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Research Article

PHYTOCHEMICAL AND ANTIBACTERIAL ANALYSIS OF AQUEOUS AND ALCOHOLIC EXTRACTS OF VERNONIA AMYGDALINA (DEL.) LEAF***Tsaku Alumbu Paul, Ibrahim Taibat, Ekeleme Ike Kenneth, Nkenne Istifanus Haruna, Oti Victor Baba and Abimiku Rejoice Helma**[\[ABSTRACT\]](#) [\[PDF\]](#) [DOI : [10.20959/wjpr20187-11567](#)]**DETECTIONS OF SOME RESPIRATORY VIRUSES BY MOLECULAR TECHNIQUES AMONG TWO SUDANESE TARGETS INDIVIDUALS****Ibrahim H. S.*, Kafi S. K., Musa H. A., Karsany M. S. and Abdel Hamid M. M.**[\[ABSTRACT\]](#) [\[PDF\]](#) [DOI : [10.20959/wjpr20187-11543](#)]**POLYUNSATURATED FATTY ACIDS INTAKE AND ITS ASSOCIATION WITH BREAST CANCER AMONG PATIENTS ATTENDING THE RADIATION AND ISOTOPE CENTER IN KHARTOUM STATE****Hafsa A. Elsaifi* and Hassan A/Aziz Musa**[\[ABSTRACT\]](#) [\[PDF\]](#) [DOI : [10.20959/wjpr20187-11199](#)]**ASSESSMENT OF CHRONIC KIDNEY FAILURE PATIENTS' AWARENESS ABOUT DISEASE AND HEMODIALYSIS COMPLICATIONS IN ALHASA REGION OF SAUDI ARABIA****Dr. Amal Khaleel Abu Alhommos* and Fahad Sami Al-Fahaid**[\[ABSTRACT\]](#) [\[PDF\]](#) [DOI : [10.20959/wjpr20187-11644](#)]**EVALUATION OF RISK FACTORS IN BREAST CANCER AMONG IRAQI FEMALE PATIENTS****Bushra Hasan Hashim*, Khulood Kareem Abed, Lina Ziyad Tareq, Arwa Ra'ed Mishaal and Haneen Sedqi Ismael**[\[ABSTRACT\]](#) [\[PDF\]](#) [DOI : [10.20959/wjpr20187-11646](#)]**SYNTHESIS OF N-4-METHOXYBENZOYL-N'-PHENYLUREA COMPOUND AND ACTIVITY TEST OF ANTICANCER AGAINST HeLa CELL LINE****Bambang Tri Purwanto***[\[ABSTRACT\]](#) [\[PDF\]](#) [DOI : [10.20959/wjpr20187-11482](#)]**DOCKING, SYNTHESIS AND CYTOTOXIC TEST ON HUMAN BREAST CANCER CELL LINE T47D OF N-(PHENYL CARBAMOTHIOYL)-BENZAMIDE****Dini Kesuma*, Siswandono, Bambang Tri Purwanto and Marcellino Rudyanto**[\[ABSTRACT\]](#) [\[PDF\]](#) [DOI : [10.20959/wjpr20187-11474](#)]**ASSESSMENT OF CINNAMON EFFECT TO REDUCE PRIMARY DYSMENORRHEA AND IMPROVE QUALITY OF LIFE AMONG FEMALES IN EASTERN REGION OF SAUDI ARABIA: A CROSS SECTIONAL SURVEY****Dr. Amal Khaleel Abu Alhommos* and Muncerah Al-Hadi**[\[ABSTRACT\]](#) [\[PDF\]](#) [DOI : [10.20959/wjpr20187-11682](#)]

DOCKING, SYNTHESIS AND CYTOTOXIC TEST ON HUMAN BREAST CANCER CELL LINE T47D OF *N*-(PHENYLCARBAMOTHIOYL)-BENZAMIDE

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ABSTRACT

Introduction: New breast anticancer compound *N*-(phenylcarbamothioyl)-benzamide have been synthesized, initiated with molecular modeling in silico which is docking between test compounds with SIRT-1 receptor PDB code: 4I5I to predict the bonding of test compounds with receptors. **Methods:** The compounds are synthesized from benzoyl chloride reaction with *N*-phenylthiourea. The molecular structure is confirmed using FTIR, ¹H-NMR, ¹³C-NMR and Mass Spectra. Anticancer activity is tested in vitro against human breast cancer cells (T47D) using an MTT assay. **Result:** RS (Rerank

