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Original Article

Synthesis, molecular docking, molecular dynamics, pharmacokinetics prediction and bioassay of N-(phenylcarbamothioyl)-4-chlorobenzamide as anti-breast cancer candidate

[Síntesis, acoplamiento molecular, dinámica molecular, predicción farmacocinética y bioensayo de N-(fenilcarbamotioil)-4-clorobenzamida como candidato contra el cáncer de mama]

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Abstract

Context: Breast cancer ranks as the leading cause of mortality among women in Indonesia. Thiourea is a compound containing sulfur atom and nitrogen in which its chemical structure resembles urea compound, which has been applied as an anticancer, such as hydroxyurea, nitrosourea, 5-fluorouracil, and sorafenib.

Aims: To develop anticancer candidates as a new compound of thiourea derivative, N-(phenylcarbamothioyl)-4-chloro-benzamide (4-Cl-PCTB).

Methods: The compound was synthesized from phenylthiourea and 4-chloro-benzoyl chloride by applying nucleophilic acyl substitution reactivity. The compound resulting from synthesis was examined for its purity and structure identification by using FTIR, ^{1}H-NMR,^{13}C-NMR, and MS. *In silico* tests included molecular docking using Molexus software, molecular dynamics simulation using Desmond and MOE software, and pharmacokinetics prediction using SCFbio, pkCSM, and Swiss ADME. Anticancer activity through cytotoxic test was done using the MTT method in T47D cancer cells and Vero normal cells.

Results: The 4-Cl-PCTB compound was obtained from the synthesis. The results of the molecular docking and molecular dynamics simulation on the checkpoint kinase 1 receptor (2YWP) showed a plant score of -67.19 kcal/mol, which was better than the native ligand and the standard reference hydroxyurea. The molecular dynamics simulation results indicated that the 4-Cl-PCTB compound exhibited better bond stability compared to hydroxyurea. Pharmacokinetic predictions for 4-Cl-PCTB showed good GIT absorption, classifying it under BCS Class I, with a low volume of distribution, no BBB penetration, a half-life of 3 hours, and no hepatotoxicity. The results of the cytotoxic test: IC_{50} T47D cells = 0.44 mM, Vero cells = 76.10 mM, hydroxyurea = 4.58 mM. SI value = 173.35 (SI >10).

Conclusions: 4-Cl-PCTB is possible to be an anticancer candidate drug better than hydroxyurea.

Keywords: anticancer; molecular docking; molecular dynamics; MTT assay; synthesis; thiourea derivative.

Resumen

Contexto: El cáncer de mama es la principal causa de mortalidad entre las mujeres en Indonesia. La tiourea es un compuesto que contiene un átomo de azufre y nitrógeno y cuya estructura química se asemeja a la de un compuesto de urea que se ha aplicado como anticancerígeno, como la hidroxiurea, la nitrosourea, el 5-fluorouracilo y el sorafenib.

Objetivos: Desarrollar candidatos anticancerígenos como un nuevo compuesto derivado de la tiourea, N-(fenilcarbamotioil)-4-cloro-benzamida (4-Cl-PCTB).

Métodos: El compuesto se sintetizó a partir de feniltiourea y cloruro de 4-cloro-benzoilo mediante la aplicación de reactividad de sustitución de acilo nucleofílica. El compuesto resultante de la síntesis se examinó para determinar su pureza e identificación de la estructura mediante FTIR, ^{1}H-NMR, ^{13}C-NMR y MS. Las pruebas *in silico* incluyeron acoplamiento molecular utilizando el software Molexus, simulación de dinámica molecular utilizando el software Desmond y MOE, y predicción farmacocinética utilizando SCFbio, pkCSM y Swiss ADME. La actividad anticancerígena a través de la prueba citotóxica se realizó mediante el método MTT en células cancerosas T47D y células normales Vero.

Resultados: El compuesto 4-Cl-PCTB se obtuvo a partir de la síntesis. Los resultados del acoplamiento molecular y la simulación de dinámica molecular en el receptor de la quinasa 1 del punto de control (2YWP) mostraron una puntuación de planta de -67,19 kcal/mol, que fue mejor que el ligando nativo y la hidroxiurea de referencia estándar. Los resultados de la simulación de dinámica molecular indicaron que el compuesto 4-Cl-PCTB exhibió una mejor estabilidad de enlace en comparación con la hidroxiurea. Las predicciones farmacocinéticas para 4-Cl-PCTB mostraron una buena absorción del tracto gastrointestinal, clasificándolo en la clase I de BCS, con un bajo volumen de distribución, sin penetración en la BHE, una vida media de 3 horas y sin hepatotoxicidad. Resultados de la prueba citotóxica: IC_{50} células T47D = 0,44 mM, células Vero = 76,10 mM, hidroxiurea = 4,58 mM. Valor SI = 173,35 (SI >10).

Conclusiones: El 4-Cl-PCTB puede ser un fármaco candidato contra el cáncer mejor que la hidroxiurea.

Palabras Clave: acoplamiento molecular; anticancerígeno; derivado de tiourea; dinámica molecular; ensayo MTT; síntesis.

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INTRODUCTION

Breast cancer and cervical cancer are significant contributors to the high number of cancer-related fatalities in females (Globocan, 2020). The increasing number of new breast cancer cases, which is a concerning trend, demands immediate and specific attention. Medical treatment of breast cancer often combines X-ray therapy, surgery, and chemotherapy. The medicine option depends on the cancer stadium: the first stadium applies X-ray therapy and surgery; meanwhile, in the last stadium, chemotherapy treatment should be done. However, the option of the drug, as well as its unexpected side effects, becomes the limitation factor in chemotherapy (Dipiro et al., 2020). Therefore, a new chemotherapy drug development with a higher anticancer activity and low side effects is needed.

Thiourea is composed of sulfur and nitrogen atoms. This compound has a chemical structure resembling the anticancer drug hydroxyurea, nitrosourea, 5-fluorouracil, and sorafenib (Kesuma et al., 2018). The utilization of hydroxyurea as a cancer drug has been declining due to reported cases of resistance among patients with essential thrombocythemia (Barosi et al., 2007). Its ability to penetrate cell membranes, influenced by its specific characteristics, is a contributing factor to the development of resistance. (Koç et al., 2004). Li et al. (2006a; 2006b) performed the synthesis and examined activity from a few thiourea analogs and found that some are correlated very well with the epidermal growth factor receptor (EGFR) so that it can impede tumor cell proliferation. It is also found that urea analogs can impede the growth of leukemia and solid tumors as well as it is very selective as a nonpeptide somatotropin release-inhibiting factor (SRIF) (Li et al., 2010).

In the research of breast cancer, N-(5-chloro-2-hydroxybenzyl)-N-(4-hydroxybenzyl)-N-phenylthiourea is the analog of phenylthiourea, which has cytotoxic effect in MCF-7 cells by impeding EGFR and HER-2 (Li et al., 2010). Compared to hydroxyurea, N-benzoyl-N-phenylthiourea has a stronger antitumor activity, according to an *in vitro* assay on T47D (Kesuma et al., 2020a; 2020b). In the previous study, it was shown that thiourea and its analogs have strong anticancer characteristics. In this study, N-(phenylcarbamothioyl)-4-chloro-benzamide is synthesized from phenylthiourea and 4-chloro-benzoyl chloride by employing modification method from nucleophilic substitution of Schotten-Baumann (Jensen, 2007). In addition, the purity and its structure are examined by using IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopy (Clayden et al., 2012). Then, the compound obtained will be analyzed *in silico* study, which includes molecular docking against checkpoint kinase I (PDB: 2YWP) (Fig. 1). molecular dynamics simulation to evaluate the stability of the ligand-receptor interaction and pharmacokinetic prediction covering absorption, distribution, metabolism, excretion, and toxicity (ADMET).

