Molecular Docking of N-benzoyl-N'-(4-fluorophenyl) thiourea Derivatives as Anticancer Drug Candidate and Their ADMET prediction

by Tri Widiandani

RESEARCH ARTICLE

Molecular Docking of *N*-benzoyl-*N'*-(4-fluorophenyl) thiourea Derivatives as Anticancer Drug Candidate and Their ADMET prediction

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ABSTRACT:
The pharmacophore group found in *N*-benzoyl-*N'*-(4-fluorophenyl) thiourea is the same as the urea derivative which has anti-cancer activity, such as hydroxyurea. Because of the presence of these pharmacophore groups, this compound is worthy of being used as parent compound for further development through structural modification. Structural modification as an effort to design the new drug is done by changing the substituted group, which will cause changes in physicochemical properties. The change in physicochemical properties can affect the pharmacokinetics process, toxicity and activity of each compound that can be predicted through molecular modeling. The aims of this present study are to obtain the *N*-benzoyl-*N'*-(4-fluorophenyl) thiourea derivatives which is predicted to have the best anticancer activity and is not toxic based on the in silico approach. One of the mechanism of action of the *N*-benzoil- *N'*-(4-fluorophenyl) thiourea derivative as an anti-cancer is to inhibit the Sirtuin1 enzyme (SIRT1). The inhibition of the enzyme causes over expression of p53 which is the gene responsible for negative regulation of the cell cycle by using the Chem Bio Draw Ultra 13.0 program which can predict physico-chemical properties of Log P, MR and Etot. Pharmacokinetic properties (ADME) and toxicity were determined using the online pkCSM program. The in silico test is carried out by documenting compounds which will be predicted by the target enzyme SIRT1 with PDB ID: 4I5I. Documentation results in the form of bond energy which is illustrated by the value of the Rerank Score (RS), using the MVD program (Molegro Virtual Docker). Compounds that have small RS values are predicted to have a activity. From the results of the in silico test using the MVD program and the online pkCSM program it can be seen that 4 (four) *N*-benzoyl-*N'*-(4-fluorophenyl)thiourea derivatives are predicted to have good pharmacokinetics (ADME) properties, causing relatively low toxicity except *N*-4-trifluoromethyl-benzoyl-*N'*-(4-fluorophenyl)thiourea which can cause hepatotoxics. All compounds have cytotoxic activity greater than the comparative ligand 4I5_601. Compounds of *N*-4-chlorobenzoyl-*N'*-(4-fluorophenyl) thiourea are compounds that are predicted to have the most activity and are not toxic.

KEYWORDS: Molecular modeling, *N*-benzoyl-*N'*-(4-fluorophenyl) thiourea, Physico-chemistry, ADME prediction.

INTRODUCTION:
The effort to develop drugs can be done by designing a drug. The purpose of drug design is to get new drugs with better activity and have lower toxicity. Drug design can be done through structural modification. Structural modification is done by synthesizing a number of parent compound derivatives, identifying the structure and testing its biological activity[1]. Changes in the structure of a compound will change the physico-chemical properties of the compound, including lipophilic, electronic and steric properties, and changes in physico-

chemical properties will cause changes in the biological activity of the compound[2,3].

Before synthesizing, an effort is needed to predict the physico-chemical properties, pharmacokinetic properties, biological activity and toxicity of the compound to be synthesized. The method now being developed is molecular modeling[4,5,6]. Molecular modeling which is also called the in silico test has a very important role in the field of medical chemistry in order to design, find and optimize bioactive compounds in the process of drug development[7,8,9,10]. The way to do the in silico test is by documenting the molecules that will be predicted for their activity on the selected target cell. Doking is an attempt to harmonize between ligands that are small molecules into the target cell which are large protein molecules[11,12]. The in silico test produces bond energy values or Rerank Score (RS). Bond energy shows the amount of energy needed to form bonds between ligands and receptors. The smaller the bond energy means the more stable the bond is. The more stable the ligand bond with the receptor can be predicted that the activity will also increase[2].

