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Original Article

Anticancer activity of *N*-(4-*t*-butylbenzoyl)-*N'*-phenylthiourea: Molecular docking, synthesis, and cytotoxic activity in breast and cervical cancer cells

[Actividad anticancerígena de la N-(4-t-butilbenzoil)-N'-feniltiourea: acoplamiento molecular, síntesis y actividad citotóxica en células de cáncer de mama y de cuello uterino]

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Abstract

Context: *N*-(4-*t*-butylbenzoyl)-*N*'-phenylthiourea, a derivative compound of *N*-benzoyl-*N'*-phenylthiourea, has relatively high lipophilicity with the epidermal growth factor receptor and silent mating type information regulation-1 enzyme as its molecular targets.

Aims: To determine the anticancer activity of *N*-(4-*t*-butylbenzoyl)-*N*'-phenylthiourea as an *in silico* and *in vitro* anticancer candidate for the breast and cervical cancer.

Methods: *In silico* test was performed to predict the cytotoxic activity using AutoDock Vina. This activity was also measured *in vitro* using the Microculture Tetrazolium Technique assays of three cancer cells (MCF-7, T47D, and HeLa) and normal cells (Vero cells).

Results: *In silico* test predicted that *N*-(4-*t*-butylbenzoyl)-*N*'-phenylthiourea was more cytotoxic at epidermal growth factor receptor than silent mating type information regulation-1 receptor. *In vitro* tests showed it exhibited cytotoxic activities against MCF-7, T47D, and HeLa without harming Vero cells.

Conclusions: *N*-(4-*t*-butylbenzoyl)-*N*'-phenylthiourea has the potential as an anticancer candidate for breast and cervical cancers.

Keywords: breast cancer; cervical cancer; EGFR; *N*-(4-*t*-butylbenzoyl)-*N*'-phenylthiourea; SIRT1.

Resumen

Contexto: La N-(4-t-butilbenzoil)-N'-feniltiourea, un compuesto derivado de la N-benzoil-N'-feniltiourea, tiene una lipofilia relativamente alta y tiene como dianas moleculares el receptor del factor de crecimiento epidérmico y la enzima de regulación silenciosa de la información de tipo apareamiento-1.

Objetivos: Determinar la actividad anticancerosa de la N-(4-t-butilbenzoil)-N'-feniltiourea como candidato anticanceroso *in silico* e *in vitro* para el cáncer de mama y de cuello uterino.

Métodos: Se realizó un ensayo *in silico* para predecir la actividad citotóxica utilizando AutoDock Vina. Esta actividad también se midió *in vitro* mediante ensayos con la técnica de microcultivo de tetrazolio en tres células cancerosas (MCF-7, T47D y HeLa) y células normales (células Vero).

Resultados: La prueba *in silico* predijo que la N-(4-t-butilbenzoil)-N'-feniltiourea era más citotóxica para el receptor del factor de crecimiento epidérmico que para el receptor de regulación-1 de la información de tipo apareamiento silencioso. Las pruebas *in vitro* mostraron que presentaba actividades citotóxicas contra las células MCF-7, T47D y HeLa sin dañar las células Vero.

Conclusiones: La N-(4-t-butilbenzoil)-N'-feniltiourea tiene potencial como candidato anticancerígeno para los cánceres de mama y de cuello uterino.

Palabras Clave: : cáncer de mama; cáncer de cuello de útero; EGFR; N-(4-t-butilbenzoil)-N'-feniltiourea; SIRT1.

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INTRODUCTION

Breast and cervical cancers account for the most cancer mortality in women (Indonesia Ministry of Health, 2019). However, the current use of chemotherapy still provides less than the desired maximum effect on cancers and tends to cause resistance, both of which underlie the necessity of developing new anticancer drugs (Kar, 2007; Tartarone et al., 2013; Tibes and Mesa, 2011).

Thiourea is a compound composed of sulfur and nitrogen atoms that shares a similar chemical structure with anticancer drugs such as hydroxyurea, nitrosourea, 5-fluorouracil, and sorafenib (Kesuma et al., 2018). However, hydroxyurea has been reported to cause resistance or intolerance in patients with essential thrombocythemia, and its use in chemotherapy has therefore started to decrease (Barosi et al., 2007). The resistance results from the poor ability of hydroxyurea to penetrate the membrane due to its hydrophilic nature (Koç et al., 2004).