Afterward, cytotoxic activity is examined through *in vitro* assay by testing the microculture tetrazolium (MTT) technique on T47D cancer cells and Vero normal cells. This study aims to result in a product of the compound 4-Cl-PCTB as a candidate anticancer drug better than hydroxyurea.

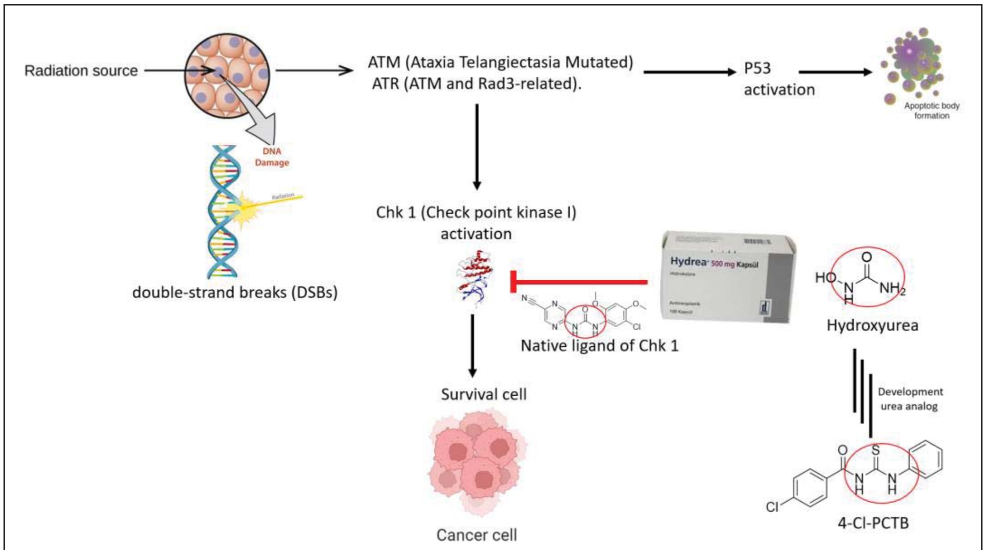


Figure 1. Designed the idea for developing hydroxyurea analog.

MATERIAL AND METHODS

Synthesis procedure

All reagents such as 4-chloro-benzoylchloride (Merck, Sigma-Aldrich), N-phenylthiourea (Merck, Sigma-Aldrich), THF (Merck, Sigma-Aldrich) and solvents such as ethyl acetate, n-hexane, chloroform, acetone were purchased from standard commercial suppliers from Merck, Sigma-Aldrich. The 4-CI-PCTB compound was synthesized by reacting N-phenylthiourea and 4-chloro-benzoylchloride on tetrahydrofuran (THF) and adding triethylamine which functions as a catalyst, then performing reflux as well as monitoring the completion of the reaction by thin layer chromatography (TLC) until forming single spot. Next, THF was evaporated in a rotary evaporator, and then recrystallization was done (Kesuma et al., 2022; 2023). The 4-CI-PCTB compound was identified by using IR spectroscopy (JASCO FT/IR-4200), ^{1}H-NMR, ^{13}C-NMR (JEOL ECS-400 spectrophotometer), and MS (HRMS-TOF spectra) (Clayden et al., 2012; McMurry, 2011; Pavia et al., 2009)

Compound purity test of synthesis result

The compound was stated purely according to TLC if there was a single spot by applying three-phase movement types of different polarity. Mobile phase: n-hexane: ethyl acetate = 3:2; chloroform: acetone=3:2; n-hexane:chloroform:acetone = 5:4:1. Stationary phase: Silica gel Merck 60 GF-254. Spot detection: UV-254 nm.

Purity test with determination of melting spot

The compound was stated purely according to melting point value if its melting range <2°C. Tool: Electrothermal Melting Point Apparatus (Sybron-Thermolyne-MP12615).

Confirmation of synthesis compound result structure

Infrared spectroscopy

Samples (0.1-2 %) were mixed and crushed with KBr powder and made into pellets with KBr. Then, the spectrum of % transmission toward wave number (v) 400–4600 cm^{-1} was observed.

Nuclear magnetic resonance spectroscopy

The sample was dissolved in DMSO-D6, which contained tetramethyl silane (TMS), proton (^{1}H-NMR), and carbon (^{13}C-NMR) resonance spectrum was observed.

Mass spectroscopy

The sample was put into a capillary pipe, and then a compound mass spectrum was made. The results of the structure fragmentation and position m/e of fragment ions were analyzed and identified (Pavia, 2009).

Molecular docking simulation

Hydroxyurea and 4-chloro-N-(phenylcarbamothioyl)benzamide (4-Cl-PCTB) were prepared as ligands by drawing them in 2-dimensions in Chembiodraw version 11. The 2-dimensional ligand was then converted into the 3-dimensional ligand in molecular operating environment (MOE) software. The 3-D ligand performs the most stable minimal energy calculation by means of the MMFF94x calculation, and the ligand is stored with the PDB file (Kesuma et al., 2023; Thomas, 1996).

Checkpoint kinase 1 (Chk1) enzyme was obtained from the Protein Data Bank (PDB) with PDB: 2YWP, which was re-prepared with Molexus Ver.7 (Li et al., 2006a). Checkpoint kinase 1 (Chk1) and its comparison ligand was re-docked to validate the Molexus Ver.7. Therefore, it could be used to dock hydroxyurea and 4-Cl-PCTB (Li et al., 2006a; 2006b; Putra et al., 2017).

Molecular dynamics simulation

Molecular dynamics simulations were conducted on three compounds: the native ligand, 4-Cl-PCTB, and hydroxyurea, using Desmond software for 10 ns simulation. The purpose of the molecular dynamics simulation was to study the stability of the interaction between the ligand and the checkpoint kinase I (2YWP) receptor. The simulation process employed the TIP4P model under normal pressure and temperature conditions (NPT). The MD simulation was run for 10 ns at 300 K and standard pressure (1.01325 bar) within a cubic water box with dimensions of 1 Å × 1 Å × 1 Å and an NPT ensemble. Energy recordings were taken at intervals of 1.2 ps. The Nose-Hoover chain and Martyna-Tobias-Klein algorithms were used to maintain the temperature of all MD systems at 300 K and the pressure at 1.01325 bar. All well-minimized and equilibrated systems were subjected to a 10-ns MD run in the NPT ensemble with periodic boundary conditions, using the OPLS 2005 force field parameters (Guo et al., 2010; Kumar et al., 2020; Murthy et al., 2018; Ruswanto et al., 2022)

Pharmacokinetics / ADMET prediction

To predict the pharmacokinetic profile of the compound, we used SCFBio (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp), the pkCSM online application (https://biosig.lab.uq.edu.au/pkcsm/), and Swiss ADME (http://www.swissadme.ch/). To obtain predicted elimination/excretion data in the form of the elimination constant (k) and half-life ($t_{1/2}$), we processed the data obtained from pkCSM, specifically total clearance (Cl) and volume of distribution (Vd), to calculate the parameters k and $t_{1/2}$ using the equations [1] (Shargel and Yu, 2019).

$$Cl = k.\, Vd \qquad [1]$$

Where $t_{1/2}$ is the half-life of the compound, ln 2 has a value of 0.693, and k is the elimination rate constant of the compound.

To obtain the elimination rate constant (k), the value of Cl was divided by the Vd of the compound. Most drugs have a first-order elimination rate constant, meaning that the half-life ($t_{1/2}$) can be calculated using the following equation [2] (Shargel and Yu, 2019).

$$t_{1/2} = \frac{\ln 2}{k} \qquad [2]$$

Where $t_{1/2}$ is the half-life of the compound, ln 2 has a value of 0.693, and k is the elimination rate constant of the compound.