The increasing number of cancers has encouraged the development of anti-cancer drugs. The number of cancer patients in the world reached 14.068 million people, 8.202 million were dead from cancer and 32.455 million people were diagnosed with cancer in the last 5 years. It is estimated that cancer will increase by 14 million new cases from 2012 to 2022[13,14].

In 2010 Saeed et al. has conducted research on thiourea derivatives by adding benzothiazole groups and found that several thiourea derivatives have anti-cancer activity in MCF-7 cells and HeLa cells[15]. In the same year Li et al. has conducted research on *N*-benzyl-*N*-(X-2-hydroxibenzyl)-*N*-phenylthiourea derivatives which show activity as breast anti-cancer[16]. There are several urea derivatives, such as thienopyridine urea derivative, aminopirazolopyridine urea derivative, and indenopirazole, which act as anticancer by inhibiting VEGFR2 receptors[17,18,19].

In 2017 Ruswanto and his colleagues have researched 1-benzoyl-3-methylthiourea derivatives as candidates for anti-cancer drugs by documenting molecules against ribonucleotide reductase enzymes, and predicting their absorption, distribution, toxicity and activity. The results of the study were predictions that the derivative had better activity than hydroxyurea, as well as its absorption and distribution predictions, and had relatively low toxicity[20].

Nasyanka (2017) has synthesized *N*-benzyl-*N'*-(4-fluorophenyl) thiourea compounds and three derivatives and determined their cytotoxic activity against MCF-7 cell lines. In silico tests have been conducted to predict cytotoxic activity four *N*-benzoyl-*N'*-(4-fluoro)phenylthiourea derivatives namely: *N*-4-methylbenzoyl-*N'*-(4-fluorophenyl)thiourea, *N*-4-methoxybenzoyl-*N'*-(4-fluorophenyl)thiourea, and *N*-4-tert-butylbenzoyl-*N'*-(4-fluorophenyl)thiourea with the target enzyme Sirtuin-1 pdb code. 4I5I. The results of the study were predictions that the four *N*-benzoyl-*N'*-(4-fluorophenyl) thiourea derivative compounds have greater cytotoxic activity than ligand compounds (4I5_601) and hydroxyurea[21].

In this present study, molecular docking as anticancer activity will be conducted on the target receptor SIRT1 using the Molegro Virtual Docker program and predict their absorption, distribution, elimination and toxicity (ADMET) of *N*-benzoyl-*N'*-(4-fluorophenyl) thiourea and four derivatives, namely: *N*-4-chlorobenzoyl-*N'*-(4-fluorophenyl) thiourea, *N*-2.3 dichlorobenzoyl-*N'*-(4-fluorophenyl) thiourea, *N*-4-bromobenzoyl-*N'*-(4-fluorophenyl) thiourea and *N*-4-trifluoromethyl-benzoyl-*N'*-(4-fluorophenyl) thiourea.

Physicochemical and pharmacokinetic properties predicted by online pkCSM program. The physicochemical properties obtained are Molecular Weight (BM), logarithm of octanol/water partition coefficient (Log P), number of bonds between rotating atoms (Torsion), Hydrogen Bond Acceptors (HBA), Hydrogen Bond Donors (HBD), and Polar Surface Activity (PSA). The pharmacokinetic properties obtained are: absorption, distribution, metabolism, excretion and toxicity.

MATERIAL AND METHODS:
Instrument and Program:
Lenovo computer, operating system Windows 10, 64bit, Intel Core i5-7200U, CPU @ 250 GHz 270 GHz, 8.00 GB RAM. Chem Bio Draw Ultra Version 12 (Cambridge Soft), Chem Bio 3D Ultra Version 12 (Cambridg eSoft), Molegro Virtual Docker Ver5.5 (Molegro ApS), SMILES Translator, pkCSM, and Protox*online tool*.