Li et al. (2006) synthesized and tested the cytotoxic activity of several thiourea derivatives and found that some of them bound well to the epidermal growth factor receptor (EGFR), inhibiting tumor cell proliferation. In addition, thiourea derivatives are known to inhibit the growth of leukemia and solid tumors and are especially selective as a nonpeptide somatotropin release-inhibiting factor (SRIF) (Li et al., 2009). In breast cancer studies, *N*-(5-chloro-2-hydroxybenzyl)-*N*-(4-hydroxybenzyl)-*N*′-phenylthiourea is a phenylthiourea derivative that produces cytotoxic effects on MCF-7 cell line by inhibiting EGFR and HER-2 (Li et al., 2010). Also, compared with hydroxyurea, *N*-benzoyl-*N*'-phenylthiourea has a stronger *in vitro* anticancer activity against T47D cells (Kesuma et al., 2020a; 2020b). These previous studies revealed that thiourea and its derivative compounds have potent anticancer properties.

A derivative of *N*-benzoyl-*N*′-phenylthiourea, *N*-(4-*t*-butylbenzoyl)-*N*′-phenylthiourea (4-*t*-butyl-BPTU), has relatively high lipophilicity with EGFR and silent mating type information regulation 1 (SIRT1) enzyme as the molecular targets. Sirtuins are class III histone deacetylase enzymes (HDACs), whose activities are linked to gene expression, metabolic control, apoptosis, cell survival, DNA repair, inflammation, and neuroprotection (Qiu et al., 2015). Interactions between 4-*t*-butyl-BPTU and its molecular targets, EGFR and SIRT1 receptors, have been observed using an *in silico* assay. A smaller binding score (BS) derived from the assay indicates that the bond formed is more stable and that the test compound is predicted to exert stronger activities against the targets (Kesuma et al., 2020b).

In the present investigation, 4-*t*-butyl-BPTU was synthesized from phenylthiourea and 4-*t*-butylbenzoyl chloride using a method modified from the Schotten-Baumann nucleophilic substitution reaction (Jensen, 2007). Its purity and structure were tested using an IR spectrometer, ^{1}H-NMR spectrometer, ^{13}C-NMR, and mass spectrometer (Clayden et al., 2012). Furthermore, the cytotoxic activity was tested *in vitro* using the microculture tetrazolium technique (MTT) assays of three cancer cells, namely, MCF-7, T47D, and HeLa, and normal cells (Vero cells). This study aimed to determine the anticancer activity of 4-*t*-butyl-BPTU as anticancer candidates for breast and cervical cancers.

MATERIAL AND METHODS

Chemicals

N-phenylthiourea (Sigma Aldrich, Germany), benzoyl chloride (Sigma Aldrich, Germany), 4-tert-butylbenzoyl chloride (Sigma Aldrich, Germany). Tetrahydrofuran (THF) p.a (E.Merck, Germany), triethylamine (TEA) p.a (E.Merck, Germany), acetone p.a (E.Merck, Germany), ethyl acetate p.a (E.Merck, Germany), N-hexane p.a (E.Merck, Germany), chloroform p.a (E.Merck, Germany), ethanol p.a (E.Merck, Germany) and sodium bicarbonate ($NaHCO_3$) p.a (E.Merck, Germany), Kieselgel 60F254 (E.Merck, Germany).

Molecular modeling

The chemical structure of 4-*t*-butyl-BPTU was depicted in 2D with Marvin Sketch 19.17.0 and transformed into a 3D shape for optimization with Avogadro 1.2.0. The geometric structure was optimized using the Merck Molecular Force Field (MMFF94) and stored in.mol2 format.

In silico cytotoxic activity prediction

The cytotoxic activity was predicted *in silico* by docking 4-*t*-butyl-BPTU with EGFR (PDB ID:1M17) and Sirtuin-1 receptor (SIRT1) (PDB ID:4ZZJ) in AutoDock Vina 1.2.0 program. The binding scores (BS) produced in the docking were compared with those of the selected reference compounds, erlotinib, and hydroxyurea (HU).