Cytotoxic activity in T47D and Vero cells

Cell growth inhibitor test was done based on an *in vitro* assay using T47D cancer cells (ATCC HTB-133) and normal kidney cells using Vero cells (ATCC CRL-1587). It was done to acknowledge the test compound cytotoxic activity and compound comparator of hydroxyurea (Campestre et al., 2006). The first step was done by planting all cell cultures in a 96-well plate and incubating it in a CO_2 incubator for 24 hours. Then, the test compound and hydroxyurea were added to each culture with various concentrations and incubated again. Afterward, media in the cup were thrown and rinsed with 100 µL PBS. Next, 100 µL of 0.5 mg/mL MTT reagent was added into the microplate and then incubated for 4 hours. MTT reaction was stopped by adding 10% SDS 0.01 N HCl to each culture to dissolve the formazan crystal formed after being incubated. Next, the microplate was covered by using paper as well as incubated for 24 hours at 37°C degree, and its absorbance was read by applying an ELISA reader at 595 nm as well as calculating the living fraction (Kesuma et al., 2022). IC_{50} values from the compound tested, reference drugs, and normal cells were obtained by using Probit analysis. Vero cells were needed as normal cells to observe the selectivity of the test compound and reference drug on T47D cells. This can be expressed as a selectivity index (SI). SI was calculated with the following formula [3] (Indrayanto et al., 2021).

$$Selectivity\ Index = \frac{IC_{50}\ normal\ cell}{IC_{50}\ cancer\ cells} \qquad [3]$$

Statistical analysis

In this research, synthesis, molecular docking, molecular dynamics simulation, anticancer *in vitro* assays, and cytotoxicity tests on normal cells were conducted in triplicate (n = 3). The accuracy of the results was calculated based on the mean values, while precision was assessed using the standard deviation (SD). For IC_{50} and CC_{50}, calculations were performed using IBM SPSS version 27 with the probit analysis method ($p \leq 0.05$).

RESULTS AND DISCUSSION

Synthesis of 4-CI-PCTB

The synthesis of 4-CI-PCTB was done to react with N-phenylthiourea and 4-chloro-benzoylchloride in tetrahydrofuran (THF) and apply triethylamine as a catalyst. It resulted in a light yellow crystal (82 ± 2%) insoluble in water, and the melting point was 126-127°C. The result of the identification of 4-Cl-PCTB is as follows: Light yellow crystal, yield 80%, m.p = 126-127°C. ^{1}H-NMR (DMSO-d6, 400 MHz). δ 7.24 (t, J = 7,2 Hz, 1H, Ar-H); δ 7.39 (t, J = 7.2 Hz, 2H, Ar-H); δ 7.58 (d, J = 8.4, 2H, Ar-H); δ 7.65 (d, J = 7.2 Hz, 2H, Ar-H); δ 7.96 (d, J = 8.4 Hz, 2H, Ar-H); δ 11.63 (s, 1H, O=C-NH-C=S); δ 12.47 (s, 1H, S=C-NH-Ar). ^{13}C-NMR (DMSO-d6, 100 MHz). δ 124.9 (2C, Ar); δ 126.9 (2C, Ar); δ 126.9 (1C, Ar); δ 129.1 (2C, Ar); δ 129.2 (2C, Ar); δ 131.2 (1C, Ar); δ 131.6 (1C, Ar); δ 138.5 (1C, Ar); δ 167.8 (1C, C=O); δ 179.5 (1C, C=S). IR (KBr), v max (cm^{-1}): 1667 (C=O amide); 1667 and 1482 (C=C aromatic); 3333 and 1593 (NH secondary strech amide); 1092 and 831 (C=S). HRMS (m/z) $C_{14}H_{10}N_2OSCl$: (M-H) = 289.0204 and calc. mass = 289.0202.

Hydroxyurea (Cytodox®; Hydrea®) has been used for the treatment of specific types of cancer over the past decade, including solid tumors, head and neck tumors, chronic myeloid leukemia, and acute lymphoblastic leukemia (Sweetman, 2009). One of the limitations of hydroxyurea is its hydrophilic (logP = -1.12), making it highly soluble but having limited penetration into small cell membranes. This deficiency has prompted researchers to introduce a benzyl moiety functional group to enhance lipophilicity, enabling better penetration of cell membranes. One derivative of hydroxyurea, benzoylthiourea, has a logP =1.47. According to the Lipinski Rule of Five, compounds exhibit good solubility and permeability when their logP = 2-5 (Ku, 2008; Papich and Martinez, 2015).

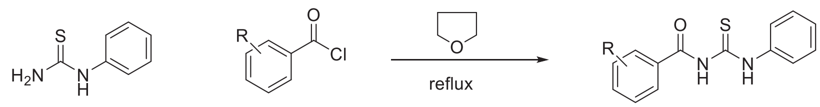


Figure 2. Reaction on benzoylthiourea with benzoylchloride derivatives.

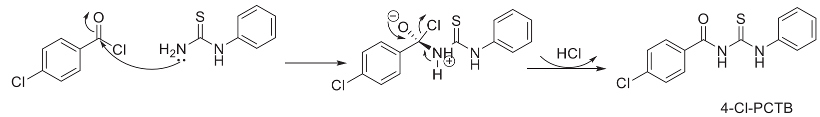


Figure 3. Reaction mechanism of 4-chloro-N-(phenylcarbamothioyl)benzamide (4-Cl-PCTB).

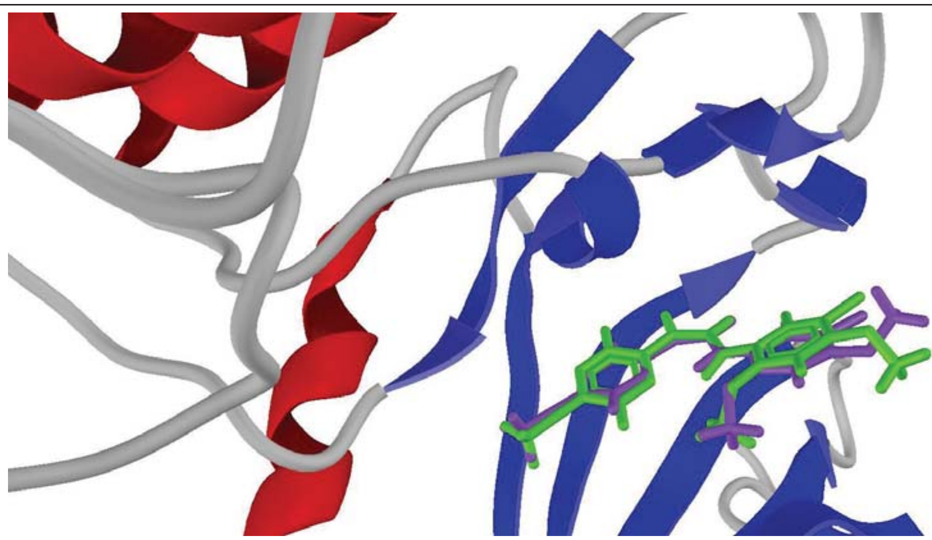


Figure 4. Comparison of the native ligand (green) with the docking result simulation (purple) by Molexus Ver.7 with RMSD of 0.58 Å.

Therefore, it is necessary to modify the chemical structure of benzoylthiourea by adding the benzyl moiety functional group through its reaction with benzoylchloride derivatives (Fig. 2).

The compound 4-Cl-PCTB (4-chloro-N-(phenylcarbamothioyl)benzamide) is one of the derivatives of benzoylthiourea that can be synthesized using the Schotten-Baumann reaction method. The compound 4-Cl-PCTB can be obtained by reacting phenylthiourea with 4-chlorobenzoyl chloride in a free water solvent, such as using THF. The nucleophilic attack by the free electron pair (-NH2) of phenylthiourea on the carbonyl carbon of 4-chlorobenzoyl chloride leads to an addition reaction followed by elimination, releasing the Cl ion as a good leaving group. The overall reaction can be observed in Fig. 3.