Procedure:
Downloading the target protein (Sirtuin-1 enzyme):
The molecular structure of the Sirtuin1 enzyme can be downloaded through protein data bank's site (http://www.rcsb.org/pdb/home/home.do). In this study the enzyme Sirtuin1 was chosen with the code PDB. 4I5I, because it contains amino ligands (2-chloro-6,7,8,9,10,10a-hexahydro-cyclo-hepta [b] indol-6-yl) methanol (indole analogue, code 4I5_601). The ligand

contains the -COHNH2 group which functions as a pharmacophore in the ligand-receptor interaction process, and the *N*-benzoyl-*N'*-(4-fluorophenyl) thiourea derivative contains similar groups, namely -CSNH-, which is also expected to function as pharmacophore[22].

Prediction of physico-chemical properties, pharmacokinetic and toxicity of compounds:
Prediction of physicochemical properties such as: Molecular Weight (BM), logarithm of octanol/water partition coefficient (Log P), molar refraction (MR) and Total Energy is carried out using Chem Bio Draw Ultra 2-D and 3-D programs. Prediction of pharmacokinetic properties (ADME: absorption, distribution, metabolism and excretion) and the toxicity of *N*-benzoyl-*N'*-(4-fluorophenyl)thiourea derivatives were also carried out using the online tool pkCSM program[15,23]. Four derivatives of N-benzoyl-N'-(4-fluorophenyl)thiourea and comparative compounds 4I5_601 were drawn 2-D molecular structure with Chem Bio Draw Ultra Version 12 program, then copied to the Chem Bio 3D Ultra Version 12 program to create a 3-D structure, then stored in the form of *.sdf or *.pdb files. Then the *N*-benzoyl-*N'*-(4-fluorophenyl)thiourea derivative compound and 4I5_60 comparative compound, the structure was translated into the SMILES format by using the help of Online SMILES Translator (https://cactus.nci.nih.gov/translate/). It is in the SMILES format that compounds are processed using the pkCSM online tool (http://biosig.unimelb.edu.au/pkCSM/prediction) to predict ADME and compound toxicity.

Molecular Docking:
The compound that will be docking is drawn by a 2-D molecular structure with the Chem Bio Draw Ultra version 12 program, then copied to the Chem Bio 3D Ultra Version 12 to create a 3-D structure. After measuring the minimum energy, it is then stored in the form of anmol2 {SYBYL2 (*.Mol2)}. After being stored then the doctoring process of the enzyme sirtuin-1 pdb.4I5I uses a Molegro Virtual Docker Version 5.5 program. The results obtained in the form of the Rerank Score (RS) value, which is the energy needed in the ligand-receptor interaction process, and from these values can be predicted anticancer activity of compounds through the inhibition of SIRT1 enzyme[8,22,23,24].

RESULTS:
The chemical structure of the *N*-benzoil-*N'*-(4-fluorophenyl) thiourea derivative compounds and the comparative indole analog compounds (4I5_601) can be seen in Table 1.

Table 1. The chemical structure of the *N*-benzoyl-*N'*-(4-fluorophenyl)thiourea compounds and the indole analog comparative compounds (4I5_601)
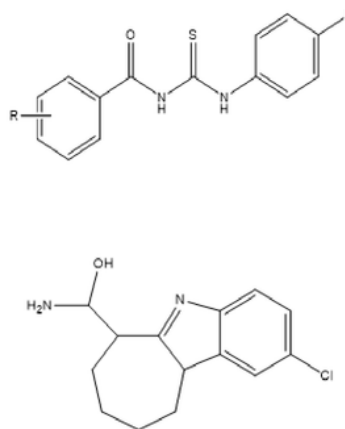
Derivatives of *N*-benzoil-*N'*-(4-fluorophenyl) tiourea Indole analoge compounds

Number	Compounds
1	*N*-benzoyl- *N'*-(4-fluorophenyl) thiourea
2	*N*-4-chlorobenzoyl-*N'*-(4-fluorophenyl)thiourea
3	*N*-2,4-dichlorobenzoyl-*N'*-(4-fluorophenyl)thiourea
4	*N*-4-bromobenzoyl-*N'*-(4-fluoro)phenylthiourea
5	*N*-4-trifluoromethyl-benzoyl-*N'*-(4-fluorophenyl)thiourea
6	Standard (indole analog compound)
7	Hydroxyurea

Physicochemical properties of *N*-benzoyl-*N'*-(4-fluorophenyl) thiourea derivatives using a program Using the ChemBioDraw Ultra 13.0 program, can be seen in Table 2.