Score) value and anticancer activity of test compound obtained are higher than Hydroxyurea as the reference compound. The Value of IC₅₀ *N*-(phenylcarbamothioyl)-benzamide is 0.53 mM (T47D cell) and 49.40 mM (Vero cel) and also IC₅₀ Hydroxyurea is 4.58 mM (T47D cells). It is predicted that the mechanism of action of these new compounds is targeted cell because it has toxic effect on cancer cells and is not toxic in normal Vero cells. **Conclusion:** This new compound are highly potential as an anticancer agent against the human breast carcinoma cell line (T47D).

KEYWORDS: *N*-(phenylcarbamothioyl)-benzamide, anticancer, T47D cell, SIRT 1.

INTRODUCTION

Cancer is one of the major causes of death in developing countries and also worldwide. In Indonesia, cancer becomes the third largest contributor to death after heart disease. Since 2007 breast cancer has reached first ranks for in-patients in hospitals, followed by cervical

cancer. Thiourea is a compound containing sulfur and nitrogen atoms whose chemical structures are similar to the urea compound already used today as an anticancer, including hydroxyurea, nitrosourea and 5-fluorouracil.^[1]

Resistance/intolerance has been reported against hydroxyurea in patients with essential thrombocythaemia.^[2] The clinical use of hydroxyurea begins to diminish, but in biochemical research and development of the anticancer drug hydroxyurea is used as a DNA replication inhibitor.^[3] The research data show that hydroxyurea activity is not maximum because it is hydrophilic with poor membrane penetration capability so it is necessary to develop new anticancer drugs of urea and thiourea derivatives which is more lipophilic with better membrane penetration so that its activity is more potent. Pirrie, 2012, has synthesized and evaluated the anticancer activity of thiourea derivatives, as 1-(4-acetamidophenyl)-3-(4-tert-butylbenzoyl) thiourea which is later named Tenovin-1. These compounds are known to increase p53 protein levels in vitro (inhibits SIRT1).^[4] Widiandani, 2016, has also proven breast anticancer activity (T47D cells) of the *N*-(allylcarbamothioyl)benzamide compound.^[5]

In this study, a new compounds *N*-(phenylcarbamothioyl)-benzamide is obtained with the presence of phenyl and benzoyl rings enhancing the lipophilic and electronic nature of the compound which in turn will improve the bonding of drugs and receptors. Breast cancer cell T47D is used to express the mutated p53 protein initiated with activity predictions by molecular modeling in silico, docking test compound with Histon deacetylase SIRT1 inhibitor code of PDB: 4I5I. This receptor has an important role in the growth of tumor cells.^[6] The test compounds are synthesized from *N*-phenylthiourea with benzoyl chloride using acyl nucleophilic substitution reactions.^[7] The compounds resulted from the synthesis are then identified in structures with IR spectrophotometers, ¹H-NMR spectrometers, ¹³C-NMR and mass spectrometers.^[8]

The anticancer activity of the test compound is determined by cytotoxic test using MTT assay (3-(4,5-dimethylthiazole-2-yl) -2,5-diphenyltetrazolium bromide) in vitro on T47D breast cancer cells and normal Vero cells. The results of anticancer activity test on T47D cells are IC₅₀ compared with Hydroxyurea as the reference compounds, also observed in normal cell Vero. The results of this study is expected to obtain a candidate for a new anticancer drug from thiourea derivatives that have potent anticancer activity on breast cancer cells T47D.^[9] This study will proceed with the synthesis of *N*-(phenylcarbamothioyl)-benzamide derivatives and molecular mechanisms, prior to preclinical and clinical trials.

MATERIALS AND METHODS

WORK PROCEDURES

Molecular Modeling

Predicting activity with molecular modeling of *N*-(phenylcarbamothioyl)-benzamide by docking with Histon deacetylase SIRT1 inhibitor PDB code: 4I5I, continued with using the MVD 5.5 software. Hydroxyurea is used as a reference compound.^[10]

Test Compounds Synthesis

The Synthesis of *N*-(phenylcarbamothioyl)-benzamide

In a round flask, *N*- phenylthiourea is mixed with tetrahydrofuran and TEA. a benzoyl chloride solution in tetrahydrofuran is added into the mixture, bit by bit through a dropping funnel over the ice bath, stirred with a magnetic tool. The mixture is refluxed and stirred in a water bath and in TLC every hour. The reaction is terminated whenever a single stain in TLC is formed. After the termination, THF is evaporated on the rotary evaporator proceeded with recrystallization.^[5]

The identification of the compound structure of the synthesis results is conducted based on the results of the examination: Infrared, ¹H-NMR, ¹³C-NMR and MS.