Synthesis

The test compound, 4-*t*-butyl-BPTU, was synthesized by first reacting *N*-phenylthiourea with 4-*t*-butyl-benzoyl chloride in tetrahydrofuran (THF) with

the addition of triethylamine as a catalyst and then refluxing the mixture and conducting hourly thin layer chromatography (TLC). If a single stain appears, the reaction is stopped and continued by evaporating the THF in a rotary evaporator. Afterward, recrystallization was performed. The structure of the compound was identified using IR spectroscopy, ^{1}H-NMR, ^{13}C-NMR, and HRMS (Clayden et al., 2012; McMurry, 2011; Pavia et al., 2009).

Cytotoxic activity in MCF-7, T47D, HeLa, and Vero cells

To determine the cytotoxic activities of the test compound, 4-*t*-butyl-BPTU, and the reference compounds, erlotinib, and HU, an *in vitro* cell growth inhibition test was conducted using MCF-7, T47D, and HeLa cancer cells and normal cells (Vero cells) (Campestre et al., 2006). First, all the cell cultures were grown in a 96-well plate and incubated in a CO_2 incubator for 24 hours. Then, each culture well was added with the test and reference compounds of various concentrations and re-incubated. Next, the media in the plate was discarded, and 100 L of PBS was used to rinse the plate and then discarded. In the next step, 100 L of 0.5 mg/mL MTT reagent was added to the microplate, followed by a 4-hour incubation. The MTT reaction was later stopped by adding 100 L of 10% SDS 0.01 N HCl into each well to dissolve the formazan crystals formed after the incubation. Afterward, the microplate was wrapped in a paper and incubated at 37°C for 24 hours, then the absorbance was read using an ELISA reader at 595 nm, and the surviving fraction was calculated (Satria et al., 2019). The IC_{50} values of the test and reference compounds for cancer and normal cells observed were obtained using probit analysis.

Statistical analysis

The results of the percentage of living cells in the in vitro cytotoxic test were analyzed using probit regression to obtain the IC_{50} value. Probit analysis was performed using SPSS version 25. Variation of data expressed in standard deviation and the number of observations is shown in Table 1 (as one example).

RESULTS AND DISCUSSION

In silico cytotoxic activity prediction

Table 2 shows the binding scores and interactions between 4-*t*-butyl-BPTU and the EGFR and SIRT1 receptors. The binding score with the EGFR was lower than with the SIRT1 receptor. The docking with the former formed nine bonds, two of which were hydrogen bonds, while the docking with the latter produced four bonds without any hydrogen bonds. Hydrogen bonds have a higher binding strength than steric and electronic interactions (Siswandono, 2016). Therefore, 4-*t*-butyl-BPTU was predicted to have better cytotoxic activity at EGFR than the SIRT1 receptor. In addition, the -4-*t*-butyl group has relatively high lipophilic properties and is an electron-driving group that is slightly higher than the methyl group, which suggests that the addition of the -4-*t*-butyl group can produce a stronger cytotoxic activity at the EGFR than erlotinib.

Synthesis

The synthesis of 4-*t*-butyl-BPTU involved reacting *N*-phenylthiourea with 4-*t*-butyl-benzoyl chloride in tetrahydrofuran (THF) using triethylamine as a catalyst. As a result, it produced white crystals, water-insoluble crystals, melting points 127-128°C. The structure of the synthesized compound and spectrums of identification of the compound are shown in detail in Fig. 1.