Molecular docking, molecular dynamics study, and ADMET prediction

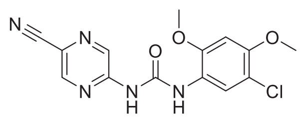
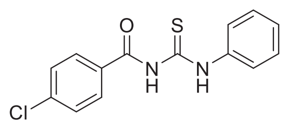
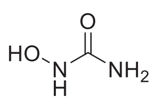
The redocking process was performed on checkpoint kinase 1 (Chk) with PDB: 2YWP. Chk is a protein kinase that plays a crucial role in cell cycle control and the DNA damage response mechanism. There are two main types of Chk in mammalian cells: Chk1 and Chk2. Both kinases play vital roles in maintaining genome integrity by preventing damaged cells from replicating and dividing further, as well as playing a key role in inhibiting cancer cell growth (Li et al., 2006a; 2006b; Putra et al., 2017).

The grid box binding site was set X = -3.88 Å; Y = 8.78 Å; Z = -18.36 Å with a cavity surrounded by 29 amino acids, they are Leu 15; Gly 16; Val 23; Ala 36; Lys 38; Lys 43; Lys 53; Lys 54; Glu 55; Lys 60; Val 68; Lys 69; Leu 84; Glu 85; Tyr 86; Cys 87; Ser 88; Gly 89; Gly 90; Glu 91; Asp 94; Asp 130; Lys 132; Leu 137; Lys 145; Ser 147; Asp 148; Phe 149; Lys 166. The result of the redocking validation process, with an RMSD of 0.58 Å, is shown in Fig. 4. These results indicate that the method is valid for the docking test of the tested compound, as the RMSD obtained is less than 2 Å (Putra et al., 2017; Sulistyowaty et al., 2020). The RMSD value shows the alignment of the ligand coordinates from the crystallographic results compared to the re-docked native ligand coordinates, with an RMSD of 0.58 Å, which meets the docking process criteria (Fig. 4).

The docking results provided a plant score, which reflects the predicted interaction between drug-receptor. A lower plant score indicates a higher compatibility between the ligand and receptor, suggesting stronger interaction. The docking data can also be visualized and analyzed to illustrate the ligand-receptor bond interactions, including hydrogen bonds, hydrophobic interactions, and electronic interactions, as shown in Table 1 and Fig. 5.

The molecular docking results were further supported by the molecular dynamics simulation, which was run from 0 to 10 ns. The native ligand and 4-Cl-PCTB compounds exhibited good bond stability, as they remained within the active site of checkpoint kinase 1, while the hydroxyurea compound did not show stable bonding, as it exited the active site of checkpoint kinase 1, as shown by the protein-ligand RMSD results in Fig. 6.

Table 1. The molecular docking result of native ligand, 4-Cl-(PCTB), hydroxyurea into active site checkpoint kinase 1 (Chk1).

Compounds	Plant score (kcal/mol)	Hydrogen bond	Steric interaction	Electronic interaction
 Native ligand	-64.94 ± 2.72	Glu 85 Cys 87	Lys 38 Leu 84	Glu 55 Asp 148
 4-Cl-(PCTB)	-67.19 ± 1.47	Cys 87	Cys 87	-
 Hydroxyurea	-33.84 ± 3.57	Cys 87	Cys 87	-

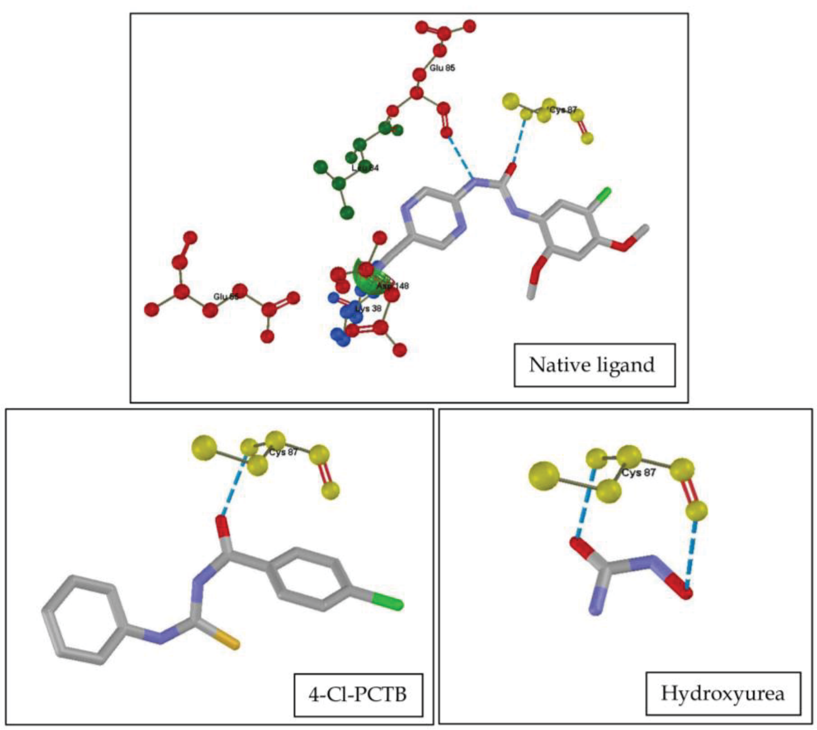


Figure 5. The molecular docking interaction reference standard (native ligand and hydroxyurea) and 4-Cl-(PCTB) into checkpoint kinase 1.

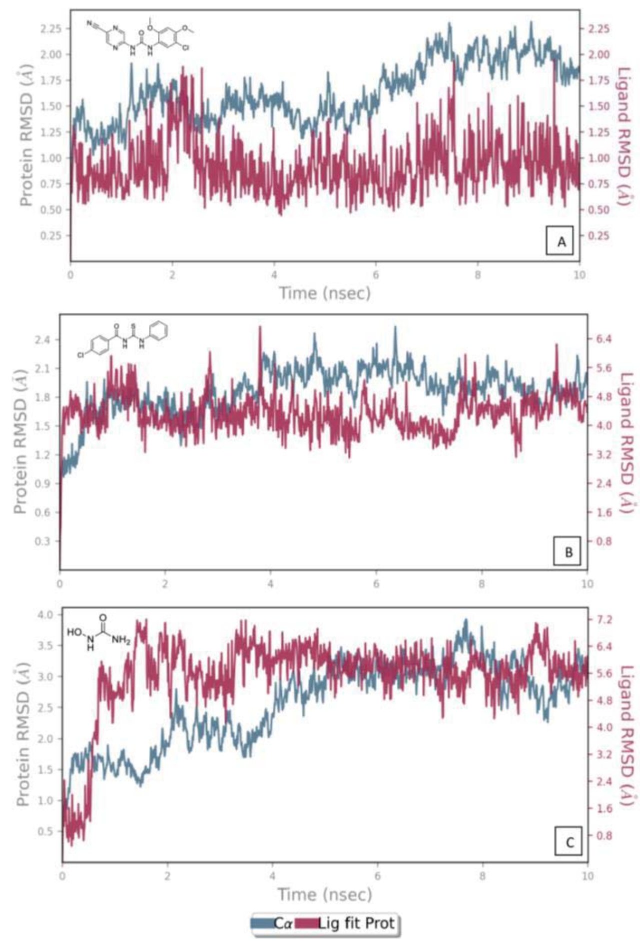


Figure 6. The protein-ligand RMSD of (**A)** native ligand, **(B)** 4-Cl-PCTB, and **(C)** hydroxyurea in 10 ns molecular dynamics simulation.