Cytotoxic Test On T47D Breast Cancer Cells and Normal Vero Cells

Anticancer activity is performed in vitro using T47D the breast cancer cells. 5 mg of test compound in 100 µl DMSO is dissolved to obtain 50.000 µg / mL concentration. The mother liquor is diluted gradually with RPMI culture medium for T47D cells to obtain a series of standard working solution. T47D cancer cell culture is prepared in microplate with 96 wells in a form of a cell suspension used in the experiment with a density of 10,000 cells / pitting. Empty wells are set on the plate for media control and afterwards CO₂ 5% incubator is added for 24 hours.

After incubated, the plate is removed and the media is discarded by 180 degrees reversion . After washed with PBS 100 µL for each well, then PBS was discarded by reversing the plate 180 degrees. A total of 100 µL of standard working solution, positive control and solvent control are included in microplate pours. Each concentration is replicated three times. Sums that do not contain T47D cancer cells are filled with media as media controls. Then incubated at incubator 5% CO₂ for 24 hours, at 37⁰C. After 24 hours the plate is removed from the incubator and the media is discarded. Within each well, 0.5 mg / ml of MTT is added to 100

μl / well, then incubated for 3 hours. After 3 hours of incubation, microplate is removed and the reaction is terminated by adding 100 μl SDS 10% in 0.1 N HCl to the hole. Microplate is wrapped with aluminum paper and incubated for 24 hours at 5% CO_2 incubator, then Elisa Reader is inserted at $\lambda = 595$ nm. With probit analysis we get IC_{50} values from test compound.^[11]

RESULTS AND DISCUSSION

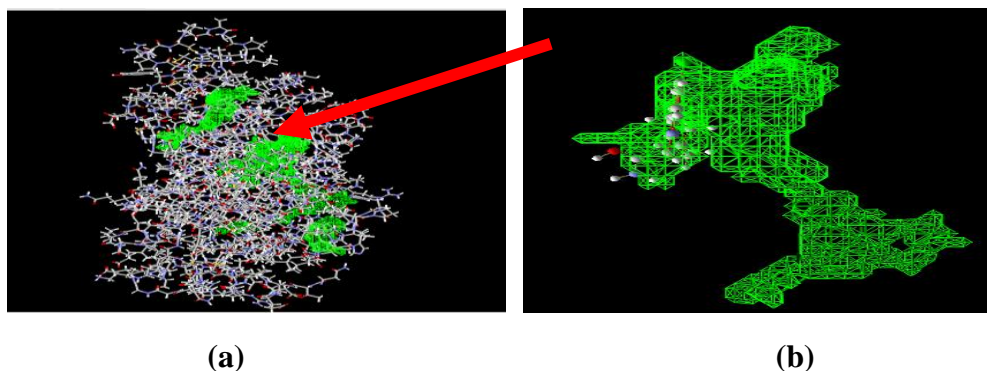


Fig 1. Preparation of protein (a) Histone deacetylase SIRT1 inhibitor code pdb: 4I5I (b) selected hole (corresponding arrow) on the 4I5I receptor where interacting ligand and receptor (cavity 1). Images are obtained from Molegro version 5.5.