Table 2. Physicochemical properties of N-benzoyl-N'-(4-fluorophenyl) thiourea derivatives

Compounds	BM	LogP	MR cm³/mol	Etot kcal/mol
1	274.31	3.46	74.46	-2.0125
2	308.76	4.02	79.07	-7.1277
3	343.20	4.58	83.08	-15.392
4	353.21	4.29	82.16	-6.5277
5	342.31	4.38	80.97	21.898
6	264.75	2.64	72.37	-10.601
7	76.06	-1.12	14.69	-43.386

The pharmacokinetics of *N*-benzoyl-*N'*-(4-fluorophenyl) thiourea derivatives using the online pkCSM program can be seen in Table 3. Prediction of cytotoxic activity (RS) of *N*-benzoyl-*N'*-(4-fluorophenyl) thiourea derivative compounds and comparison using Molegro Virtual Docker programs can be seen in Table 4.

Table 3. In silico prediction of pharmacokinetic properties (ADME), toxicity, and cytotoxic activity (Rerank Score) of N-benzoyl-N'-(4-fluorophenyl)thiourea derivatives and comparative compounds using pkCSM online tool and Molegro Virtual Docker

No	Absorption		Distribution		Metabolism		Excretion		Toxicity		
	Intestinal absorption (human) (%)	*Skin permeability (log Kp, cm/h)*	*VDss (human) (logL/kg)*	*BBB permeability (logBB)*	*CYP2D6 substrate*	*CYP2D6 inhibitor*	*Total Clearance (log ml /min/kg)*	*Renal OCT2 substrate*	*Ames Toxicity*	*LD50 (mg/kg)*	*Hepato-toxic*
1.	88,798	-3,054	-0,176	0,359	No	No	-0,341	No	No	2092	No
2.	89,055	-3,078	-0,100	0,388	No	No	-0,563	No	No	2221	No
3.	87,853	-3,046	-0,102	0,243	No	No	-0,37	No	No	2264	No
4.	88,988	-3,076	-0,085	0,337	No	No	-0,584	No	No	2225	No
5.	87,496	-3,064	-0,228	0,307	No	No	-0,513	No	No	2288	Yes
6.	90,052	-2,979	-0,802	0,027	No	No	0,674	Yes	Yes	3024	No
7.	73,127	-4,319	-0,495	-0,545	No	No	0,659	Yes	Yes	2116	No

Note: VDss: *Steady State of Volume Distribution*, BBB: *Blood Brain Barrier*, CYP2D6: *Cytochrome* P2D6, Renal OCT2: *Renal Organic Cation Transporter* 2.
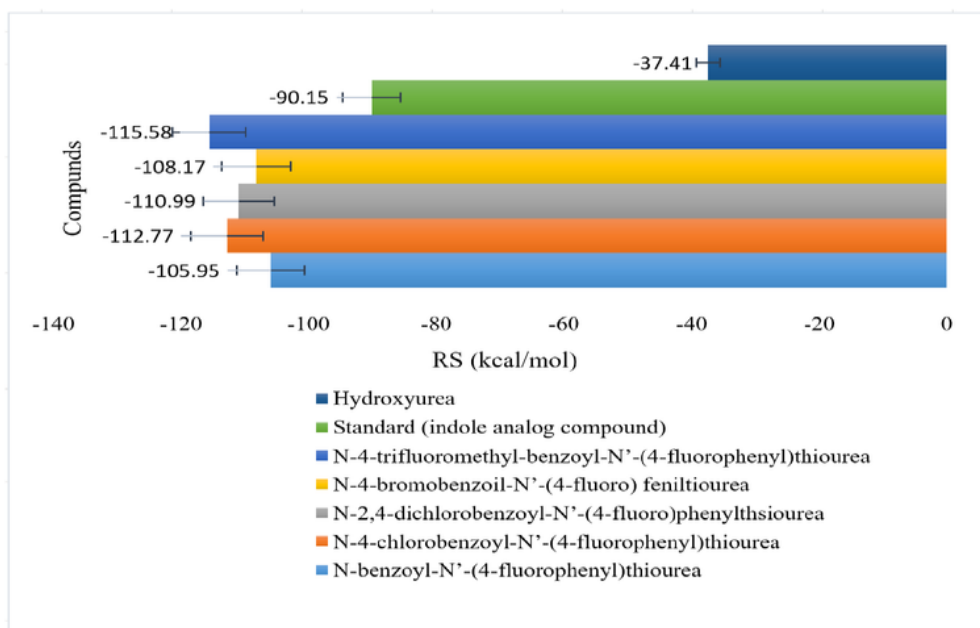

