



## Research Article

# Quantitative structure-cytotoxic activity relationship of phenylthiourea derivatives from ChemBL database on sirtuin-1 receptor by in silico

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### ABSTRACT

Rational drug design becomes a necessity amid the development of drugs that are inefficient and time-consuming. Hansch's QSAR helps reduce these shortcomings supported by the role of biocomputation. Some of the roles of biocomputation that can be used include in silico testing and the availability of databases for new drug-receptor and ligand candidates. This study aims to determine the QSAR through the search for the best equations analyzed by ANOVA statistics between cytotoxic activity in silico (Log 1/c) anticancer compounds derived from phenylthiourea stored in the ChemBL database with lipophilic parameters (ALPP and AlogP), electronic (ACDpKa), and its sterics (PMW). The best equation is obtained  $\text{Log } 1/c = -46,194 - 0,152 \text{ PMW} - 3,769 \text{ AlogP} - 1,336 \text{ ACDpKa}$  with a value of  $N = 28$ ;  $F = 20,866$ ;  $r = 0,850$ ;  $P = 0,000$ ;  $SE = 5.82160$ . In the future, this equation can be used to find other new phenylthiourea derivatives that have better cytotoxic activity.

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## INTRODUCTION

Millions of years ago, drug development was carried out through trial and error. This method consumes time and money, so it requires a technique that is efficient in drug development (Siswandono, 2016). To overcome this challenge, several multidisciplinary approaches are needed in the drug development process. These collective approaches will form the basis of rational drug design (Mandal, Moudgil & Mandal, 2009).

The development of cancer drugs, for example, is still being carried out to this day due to increased cancer deaths. Some data show that of the 14.1

million cancer patients in the world, 8.2 million deaths from cancer, and 32.6 million people were diagnosed with cancer in the last five years. Also, it is estimated that cancer disease will increase by 14 million new cases from 2012 to 2022 (WHO, 2012). In the same year, people with cancer disease in Indonesia reached 244.8 million, and cancer deaths 194.5 million with a risk of cancer patients under the age of 75 years by 14% (Cancer Index, 2012).

The rational design of anticancer drugs is one of the most promising strategies to improve cytotoxicity and to minimize the toxicity of prospective drugs. The ligand or complex structure manipulation is a

possible strategy for modifying the mechanism of action potential against cancer cells (Plutin et al., 2014).

The basic approach of rational drug design is knowledge about the relationship between chemical structures and biological activity, which is influenced by physicochemical properties, namely lipophilicity, electronics, and sterics. Lipophilic properties will affect the distribution or transport of drugs in penetrating biological membranes, electronic properties affect the ionization of drugs to penetrate and increase drug interactions with receptors, and sterics to strengthen drug-receptors binding in terms of stereochemistry or molecular size (Siswando, 2016). An equation will be made to describes the relationship of these parameters to biological activity, which known as the quantitative structure-activity relationship (QSAR).

There are several stages in the design of a synthetic compound to be used as a drug that is: discovery of the initial lead, development of structure-activity relationships, and refinement of the structure-activity hypothesis (Martin, 2010).

The use of computational methods to facilitate the process of drug discovery is currently well established and plays a vital role in new multidisciplinary drug discovery projects. Various computational methods are used to find new active compounds and to optimize these compounds to produce new candidate drug molecules (Blundell et al., 2006).

Several studies that have produced the mechanism of action of phenylthiourea derivatives as potential anticancer drugs, McCarthy et al., (2012), have synthesized and evaluated the anticancer activity of a thiourea derivative, namely 1-(4-acetamidophenyl)-3-(4-tertiary-butylbenzoyl)thiourea which was later named Tenovin-1. This compound is known to increase protein levels of p53 in vitro. Tenovin-1 is also active in vivo and shows significant activity in various tumor cells. In the same year, tenovin-1 derivatives (tenovin-6), which were more soluble in water, were developed and had reduced activity in CML (Chronic Myelogenous) (Li et al., 2012).