The RMSD graph for the native ligand from 0-10 ns remained below the protein RMSD graph, indicating stable ligand-receptor interaction, proving that the compound stayed within the active binding site of checkpoint kinase 1. Similarly, the 4-Cl-PCTB RMSD graph from 0-10 ns also remained below the protein RMSD graph. However, the RMSD graph for the hydroxyurea ligand from 0-10 ns was above the protein RMSD graph, demonstrating that hydroxyurea did not exhibit stable bonding with checkpoint kinase 1 and exited the active site.

This was further supported by the protein-ligand interaction contacts (Fig. 7), where both the native ligand and 4-Cl-PCTB showed similar interactions to the molecular docking results, including strong hydrogen bonds with the amino acid Cys 87. In contrast, hydroxyurea only exhibited weak hydrogen bond interactions with Cys 87, differing from the molecular docking results.

Absorption prediction

Based on absorption predictions using the SCFBio online tool (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp), the native ligand, 4-Cl-PCTB, and hydroxyurea met the criteria of Lipinski's Rule of Five, which includes molecular weight (MW) ≤500, molar refractivity (MR) 40-130 Å, hydrogen bond acceptors (HBA) ≤10, and hydrogen bond donors (HBD) ≤5. Therefore, all the compounds are predicted to be well-absorbed through the gastrointestinal tract (GIT) (Jayaram et al., 2013; Lipinski, 2004). Hydroxyurea also has an oral tablet form, as it meets the Lipinski's Rule of Five criteria (Samineni et al., 2022; Sweetman, 2009).

Permeability prediction

The native ligand and hydroxyurea are predicted to have low permeability in the GIT, as both compounds have Caco-2 permeability values of <8.10^{-6} cm/s. Meanwhile, 4-Cl-PCTB is classified as having high permeability, with a Caco-2 permeability value of >8.10⁻⁶ cm/s. Caco-2 cell lines, derived from human epithelial colorectal adenocarcinoma cells, consist of a monolayer often used as an *in vitro* model of human intestinal mucosa for predicting oral drug absorption. Based on water solubility, the native ligand is predicted to be freely soluble, as its log S value falls within the range of -2 to 0. Hydroxyurea is classified as very soluble, with a log S value >0. Meanwhile, 4-Cl-PCTB is classified as sparingly soluble, with a log S value in the range of -5 to -4 (Ku, 2008; Putra et al., 2024).

Biopharmaceutical classification system (BCS) prediction

Based on the BCS, hydroxyurea and the native ligand are categorized as BCS Class III, characterized by low permeability and high solubility. Meanwhile, 4-Cl-PCTB is classified as BCS Class I, characterized by high permeability and high solubility. BCS Classes I and III are considered suitable for oral drug formulations, as they can dissolve and effectively penetrate the GIT membrane (Ku, 2008; Papich and Martinez, 2015; Putra et al., 2024).

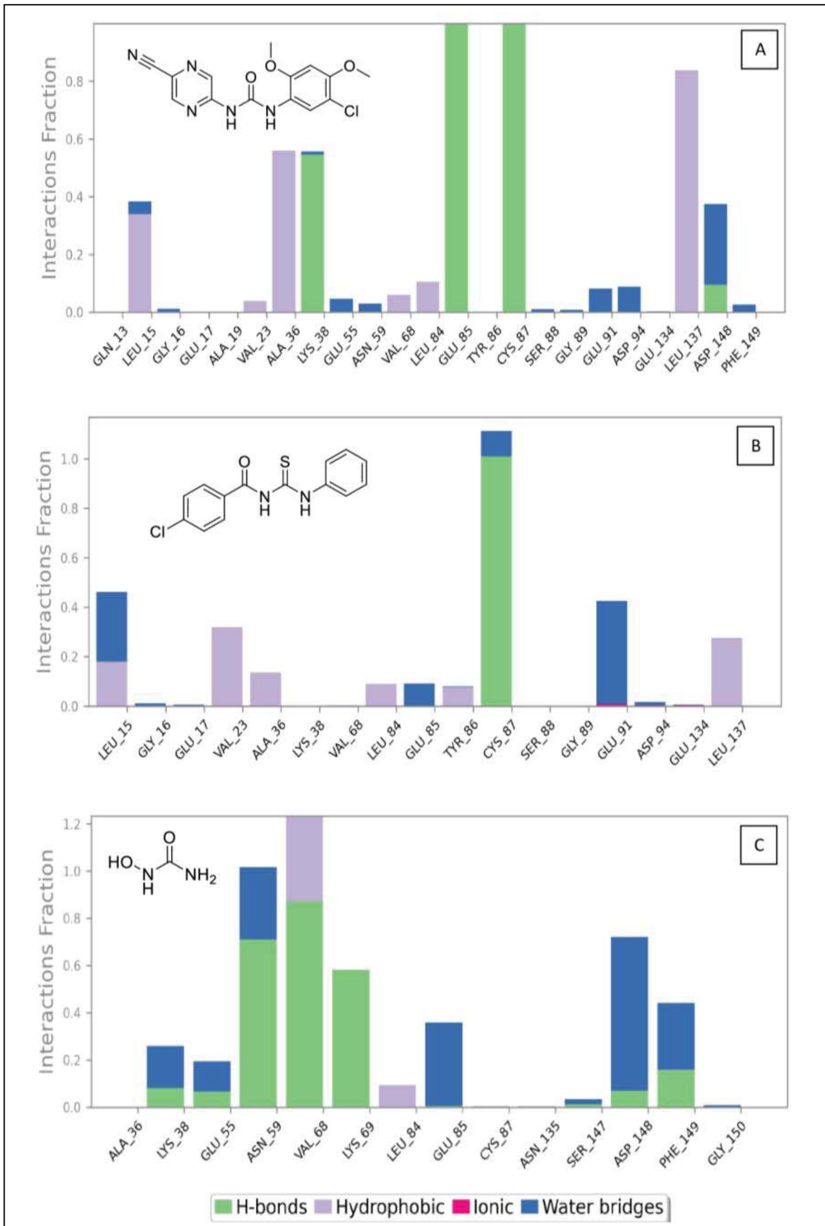


Figure 7. The protein-ligand interaction contacts with checkpoint kinase 1.
(A) native ligand, **(B)** 4-Cl-PCTB, and **(C)** hydroxyurea in 10 ns molecular dynamics simulation.

Table 2. The result of ADMET predictions.

Compound	Absorption		Distribution		Metabolism (CYP inhibitor)					Excretion			Toxicity	
	Caco2 Perm. 10^{-6} cm/s	Log S	Vd (L/kg)	BBB Log BB	2D6	3A4	1A2	2C9	2C19	Total Cl (L/hour/kg)	k (1/hour)	t ½ (hour)	ORAT mol/kg (LD_{50})	Hepato toxicity
Native ligand	1.04	-2.72	0.10	-1.029	No	No	No	No	No	0.2422	2.422	0.29	2.76	Yes
4-Cl-PCTB	37.07	-4.69	0.10	0.293	No	No	Yes	No	Yes	0.0231	0.231	3.00	2.25	No
Hydroxyurea	3.07	0.89	0.13	-0.955	No	No	No	No	No	0.2711	2.086	0.33	3.01	No

Distribution and blood-brain barrier (BBB) prediction

The distribution prediction indicates that all three compounds are classified as drugs with low volume distribution (Vd <0.71 L/kg), meaning they have higher concentrations in the plasma than in the tissues (Pires et al., 2015). The three compounds are also predicted to be unable to cross the BBB, as they have Log BB values <0.3. The BBB is a protective layer in the brain that prevents chemicals from easily reaching the brain's nerve cells. Drugs are predicted to easily cross the BBB if their Log BB is >0.3. Compounds that can penetrate the BBB can affect the central nervous system and patient consciousness. Some drugs are designed to penetrate the BBB, such as antibiotics for meningitis, Parkinson's drugs, and general anesthetics. The compound in this study is designed for breast cancer treatment, so it is not expected to cross the BBB (Pires et al., 2015).