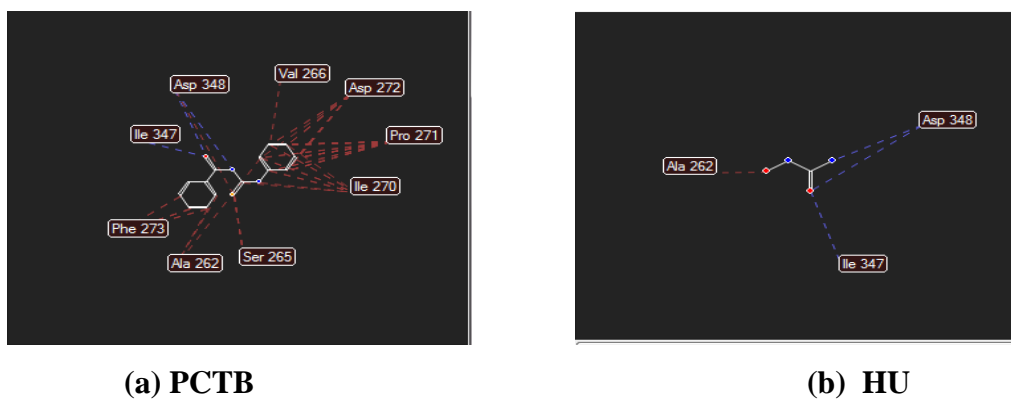


Fig. 2: 2D pictures show hydrogen bonds (blue dashed-line) and steric interaction (red dashed-line) of *N*-(phenylcarbamothioyl)-benzamide compound (PCTB) (a), reference drug HU (b) with amino acid in SIRT1 binding site. Images are obtained from Molegro version 5.5.

Table 1. The results of the docking value as a Rerank Score (RS).

No	Compounds	RS (PDB 4I5I)
1	PCTB	-119.4130
2	HU	-40.0237

Table 2: Hydrogen and steric bonds performed by interaction between tested compounds and amino acids in binding site of SIRT1.

NO	COMPOUNDS	AMINO ACIDS											
		ALA 262	ASN 346	ASP 272	ASP 348	ILE 270	ILE 347	PHE 273	PRO 271	SER 265	GLY 263	VAL 266	GLY 261
1.	PCTB	2S		4S	1H/1S	5S	1H	3S	5S	1S		1s	
2.	Hydroxyurea	1S			2H		1H						

Description: H: Hydrogen bond and S: Steric bond (Van der Waals and Hydrophobic)

The RS values describe drug activity in silico. Based on the results of in silico test (table 1) obtained the results of RS PCTB: --119.4130 and RS HU: -40.0237. The smaller the RS value, the more stable the resulting drug-receptor bonds are, the more predictable the activity will be (Hinchliffe, 2008).^[12] The number and types of amino acids in Table 2 and Figure 2. Based on the bonding of drugs and amino acids, the greater the number of hydrogen bonds and steric bonds (Van der Waals and Hydrophobic), it can be predicted that the bonds between the drug and the receptor will be more stable.

The new compound *N*-(phenylcarbamothioyl)-benzamide is synthesized from benzoyl chloride with *N*-phenylthiourea in one stage. The synthesized result compound is yellow solid and in water insoluble substance. The structure of the synthesis compound is identified by IR, ¹H-NMR, ¹³CNMR, and HRMS spectroscopy as follows.

***N*-(phenylcarbamothioyl)-benzamide.** Yield 71% as yellow crystal, m.p. 108⁰C. ¹H-NMR (DMSO-D6, 400 MHz) : δ 7.30 (t, J=7.2 Hz, 1H, Ar-H); δ 7.43 (dd, J=7.2;8.0 Hz, 2H,Ar-H); δ 7.54 (t, J=7.2 Hz, 2H, Ar-H); ; δ 7.65 (dd, J=7.2;1.2 Hz, 1H, Ar-H);); δ 7.69 (d, J=8.0 Hz, 2H, Ar-H); δ 7.98 (dd, J=7.2;1.2 Hz, 2H, Ar-H); δ 11.56 (s, 1H,O=C-NH-C=S); δ 12.61 (s, 1H,S=C-NH-CH₂); NMR ¹³C (DMSO-D6, 400 MHz) ; δ 124.87 (2C, Ar); δ 126.87 (2C, Ar); δ 128.99 (2C, Ar); δ 128.99 (1C, Ar); δ 129.21 (2C, Ar); δ 132.69 (1C, Ar); δ 133.67 (1C, Ar); δ 138.53 (1C, Ar); δ 168.83 (1C, C=O); δ 179.65 (1C, C=S). IR (KBr),v maks (cm⁻¹) : 1672 (C=O amide) ; 1672&1451 (C=C Ar); 3219&1592 (NH stretch sec.amides); 1085&811 (C=S). HRMS (m/z) C₁₄H₁₁N₂OS: (M-H)⁻: 255.0590, Calc. Mass : 255.0592 δ m/z = 0.0002 < 0.005.