There are several database sites of active compounds that can be used along with lipophilic, electronic, and steric parameters that can be downloaded for free. One of them is ChemBL on the site <https://www.ebi.ac.uk/chembl/>. Some phenylthiourea derivative compounds in the database were predicted for activity in the sirtuin-1 enzyme (4i5i.pdb). Then the docking results are used as cytotoxic activities in silico and are associated with

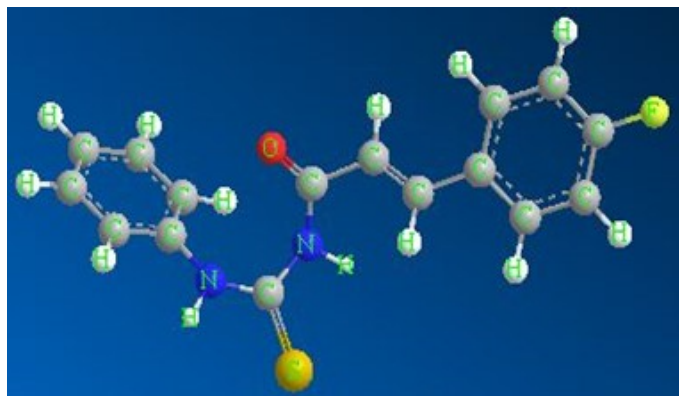


Figure 1. Preparation ligand CHEMBL1329243 (minimum energy -20.5672 kcal/mol)

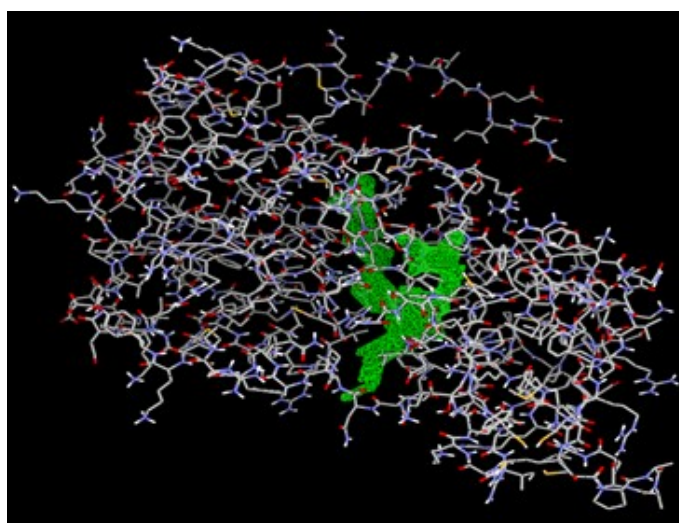


Figure 2. Sirtuin-1 receptor (4i5i.pdb) in 2D, green picture were a cavity (the place of interaction drug-receptor).

lipophilic, electronic, and steric parameters through Anova statistics to get the best equation.

## RESEARCH METHOD

### Tools

Asus portable computer with specification Windows 10.1, Intel Core i5, and 4 GB RAM. ChemBioDraw Ultra 13.0, Molegro Virtual Docker 5.5, IBM® SPSS® 20.0 was the software used for research.

### Materials

The sirtuin-1 enzyme (SirT1) downloaded from protein data bank (<http://www.rcsb.org/pdb>) with code 4i5i. Phenylthiourea derivatives and their lipophilic, electronic, and steric were downloaded from the ChemBL database (<https://www.ebi.ac.uk/chembl/>).

### Method

Phenylthiourea derivatives preparation Twenty-eight phenylthiourea derivatives were downloaded from the ChemBL database. Then, converted to .mol2. Minimized 3D Ligands by using

**Table 1.** 28 Phenylthiourea derivatives and their minimum energy and Rerank Score

No.	Ligand Database	Energy Minimum (Kcal/mol)	Rerank Score
1	CHEMBL1329243	-20.5672	-122.784
2	CHEMBL1345002	12.232	-120.589
3	CHEMBL1361130	14.0834	-129.503
4	CHEMBL1418742	22.3353	-140.29
5	CHEMBL1419641	24.663	-136.708
6	CHEMBL1448029	14.6901	-118.113
7	CHEMBL1450561	-4.37506	-109.637
8	CHEMBL1460935	20.3201	-133.086
9	CHEMBL1462426	23.5617	-134.694
10	CHEMBL1467322	-3.06285	-126.74
11	CHEMBL1479629	22.5952	-144.651
12	CHEMBL1517676	4.68609	-113.73
13	CHEMBL1571513	4.36009	-112.593
14	CHEMBL1574268	12.5253	-109.877
15	CHEMBL1602151	-2.94543	-125.003
16	CHEMBL1834362	9.35305	-112.806
17	CHEMBL1834365	6.02541	-116.997
18	CHEMBL1889325	20.0494	-130.08
19	CHEMBL1890351	2.39201	-110.162
20	CHEMBL1896657	25.6687	-137.423
21	CHEMBL1996258	4.81485	-117.313
22	CHEMBL2236347	7.13225	-111.732
23	CHEMBL2236348	-0.0015429	-112.526
24	CHEMBL3087543	28.0624	-108.896
25	CHEMBL3087548	14.0203	-117.283
26	CHEMBL3087549	-5.42623	-123.422
27	CHEMBL3087554	13.179	-114.36
28	CHEMBL3087557	10.7771	-121.022

MMFF94 and then save with Sybyl (.mol2).