Prediction of metabolism

The metabolism inhibition prediction suggests that the native ligand and hydroxyurea do not inhibit any drug-metabolizing enzymes, indicating minimal drug-drug interaction in the metabolic phase. However, 4-Cl-PCTB inhibits CYP1A2 and CYP2C19 enzymes. While these two CYP enzymes play a minor role in drug metabolism compared to CYP2D6 and CYP3A4 (which metabolize nearly 90% of drugs), certain medications require attention due to inhibition of CYP2C19 (e.g., diazepam, phenytoin, topiramate) and CYP1A2 (e.g., acetaminophen, clozapine, haloperidol, theophylline, TCAs) (Trevor et al., 2015).

Total clearance and half-life prediction

Total clearance represents the rate at which the body clears a drug, combining hepatic clearance (liver metabolism and biliary clearance) and renal clearance (Shargel and Yu, 2019). Total clearance is directly proportional to Vd and the elimination constant (k), and can be formulated as Cl = Vd.k (Shargel and Yu, 2019). Therefore, the value of k is directly proportional to Cl and inversely proportional to Vd. A larger k-value results in a shorter half-life (t½), meaning the compound remains in the body longer before excretion. The native ligand and hydroxyurea have half-lives (t½) of less than 1 hour, falling into the ultra-short half-life category. In contrast, 4-Cl-PCTB has a half-life (t½) of 3 hours, placing it in the short half-life category (1-4 hours).

Toxicity prediction

According to toxicity predictions, neither 4-Cl-PCTB nor hydroxyurea were hepatotoxic, while the native ligand was hepatotoxic. Based on oral rat acute toxicity (ORAT), 4-Cl-PCTB has an LD_{50} of 2.25 mol/kg, making it the most toxic compound among the tested compounds. Overall, the pharmacokinetic or ADMET prediction results for the three compounds, generated using the pkCSM and SIB online software, are summarized in Table 2.

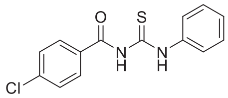
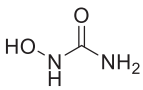
In vitro cytotoxic activities

The value of test compound IC_{50} and hydroxyurea toward T47D cancer cells can be seen in Table 3 and Fig. 8. The addition of the 4-chlorobenzoyl group leads to an increase in the lipophilic parameter, specifically the Log P value. Based on calculations using various applications, the Log P value of the compound 4-Cl-PCTB ranges from 3.54 to 4.31, while the Log P value of hydroxyurea is -1.12. The Log P value of the 4-Cl-PCTB compound meets the Lipinski Rule of Five, indicating good solubility and permeability. This aligns with the in vitro anticancer testing against the human breast cancer cell line T47D, showing higher potential compared to hydroxyurea (Table 3). The selectivity index (SI) value of the 4-Cl-PCTB compound is also greater than that of hydroxyurea, which implies it is safer compared to the standard drug, hydroxyurea (Indrayanto et al., 2021).

CONCLUSION

Based on *in silico* studies, including molecular docking, molecular dynamics, pharmacokinetics predictions, and *in vitro* assays, the 4-Cl-PCTB compound exhibits better anticancer activity against T47D breast cancer cells compared to the reference drug (hydroxyurea).

Table 3. IC_{50} value and selectivity index (SI) of 4-Cl-PCTB and hydroxyurea toward cancer and normal cells.

Compound	T47D cell (mM)	Vero cell (mM)	SI
 4-Cl-PCTB	0.44 ± 0.72	76.10 ± 0.51	172.95
 Hydroxyurea	4.58 ± 0.85	369.88 ± 0.91	80.76

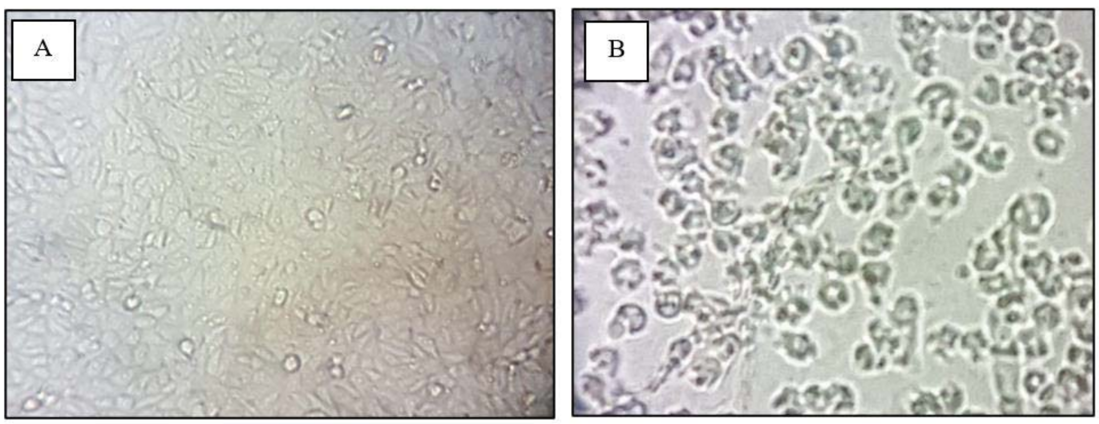


Figure 8. (A) T47D cell before treatment with 4-Cl-PCTB. **(B)** T47D cells after treatment with 4-Cl-PCTB with concentration 125 ppm.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Kesuma D	Yuniarta TA	Suherto AD	Putra GS	Sutrisno S	Anwari F
Concepts or ideas	x					
Design	x					
Definition of intellectual content	x					
Literature search	x	x	x	x	x	x
Experimental studies			x			
Data acquisition	x	x	x	x		
Data analysis		x	x	x		x
Statistical analysis			x	x	x	
Manuscript preparation				x	x	
Manuscript editing	x	x		x		
Manuscript review	x	x	x	x	x	x

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Supplementary data

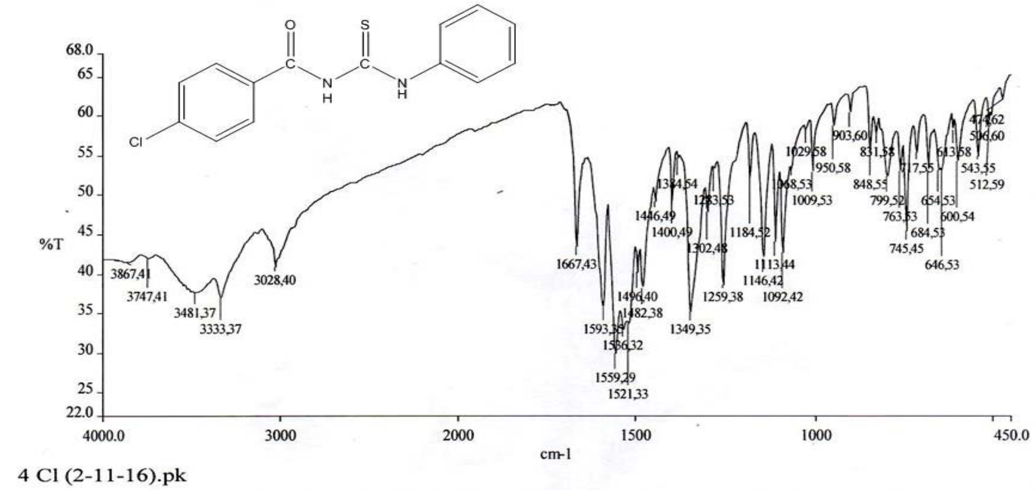

Figure 1S. FTIR of 4-Cl-PCTB (4-chloro-N-(phenylcarbamothioyl)benzamide).