Fig 1. Cytotoxic activity (RS) of *N*-benzoyl-*N'*-(4-fluorophenyl)thiourea derivatives and its comparison using the Molegro Virtual Docker program.

Table 5. Amino acids which become the targets of Sirtuin-1 enzyme receptor pdb code. 4I5I which are involved in interactions with *N*-(benzoyl)-*N'*-(4-fluorophenyl) thiourea derivatives and its comparative compounds (analogues of indole compounds)

| No	Compounds	Hidrogen Bond	Steric Bond
1	*N*-benzoil-*N'*-(4-fluoro) phenylthiourea	Leu 443(A), Ser 441(A) Ser 442(A), Gly 440(A)	Phe 273(A)
2	*N*-4-chlorobenzoyl-*N'*-(4-fluorophenyl) thiourea	Asn 465(A)	Asn 465(A), Ser 442(A), Glu 467(A)
3	*N*-2,4-dichlorobenzoyl-*N'*- (4-fluoro)-phenylthiourea	Asn 465(A)	Arg 274(A), Arg 466(A)
4	*N*-4-bromobenzoyl-*N'*-(4-fluoro)-phenylthiourea	Ser 275(A), Asp 272(A)	Arg 272(A)
5	*N*-trifluoromethyl-benzoyl-*N'*-(4-fluoro)phenylthiourea	Ser 275(A), Arg 274(A)	Arg 272(A)
6	Standand (indole analog compound)	Arg 274(A), Glu 467(A)	Phe 273(A)
7	Hydorxyurea	Gly 319(A), Gln 320(A) Asp 348(A), Phe 321(A)	Leu 350(A)
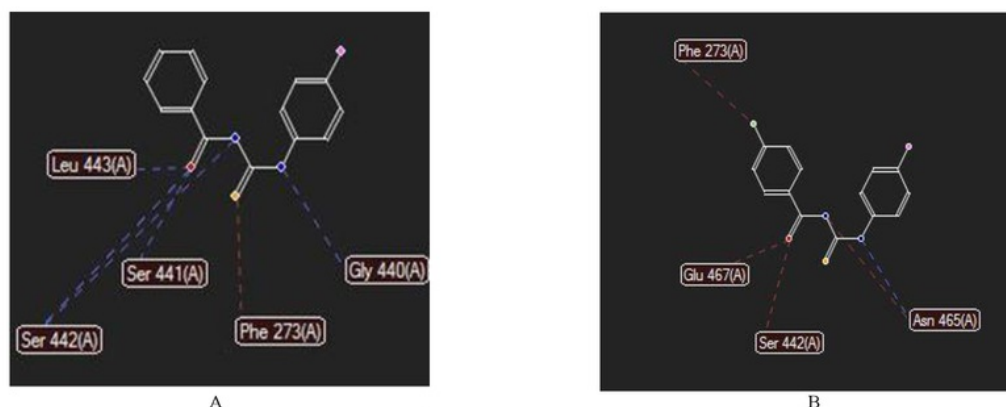
Fig 2. Figure of 2-D interactions between *N*-(benzoyl)-*N'*-(4-fluorophenyl)thiourea (A) parent compound and its derivative *N*-4-chlorobenzoyl-*N'*-(4-fluorophenyl)thiourea (B) with SIRT1 target receptor. The H-bond interaction is illustrated by a dashed blue line and the Steric-van Der Walls bond is illustrated by a dashed red line.
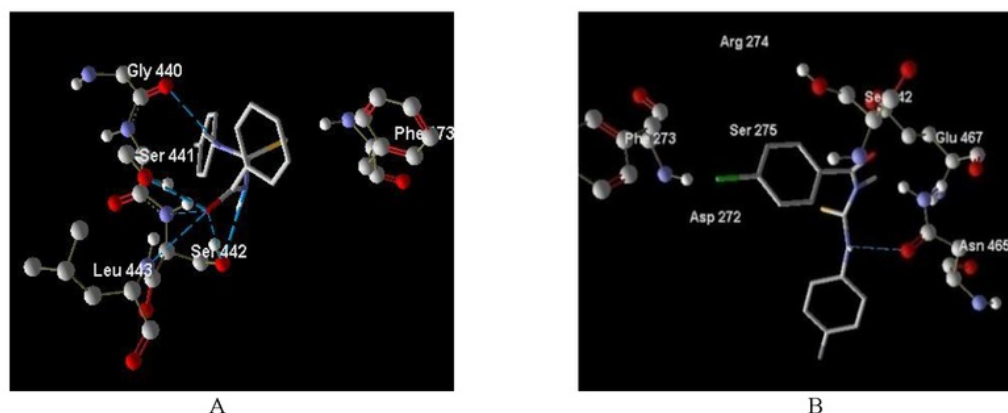