Cytotoxic Activity**Table 3: Cytotoxic Effect of PCTB compound on T47D Cell Line.**

S.NO	CONCENTRATION ($\mu\text{g/mL}$)	ABSORBANCE	CELL VIABILITY (%)
1	12.5	0.619	87
2	25	0.609	86
3	50	0.565	78
4	100	0.437	57
5	200	0.336	40
6	400	0.247	25
7	CELL CONTROL	0.693	100

IC_{50} : 0.53 mM

Table 4: Cytotoxic Effect of Hydroxyurea compound on T47D Cell Line.

S.NO	CONCENTRATION ($\mu\text{g/mL}$)	ABSORBANCE	CELL VIABILITY (%)
1	31.25	0.621	90
2	62.5	0.589	84
3	125	0.554	78
4	250	0.424	56
5	500	0.330	40
6	1000	0.245	25
7	CELL CONTROL	0.680	100

IC_{50} : 4.58 mM

Table 5: Cytotoxic Effect of PCTB compound on Vero Cell Line.

S.NO	CONCENTRATION ($\mu\text{g/mL}$)	ABSORBANCE	CELL VIABILITY (%)
1	31.25	0.200	100
2	62.5	0.197	98
3	125	0.195	96
4	250	0.191	92
5	500	0.187	89
6	1000	0.183	86
7	CELL CONTROL	0.200	100

IC_{50} : 49.40 mM

Table 6: RS, IC_{50} T47D cell and IC_{50} Vero cell values of test and reference compounds.

Compound	RS	IC_{50} T47D Cell Line	IC_{50} Vero Cell Line
PCTB	-119.4130	0.53 mM	49.40 mM
HU	-40.0237	4.58 mM	-

Table 3 to table 5 are the data of the cytotoxic test result on T47D cancer cells and the normal cell Vero. The IC_{50} values of the test compound obtained from probit analysis are better than the Hydroxyurea reference compound. There is a corresponding result between the insilico and invitro tests of the test compound and the reference compound (Table 6). The better the value of the RS (stable bonding of the drug and the receptor) the better the anticancer activity is.

The cytotoxic effect of the T47D cells from the test compound could be seen on figure 3.

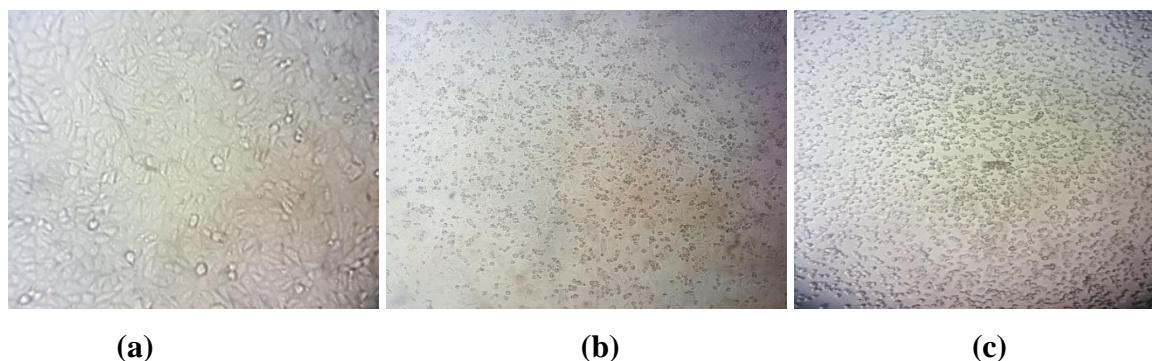


Figure 3:

- T47D cells before given a test compound
- T47D cells after given the test compound (dose 500 $\mu\text{g} / \text{mL}$)
- T47D cells after given a test compound (dose 1000 $\mu\text{g} / \text{mL}$)

CONCLUSION

This study concludes that a new compound of *N*-(phenylcarbamothioyl)-benzamide show in vitro anticancer activity against human breast cancer cells (T47D) higher than the anticancer drug hydroxyurea. In the in silico study it can be explained that better inhibitory activity is associated with higher affinity with SIRT1 binding sites. The value of IC_{50} *N*-(phenylcarbamothioyl)-benzamide is 0.53 mM, is more active than Hydroxyurea which is 4.58 mM. This new compound is more suitable for binding enzymes compared to Hydroxyurea, as it can illustrate better inhibitory activity. It is predicted that the activity of this new compound is targeted cell because it has toxic effects on cancer cells and are not toxic to normal Vero cells (Vero cell death <15%). Further researches are required to examine the molecular mechanism of this new compound.

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