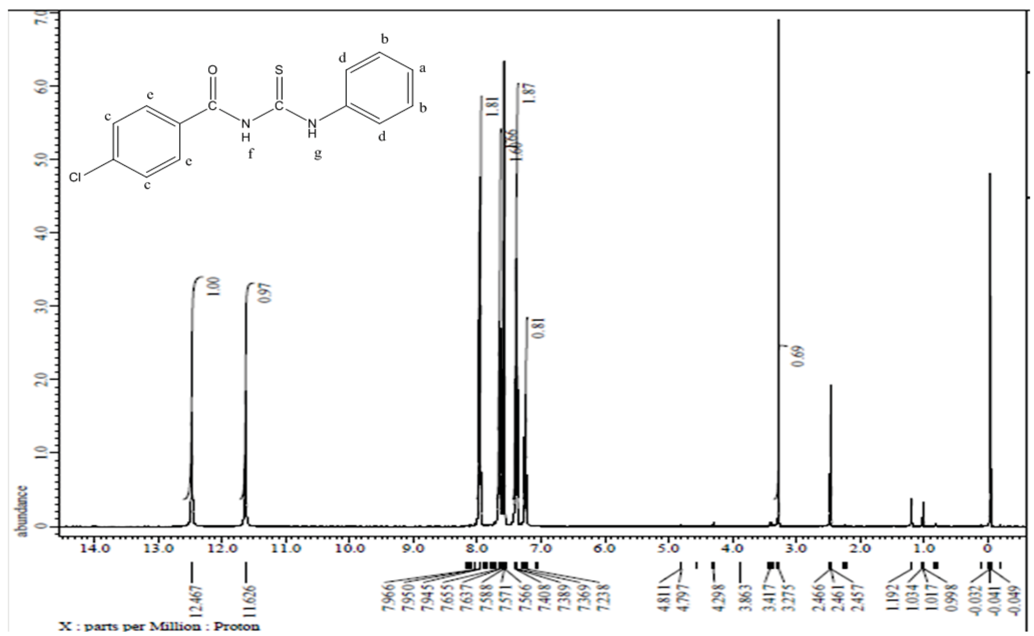

Figure 2S. H^1-NMR of 4-Cl-PCTB (4-chloro-N-(phenylcarbamothioyl)benzamide).

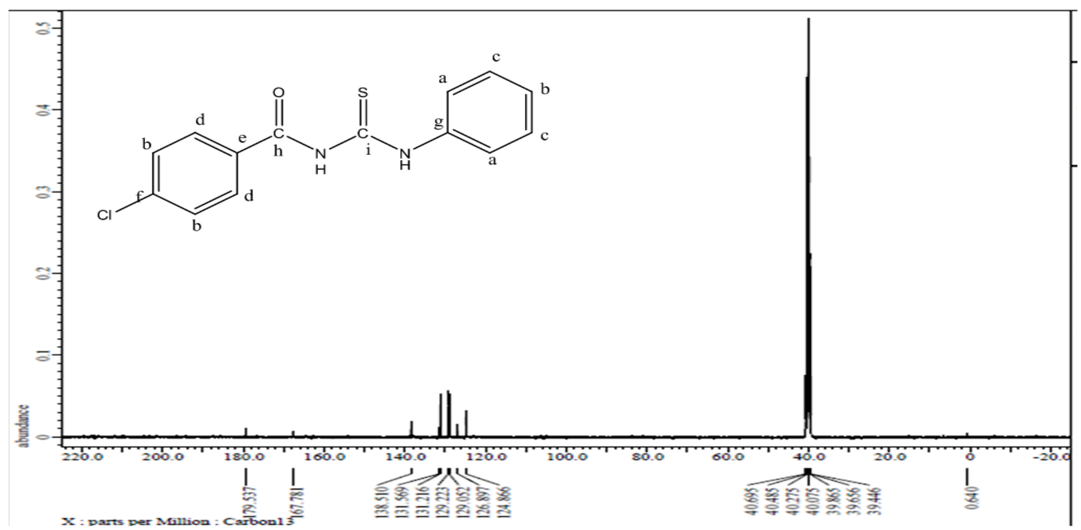

Figure 3S. C^{13}-NMR of 4-Cl-PCTB (4-chloro-N-(phenylcarbamothioyl)benzamide).

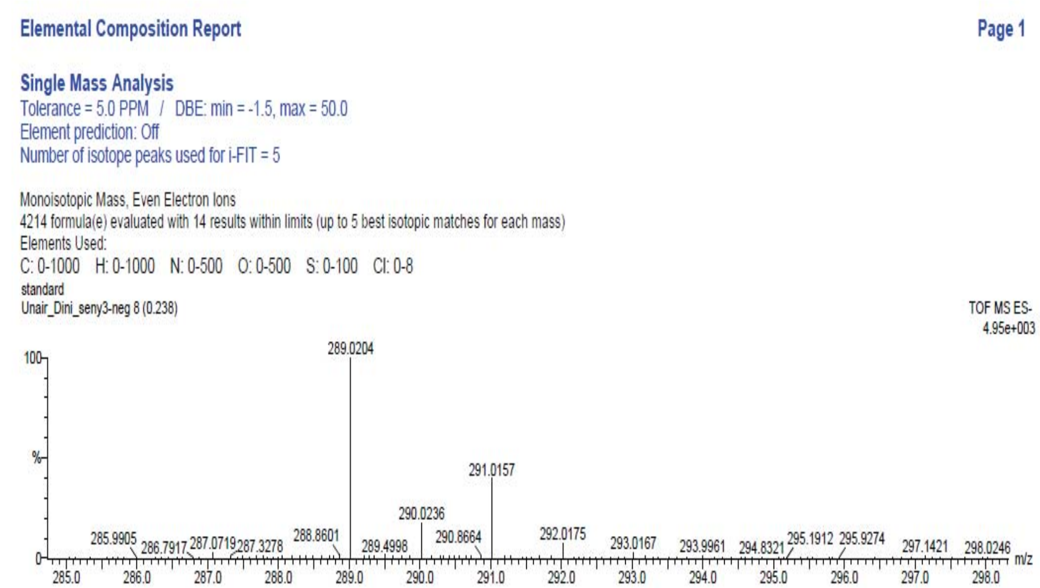

Figure 4S. HRMS of 4-Cl-PCTB (4-chloro-N-(phenylcarbamothioyl)benzamide).

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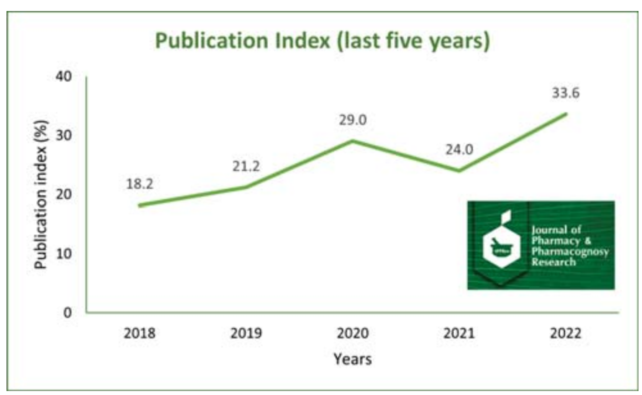

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2.- Review

Silvi Zakiyatul Ilmiyah, Ages Mamamia, Sofy Permana, Edwin Widodo, Eviana Norahmawati, Sharida Fakurazi, Nik Ahmad Nizam Nik Malek, Agustina Tri Endharti (2025) **Recent advances and mechanism of action of *Anredera cordifolia* (Ten.) Steenis as anticancer approach: A systematic review**. | [Avances recientes y mecanismo de acción de *Anredera cordifolia* (Ten.) Steenis como tratamiento anticancerígeno: Una revisión sistemática]. J Pharm Pharmacogn Res 13(2): 369-380. https://doi.org/10.56499/jppres24.2044_13.2.369 [638 Kb] [ABSTRACT]