Fig 3. Figure of 3-D interactions between *N*-(benzoyl)-*N'*-(4-fluorophenyl)thiourea (A) parent compound and *N*-4-chlorobenzoyl-*N'*-(4-fluorophenyl)thiourea derivative (B) with SIRT1 target receptor.

DISCUSSION:

In 1997 Lipinski et al. has analysed 2,245 drugs from the basic data of the World Drugs Index[25]. This analysis is known as the five Lipinski law because all values are multiples of five The conclusion from this analysis states that the compound will be difficult to absorb and the permeability is low if the molecular weight is greater than 500, has a log coefficient of octanol/water (log P) greater than +5; has donor H-bond (HBD), which is expressed by the number of O-H and N-H groups, greater than 5; and has an H-receptor (HBA) bond, which is expressed by the number of atoms O and N, greater than 10. From Table 2 it can be seen that the compound studied has a molecular weight of less than 500 and a logP value of less than 5. Of all the structure of the compound examined the number of OH and NH groups is not more than 5, while the number of O and N atoms is less than 10. From this fact it can be said that all the compounds studied are easily absorbed and the permeability is high.

The compound is have good absorption if the absorption value is > 80%, and the absorption is bad if < 30%. The intestine is the main place for absorption of drugs given orally. From Table 3 it can be seen that all the compounds studied have absorption > 80, so that absorption can be expressed well. According to Pires et al. (2015), the compound is said to have relatively low skin permeability if it has a value of Skin Permeability (log Kp) > -2.5. From Table 3 it can be seen that all compounds have log values of Kp < -2.5, meaning that all compounds have good permeability on the skin[26].

Distribution volume (VDSS) is the theoretical volume that the total dose of the drug needs to be distributed evenly to give the same concentration as in blood plasma. The higher the VD value, the more drugs are distributed on the network rather than plasma. According to Pires et al. (2015), the compound is said to have a low Distribution Volume if the Log VD value is < -0.15, and high if > 0.45. From Table 3 it can be seen that compound number 2, 3 and 4 have a log value of VD > -

0.15 so that it can be said to have a fairly good distribution volume[26]. While compounds 1,5 and comparative compounds have logVD values < -0.15, which means the distribution volume is low.