N-(4-t-butylbenzoyl)-N'-phenylthiourea

White crystal, yield 87%, m.p. 127–128°C. ^{1}H NMR (DMSO-d6, 500 MHz). δ 1.36 (s, 9H, C(CH_3)$_3$; δ 7.28 (t, J=7.6 Hz, ^{1}H, Ar-H); δ 7.42 (t, J=7.6 Hz, 2H, Ar-H); δ 7.54 (d, J=8.6 Hz, 2H, Ar-H); δ 7.72 (d, J=7.6 Hz, 2H, Ar-H); δ 7.84 (d, J=8.6 Hz, 2H, Ar-H); δ 9.17 (s, ^{1}H, O=C-NH-C=S); δ 12.67 (s, ^{1}H, S=C-NH-Ar). ^{13}C NMR (DMSO-d6, 125 MHz). δ 31.1 (3C, C(CH_3)$_3$;); δ 35.3 (1C, C(CH_3)$_3$); δ 124.2 (2C, Ar); δ 126.3 (2C, Ar); δ 126.9 (2C, Ar); δ 127.6 (1C, Ar); δ 128.7 (2C, Ar); δ 128.9 (1C, Ar);137.7 (1C, Ar); δ 157.8 (1C, Ar); δ 167.0 (1C, C=O); δ 178.5 (1C, C=S). IR (KBr), v max(cm-1): 1676 (C=O amide); 1602 and 1497 (C=C Aromatic); 3224 and 1602 (NH stretch sec. amides); 1075 and 830 (C=S). HRMS (m/z) $C_{18}H_{19}N_2OS$: (M-H)- = 311.1210 and Calc. Mass = 311.1218.

In vitro cytotoxic activities

Table 3 summarizes the IC_{50} values of the test and reference compounds against MCF-7 and T47D breast cancer cells, HeLa cervical cancer cells, and Vero (normal cells). It shows that 4-*t*-butyl-BPTU had the lowest IC_{50} against MCF-7 cells among the cancer cells observed, meaning that its cytotoxic properties are the most potent to MCF-7 cells. In this case, it is better than HU and erlotinib. However, compared with 4-*t*-butyl-BPTU, erlotinib exhibited better cytotoxic activities against T47D and HeLa. To see the selectivity of the test and reference compounds against MCF-7, T47D, and HeLa cancer cells, Vero cells were used as normal cells. Selectivity Index (SI) is a selectivity parameter to measure the safety of a drug. SI is calculated using the formula [1].

$$Selectivity\ Index = \frac{IC_{50}\ normal\ cell}{IC_{50}\ cancer\ cells} \quad [1]$$

SI value of more than 2 indicates high selectivity (Purwanto et al., 2021; Rashidi et al., 2017). Based on Table 3, 4-*t*-butyl-BPTU had the highest selectivity for MCF-7 cells, followed by HeLa and T47D cells. Erlotinib had the highest selectivity against HeLa cells. The selectivity of 4-*t*-butyl-BPTU is the best compared to Hydroxyurea and Erlotinib.

The *in vitro* test results agree with the *in silico* predictions, 4-*t*-butyl-BPTU has the best *in vitro* cytotoxic activity against MCF-7 cells, which are known to express the EGFR, and the best *in silico* cytotoxic activity at the EGFR (GDP: 1M17) with a binding score of -8.51 kcal/mol (Li et al., 2010).

Furthermore, the *in silico* prediction revealed a weak cytotoxic activity at the SIRT1 receptor, which corresponds to the *in vitro* test results showing less potent cytotoxicity in T47D and HeLa cells than erlotinib. T47D cells express a mutated p53 protein, thus inactivating the p53 gene's ability to regulate the cell cycle (Schafer et al., 2000). HeLa cells also have the p53 gene, whose activity is inhibited by the expression of the E6 and E7 proteins of the human papillomavirus (HPV) (Goodwin and DiMaio, 2000). In addition, the activation of SIRT1 also contributes to disabling the tumor-suppressing function of the p53 gene, which is one of the keys to cell cycle regulation that drives cancer initiation, progression, invasion, and metastasis (Ong and Ramasamy, 2018). Therefore, SIRT1 activities can be found in T47D and HeLa.

Compared with 4-*t*-butyl-BPTU, HU demonstrated a significantly weaker cytotoxic activity due to poor membrane penetration, resulting from its hydrophilic characteristic.

The cytotoxic activity of 4-*t*-butyl-BPTU was very weak in Vero cells. It means that the compound can kill breast and cervical cancer cells with little to no impact on normal cells.

Table 1. Cytotoxic test of 4-*t*-butyl-BFTU on MCF-7 cells.