3.- Original Article

Riska Prasetiawati, Elva Nurfadilah Febrianti, Siva Hamdani, Nur Kusaira Khairul Ikram, Taufik Muhammad Fakih, Dhania Novitasari, Muchtaridi Muchtaridi (2025) **Alpha-mangostin from *Garcinia mangostana* L.: A potential Nrf2 inhibitor for long COVID-19 explored through molecular dynamics**. | [Alfa-mangostina de *Garcinia mangostana* L.: Un posible inhibidor de Nrf2 para la COVID-19 prolongada explorado a través de la dinámica molecular]. J Pharm Pharmacogn Res 13(2): 381-392. https://doi.org/10.56499/jppres24.2066_13.2.381 [977 Kb] [ABSTRACT]

4.- Original Article

Chawalit Yongram, Juthamat Ratha, Pimolwan Siriparu, Suthida Datham, Somporn Katekaew, Suthasinee Thapphasaraphong, Natthida Weerapreeyakul, Ploenthip Puthongking (2025) **Anticancer activity and HPLC analysis of bioactive compounds in *Dipterocarpus alatus* Roxb. ex G.Don oleo-resin and its biodiesel byproducts**. | [Actividad anticancerígena y análisis por HPLC de compuestos bioactivos en la oleorresina de *Dipterocarpus alatus* y sus subproductos de biodiésel]. J Pharm Pharmacogn Res 13(2): 393-401. https://doi.org/10.56499/jppres24.1961_13.2.393 [701 Kb] [ABSTRACT]

5.- Original Article

Fatchiyah Fatchiyah, Feri E. Hermanto, Regina P. Virgirinia, Rista N. Rohmah, Lidwina F. Triprisila, Eko Suyanto, Katsuhiro Miyajima (2025) **Inhibition of adipocyte senescence by ferulic acid present in pigmented rice through the PPAR-γ and NF-κB protein signaling pathways**. | [Inhibición de la senescencia de los adipocitos por el ácido ferúlico presente en el arroz pigmentado a través de las vías de señalización de las proteínas PPAR-γ y NF-κB]. J Pharm Pharmacogn Res 13(2): 402-415. https://doi.org/10.56499/jppres24.2080_13.2.402 FREE PDF [1.35 Mb] [ABSTRACT]

6.- Original Article

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7.- Original Article

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Maharani Maharani, Sutrisno Sutrisno, I Wayan Arsana Wiyasa, Sri Winarsih, Setyawati Soeharto, I Wayan Agung Indrawan, Agustina Tri Endharti (2025) **Molecular docking of flavonoids from *Phaleria macrocarpa* on the NF-kB p65, VEGFR2, Ki67, COX-2, and CXCR4 pathways in endometriosis**. | [Acoplamiento molecular de flavonoides de *Phaleria macrocarpa* en las vías NF-kB p65, VEGFR2, Ki67, COX-2 y CXCR4 en la endometriosis]. J Pharm Pharmacogn Res 13(2): 527-537. https://doi.org/10.56499/jppres24.2090_13.2.527 [622 Kb] [ABSTRACT]

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Gugulethu M. Miya, Pallab Kar, Ayodeji O. Oriola, Adebola O. Oyedeji (2025) **Antidiabetic potential of isolated compounds from *Cyperus sexangularis* Nees: An *in silico* molecular docking and dynamic-based approach**. | [Potencial antidiabético de compuestos aislados de *Cyperus sexangularis* Nees: Un enfoque basado en la dinámica y el acoplamiento molecular *in silico*]. J Pharm Pharmacogn Res 13(2): 647-661. https://doi.org/10.56499/jppres24.2050_13.2.647 [1.34 Mb] [ABSTRACT]

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Honnesh N. Honnappa, Basavaraj Metikurki, V. Kusum Devi, Santanu Saha (2025) **Anti-inflammatory activity and phytochemical analysis of *Macaranga peltata* Boiv. Ex Baill. leaves and *Pongamia pinnata* (L.) Pierre. seeds**. | [Actividad antiinflamatoria y análisis fitoquímico de hojas de *Macaranga peltata* Boiv. Ex Baill. y semillas de *Pongamia pinnata* (L.) Pierre.]. J Pharm Pharmacogn Res 13(2): 662-671. https://doi.org/10.56499/jppres24.1997_13.2.662 [430 Kb] [ABSTRACT]

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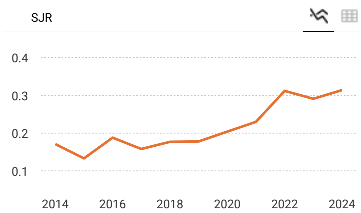

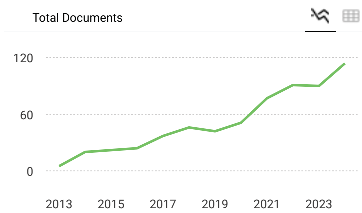

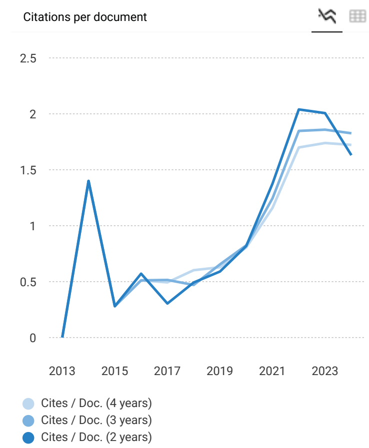

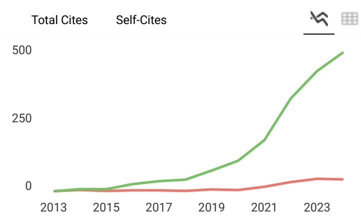

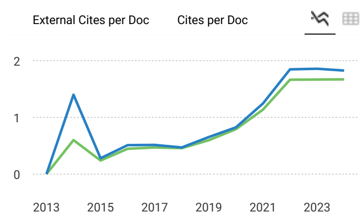

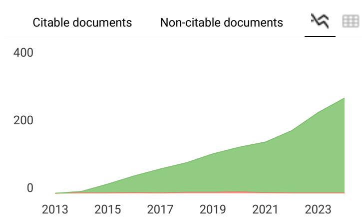

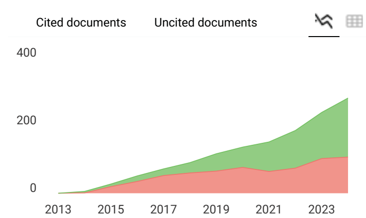

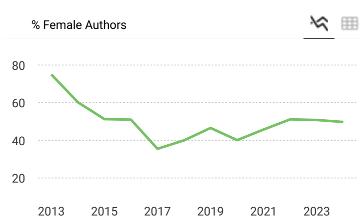

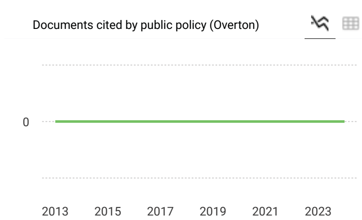

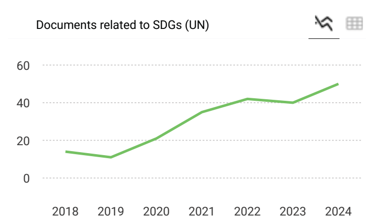

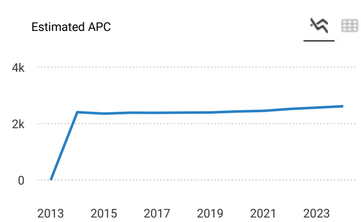

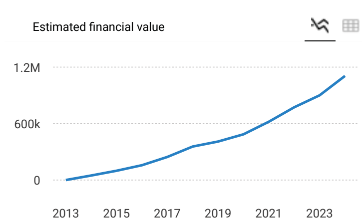

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