The ability of the drug to penetrate the Blood Brain Barrier is an important parameter to reduce the side effects and toxicity or to increase the efficacy of drugs whose pharmacological activity is in the brain. Brain-blood permeability is measured in vivo in animal models as logBB, namely the logarithmic ratio of the brain to plasma[26]. According to Pires et al. (2015), the compound to be able to penetrate the Blood Brain Barrier well if it has a Log BB value of > 0.3 and cannot be distributed properly if log BB is < -1[26]. From Table 3 it can be seen that compounds 1, 2, 4 and 5 can penetrate the blood-brain barrier because they have a log BB value > 0.3. While compound 3 has a logBB value of 0.243 and is almost close to 0.3 and the comparison has a log BB value < 0.3. This means that the compounds of compound 3 are low, whereas the comparison compound cannot penetrate the blood-brain barrier because the logBB value is 0.027.

It is generally known that most metabolic reactions will involve the oxidation process. Cytochrome P450 is an important detoxification enzyme in the body, and is mainly found in the liver. It works by oxidizing foreign organic compounds, including drugs, and facilitating the excretion of these compounds. These enzyme inhibitors, such as grapefruit juice, can affect the metabolism of drugs so they are contraindicated against cytochrome P450 enzymes[26]. Therefore it is important to assess the ability of compounds that can inhibit cytochrome P450, which in this study was represented by cytochrome P2D6 isoform (CYP2D6). From Table 3 it can be seen that all compounds and comparative compounds do not affect cytochrome P450.

To predict the compound excretion process can be done by measuring the total clearance (CLTOT) and Renal Organic Cation Transporter 2 (OCT2) substrate. CLTOT is a combination of hepatic clearance (metabolism in the liver and bile) and renal clearance (renal excretion). This is related to bio-availability, and it is important to determine dosage levels in achieving steady-state concentration[26]. The excretion of the compounds studied when viewed from Table 3 shows that the CLTOT values ranged from -0.341 to -0.584 (log ml/min/kg), from this value it was predicted the rate of excretion of the compound.

Organic Cation Transporter 2 (OCT2) is a transporter in the kidney that plays an important role in the disposition and clearance of drugs and endogenous compounds. OCT2 substrate also has the potential to cause side interactions when given together with OCT2 inhibitors[26].

From Table 3 it can be seen that all the compounds studied did not affect the OCT2 substrate, so that the *N*-benzoyl-*N'*-(4-fluorophenyl)thiourea derivative could be predicted. It was not an OCT2 substrate.

To determine the toxicity of the compound can be done by the Ames Toxicity test. Ames Toxicity Test is a method that is widely used to assess the mutagenic potential of compounds using bacteria. Positive test results indicate that the compound is mutagenic and therefore can act as a carcinogen[26]. From Table 3 it can be seen that compounds 1 to 4 do not have mutagenic potential and are not hepatotoxic. The LD50 value in mice is 2092 to 2288 (mg/Kg). From this value it can be predicted that all the compounds studied have low toxicity. Because to kill 50% of animals, a dose of 2092 mg/kg body weight or 2,092 g/kg body weight is needed.

The in silico test to predict the cytotoxic activity (RS) of *N*-benzoyl-*N'*-(4-fluorophenyl)thiourea derivatives and comparison using Molegro Virtual Docker program can be seen in Table 3. From the table it can be seen that compound 5 which is *N*-4-trifluorometilbenzoyl-*N'*-(4-fluorophenyl)thiourea has the smallest RS value of -115.58 ± 12.55. However, from the prediction of the toxicity of this compound, it is predicted that it can cause hepatotosic, therefore compound 2 is *N*-4-chlorobenzoyl-*N'*-(4-fluorophenyl)thiourea which has RS -112/77 ± 1.93 and does not have the potential to cause mutagenic and not hepatotoxic.

CONCLUTIONS:
From the description above it can be concluded that the predicted compounds have good pharmacokinetic properties, the highest compound which has cytotoxic activity and not mutagenic and not hepatotoxic is *N*-4-chlorobenzoyl-*N'*-(4-fluorophenyl) thiourea.

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CONFLICT OF INTEREST:
The authors declare no conflict of interest.

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