### Receptor Preparation

The receptor has been downloaded from Protein Data Bank (PDB) then opened in Molegro Virtual Docker (MVD) Ver.5.5.

### Determined QSAR Parameter

QSAR parameters of 28 compounds in this study are lipophilic (ALogP and ALogP2), electronic (ACDpKa), and steric (PMW) were copied from the ChemBL database (<https://www.ebi.ac.uk/chembl/>).

### Docking

The twenty-eight compound had been docked in

MVD to the sirtuin-1 receptor. One of the parameters in this result is the rerank score. Rerank score has been used to predict the interaction of drug-receptor. In this study, the rerank score became the cytotoxic activity of 28 derivatives (Log 1/c).

### Statistical Analysis

All of QSAR parameters and cytotoxic predictions were analyzed with Anova one way by using SPSS.

## RESULT AND DISCUSSIONS

### Ligand Preparation

Ligand preparation is used to ensure the ligand that we have downloaded from the database has

**Table 2.** Lipophilic, electronic, and steric parameters of each compound in the database

Ligand Name	Lipophilic		Electronic	Steric
	A <sub>LogP</sub>	A <sub>LogP</sub> <sup>2</sup>	ACD ApKa	Molecular Weight
CHEMBL1329243	4.44	19.714	9.08	300.35
CHEMBL1345002	4.74	22.468	9.06	284.38
CHEMBL1361130	4.17	17.389	8.27	332.8
CHEMBL1418742	6.48	41.990	9.05	396.89
CHEMBL1419641	5.99	35.880	8.44	382.86
CHEMBL1448029	3.96	15.682	8.64	304.34
CHEMBL1450561	4.43	19.625	8.65	290.77
CHEMBL1460935	5.99	35.880	8.8	382.86
CHEMBL1462426	5.28	27.878	9.32	332.42
CHEMBL1467322	4.62	21.344	9.4	314.4
CHEMBL1479629	4.8	23.040	8.67	365.42
CHEMBL1517676	3.36	11.290	8.24	336.21
CHEMBL1571513	2.6	6.760	7.67	287.34
CHEMBL1574268	2.62	6.864	8.39	257.31
CHEMBL1602151	4.1	16.810	9.4	300.38
CHEMBL1834362	3.77	14.213	9.49	256.32
CHEMBL1834365	3.97	15.761	8.62	274.31
CHEMBL1889325	5.28	27.878	8.85	332.42
CHEMBL1890351	3.28	10.758	7.9	291.76
CHEMBL1896657	5.77	33.293	8.71	346.45
CHEMBL1996258	4.96	24.602	6.85	298.4
CHEMBL2236347	4.25	18.063	8.44	270.35
CHEMBL2236348	4.51	20.340	9.66	335.22
CHEMBL3087543	4.43	19.625	6.7	290.77
CHEMBL3087548	5.1	26.010	3.02	325.21
CHEMBL3087549	5.1	26.010	4.5	325.21
CHEMBL3087554	3.75	14.063	8.27	286.35
CHEMBL3087557	5.62	31.584	3.06	312.43

minimized its energy. The purpose of minimizing energy in each compound so that the compound has the most stable form to interact when the docking process is carried out at a later stage.

### Docking

The rerank score value of each of the 28 phenylthiourea derivatives was used as the value of anticancer activity in silico (Log 1/c) to obtain predictions of the quantitative relationship of the activity structure.

### Determined QSAR parameters

The quantitative relationship of activity structure, according to Hansch, consists of three parameters.

Hydrophobic parameters which are parameters involved in the distribution or transport of drugs and the penetration of biological membranes. Electronic parameters are included in the process of distribution or transport of drugs, penetration of biological membranes, and drug-receptor interactions. Steric parameters are mainly involved in drug-receptor interactions and can be measured based on the properties of groups and group effects on drug contact with adjacent receptor sides (Siswando, 2016).

