.99 (Yes)	0.99 (Yes)	0.99 (Yes)	0.99 (Yes)	0.99 (Yes)
	CYP2C9 inhibitor		0.99 (Yes)	1.00 (Yes)	0.99 (Yes)	0.99 (Yes)	0.99 (Yes)
	CYP3A4 inhibitor		0.99 (Yes)	0.99 (Yes)	0.99 (Yes)	0.99 (Yes)	0.99 (Yes)
Excretion	Clearance rate	• High: >15 mL/min/Kg • Moderate: 5–15 mL/min/Kg • Low: <5 mL/min/Kg	3.78	6.41	4.25	4.15	4.79
	T $^{1}/_{2}$ (Half lifetime)	• Long > 3hrs • Short <3 hrs	0.94	0.57	0.88	0.74	0.89
Toxicity	Human Hepatotoxicity	• Excellent: 0–0.3 • Medium: 0.3–0.7 • Poor: 0.7–1.0	0.76	0.75	0.78	0.77	0.75
	Ames Mutagenicity		0.26	0.69	0.37	0.40	0.46
	Carcinogenicity		0.61	0.75	0.69	0.65	0.73

Table 8. LD_{50} prediction.

Compounds	Predicted Toxicity Class	Predicted LD_{50} (mg/Kg BW)
Pyrazoline A	4	1000
Pyrazoline B	4	1000
Pyrazoline C	4	1000
Pyrazoline D	4	1000
Pyrazoline M	4	1000

5-50 mg/kg), category III (toxic 50-500 mg/kg), category IV (moderately toxic 500-2000 mg/kg), category V (mildly toxic> 2000-5000 mg/kg), and category VI (non-toxic> 5000 mg/Kg).[40] The analysis showed that Pyrazoline A, B, C, D, and M were predicted to have an LD_{50} of 1000 mg/Kg and were included in category IV (moderate toxicity). However, further toxicity tests are needed to confirm this, especially in long-term use.

Conclusion

Based on docking results, Pyrazoline compounds, especially Pyrazoline M, are predicted to have activity as breast cancer drugs. Predictions of ADMET and LD_{50} of this compound are also crucial as a guide for future development.

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Authors' declaration

- Conflicts of Interest: None.
- We hereby confirm that the figures and tables in the manuscript are ours. Furthermore, figures and images that are not ours have been included with the necessary permission for re-publication, which is attached to the manuscript.
- No animal studies are present in the manuscript.
- Authors signed on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee at Universitas Sumatera Utara, Medan, Indonesia.

Authors' contribution statement

This manuscript was created in collaboration with all authors: D.S. conceptualized and took care of the publication, S.B.W. drafted and edited the manuscript with revisions, E.N.S. designed and acquired data, M. supervised and did proofreading, P.B.S. interpreted the results, T.D.W. did the docking analysis, H.L.W. did the revision and final check, E.D. did the pharmacokinetic prediction analysis. All authors read and approved the final manuscript.

Data availability

The datasets generated and/or analyzed during the current study are available from publicly accessible databases. The 3D protein structures of PI3K (PDB ID: 6XRM) and PR (PDB ID: 2OVM) were obtained from the RCSB Protein Data Bank (https://www.rcsb.org/). Ligand structures and SMILES information were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/). ADMET properties were predicted using ADMETlab 2.0 (https://admetmesh.scbdd.com/service/evaluation/cal), and acute oral toxicity (LD50) prediction was performed using ProTox-II (https://tox-new.charite.de/protox_II/index.php?site$ = $compound_input)."

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في دراسة حاسوبية للمركبات المشتقة من N-pyrazoline كمضاد للسرطان من خلال تثبيط تعبير PI3K وPR

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الخلاصة

يوجد العديد من الخيارات لعلاج سرطان الثدي والتي تستهدف أهدافًا علاجية، ولكن بعضها لا يزال غير قابل للشفاء، لذا هناك حاجة إلى علاجات جديدة. وقد أظهر البيرازولين العديد من الأنشطة البيولوجية، أحدها فعالية مضادة للسرطان. وكان الغرض من هذه الدراسة إجراء تحليل حاسوبي لتثبيط البيرازولين لبروتينات PI3K و PRباستخدام طرق الالتحام ومحاكاة .MD كما تم إجراء تنبؤات السمية والدوائية، بما في ذلك الامتصاص والتوزيع والأيض والإخراج والسمية، بشكل حسابي. وأظهر التحليل أن مركب البيرازولين كان له تفاعلات مع ربيطات بروتينات PI3K وبروتينات .PR وأظهرت تنبؤات الدوائية أن المركب في الأمعاء البشرية يمتص بشكل سيئ، ولا يمكنه عبور حاجز الدم في الدماغ، ولديه القدرة على أن يكون ركيزة أو مثبطًا لـCYP ، وله ارتباط جيد ببروتينات البلازما، وتصفية منخفضة، ومعدل إفراز بطيء، ونصف عمر قصير، وخطر السمية الكبدية، والسرطان، والطفرات. من المتوقع أن تبلغ الجرعة المميتة 1000 مجم/كجم، وهي مدرجة في الفئة الرابعة. ويمكن لهذه النتائج أن توجه تطويرها، ولكن هناك حاجة إلى مزيد من الاختبارات لتأكيد ذلك.

الكلمات الرئيسية: التنبؤ بـ ADMET، سرطان الثدي، البيرازولينات، الالتحام الجزيئي، محاكاة خلل التنسج الجزيئي.