The determination of these parameters was carried out by looking at data of each ligand in the database, so A<sub>LogP</sub> and A<sub>LogP</sub><sup>2</sup> (lipophilic), ApKa ACD

**Table 1.** Equation between mixed parameter (lipophilic, electronic, and steric) and prediction of cytotoxic activity.

No.	Equation	F	r	P	Se
1	$\text{Log } 1/c = -87.01 - 7.66 \text{ ALogP}$	26.859	0,713	0,000	7.4514
2	$\text{Log } 1/c = -113.75 + 4.78 \text{ ALogP} - 1.38 \text{ ALogP}^2$	14.238	0,730	0,000	7.4083
3	$\text{Log } 1/c = -113.08 - 1.09 \text{ ACDpKa}$	0,904	0,183	0,350	10.4445
4	$\text{Log } 1/c = -50.68 - 0,23 \text{ PMW}$	46.863	0,802	0,000	6.3466
5	$\text{Log } 1/c = -70.41 - 8,16 \text{ A LogP} - 1,79 \text{ ACDpKa}$	18.433	0,772	0,000	6.8876
6	$\text{Log } 1/c = -55.08 - 2,87 \text{ ALogP} - 0,17 \text{ PMW}$	26,046	0,822	0,000	6.1701
7	$\text{Log } 1/c = -43,15 - 0,98 \text{ ACDpKa} - 0,23 \text{ PMW}$	25,404	0,819	0,000	6.2222
8	$\text{Log } 1/c = -96,47 - 1,77 \text{ ACDpKa} + 3,91 \text{ ALogP} - 1,34 \text{ ALogP}^2$	12,987	0,787	0,000	6.8275
9	$\text{Log } 1/c = -52,38 - 0,17 \text{ PMW} - 3,86 \text{ ALogP} + 0,12 \text{ ALogP}^2$	16,681	0,822	0,000	6.2959
10	$\text{Log } 1/c = -46,19 - 0,15 \text{ PMW} - 3,77 \text{ ALogP} - 1,34 \text{ ACDpKa}$	20,866	0,850	0,000	5.8216
11	$\text{Log } 1/c = -47,13 - 0,15 \text{ PMW} - 1,34 \text{ ACDpKa} - 3,42 \text{ ALogP} - 0,04 \text{ ALogP}^2$	14.999	0,850	0,000	5.9466

(Electronic), and MW (Steric) were selected for parameters.

### Determined the best equation of QSAR

The results of ANOVA statistical analysis based on data from 28 ChemBL ligands in the form of lipophilic, electronic, and steric parameters associated with the prediction of  $\text{Log } 1/c$  cytotoxic activity (rerank score) were obtained eleven equations (Table 3). Determination of best equations for the explanation of the quantitative structure-cytotoxic activity relationship of phenylthiourea by choosing a significance value  $< 0.05$ , the correlation coefficient ( $r$ ) is close to 1, the value of  $F$  is significant, and finally the standard error is minimal (Siswandono, 2016).

There are eleven equations based on the ANOVA analysis (Table 3). The best equation is Equation 10, which contains components of three parameters, namely lipophilic, electronic, and steric, and fulfills the requirements of the best equation, the significance value  $< 0.05$  illustrates the relationship between physicochemical properties and in silico cytotoxic activity. Meanwhile, the most considerable  $F$  value compared to other equations demonstrates that the equation is obtained, among other results. As well, the value of  $r$  approaching one illustrates the relationship between the two variables is quite good, and the minimum standard error describes if the event is repeated, then the results can still be trusted (Siswandono, 2016).

Based on the above equation, the prediction of the quantitative relationship of the structure of cytotoxic activity of phenylthiourea derivative compounds is that there is a significant influence on lipophilic parameters (ALogP), which can be seen from the

most significant coefficient of electronic parameters (ACDpKa) and steric (PMW). The presence of a reduction sign before these parameters illustrates that the value of in silico cytotoxic activity will be higher with increasing lipophilic, electronic, and steric activity in which prediction activity is described by the rerank score (negative form). The smaller rerank score value indicates more significant activity (Chan & Labute, 2010).

The results of the above QSAR equation can be used to find new drug candidates that will be modified by including the value of ALogP, ACDpKa, and PMW groups to determine the prediction of cytotoxic activity, thus minimizing trial and error which costs time and money.

### CONCLUSION

There was a quantitative relationship between the structure of activity between the cytotoxic activity of phenylthiourea derivatives in the sirtuin-1 enzyme in silico with lipophilic, electronic, and steric parameters determined by the Anova test. The best equation obtained through the Anova test above in equation 10, which contains mixed parameters between lipophilic, electronic, and steric.

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