No.	Concentration (µg/mL)	Absorbance					Living cells (%)	Dead cells (%)	IC_{50} (µg/mL)
		I	II	III	Average	SD			
1	31.25	0.382	0.382	0.373	0.379	0.005	52	48	0.24 mM
2	62.5	0.378	0.396	0.339	0.371	0.029	51	49	
3	125	0.361	0.354	0.383	0.366	0.015	50	50	
4	250	0.339	0.342	0.345	0.342	0.003	45	55	
5	500	0.331	0.347	0.333	0.337	0.009	44	56	
6	1000	0.325	0.295	0.304	0.308	0.015	38	62	

Table 2. Binding scores and interaction binding between *N*-(4-*t*-butylbenzoyl)-*N*'-phenylthiourea and receptors.

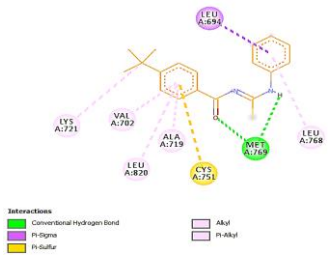
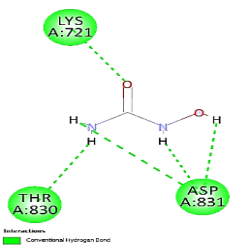
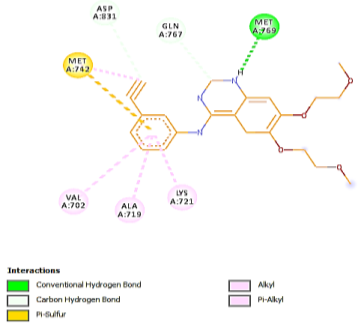
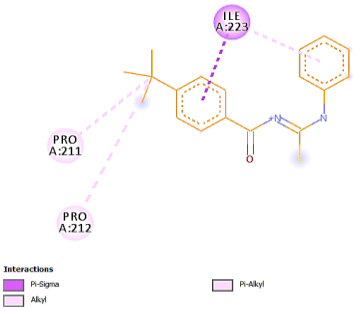
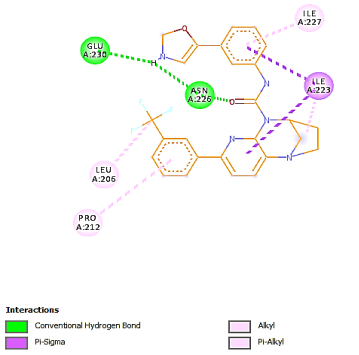
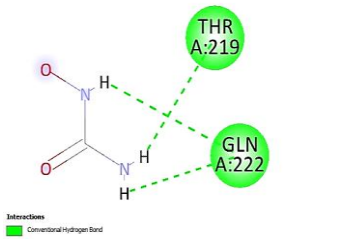
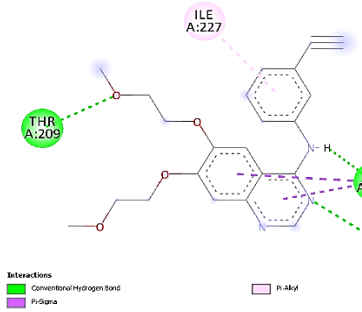
Ligands	PDB codes	Binding scores (kcal/mol)	Interaction binding
4-*t*-butyl-BPTU	1M17 (EGFR Receptor)	-8.51	
Hydroxyurea	1M17	-3.49	

Table 2. Binding scores and interaction binding between *N*-(4-*t*-butylbenzoyl)-*N*'-phenylthiourea and receptors (continued...)

Ligands	PDB codes	Binding scores (kcal/mol)	Interaction binding
Erlotinib (Original ligand)	1M17	-6.59	
4-*t*-butyl-BPTU	4ZZJ (SIRT1 Receptor)	-4.33	
(3S)-1,3-dimethyl-N-[3-(1,3-oxazole-5-il)phenyl]-6-[3-(trifluorome-thyl)phenyl]-2,3-dihydropyrido[2,3-b]pyrazin-4(1H)-carboxamide (Original ligand)	4ZZJ	-6.78	
Hydroxyurea	4ZZJ	-2.38	
Erlotinib	4ZZJ	-4.92	

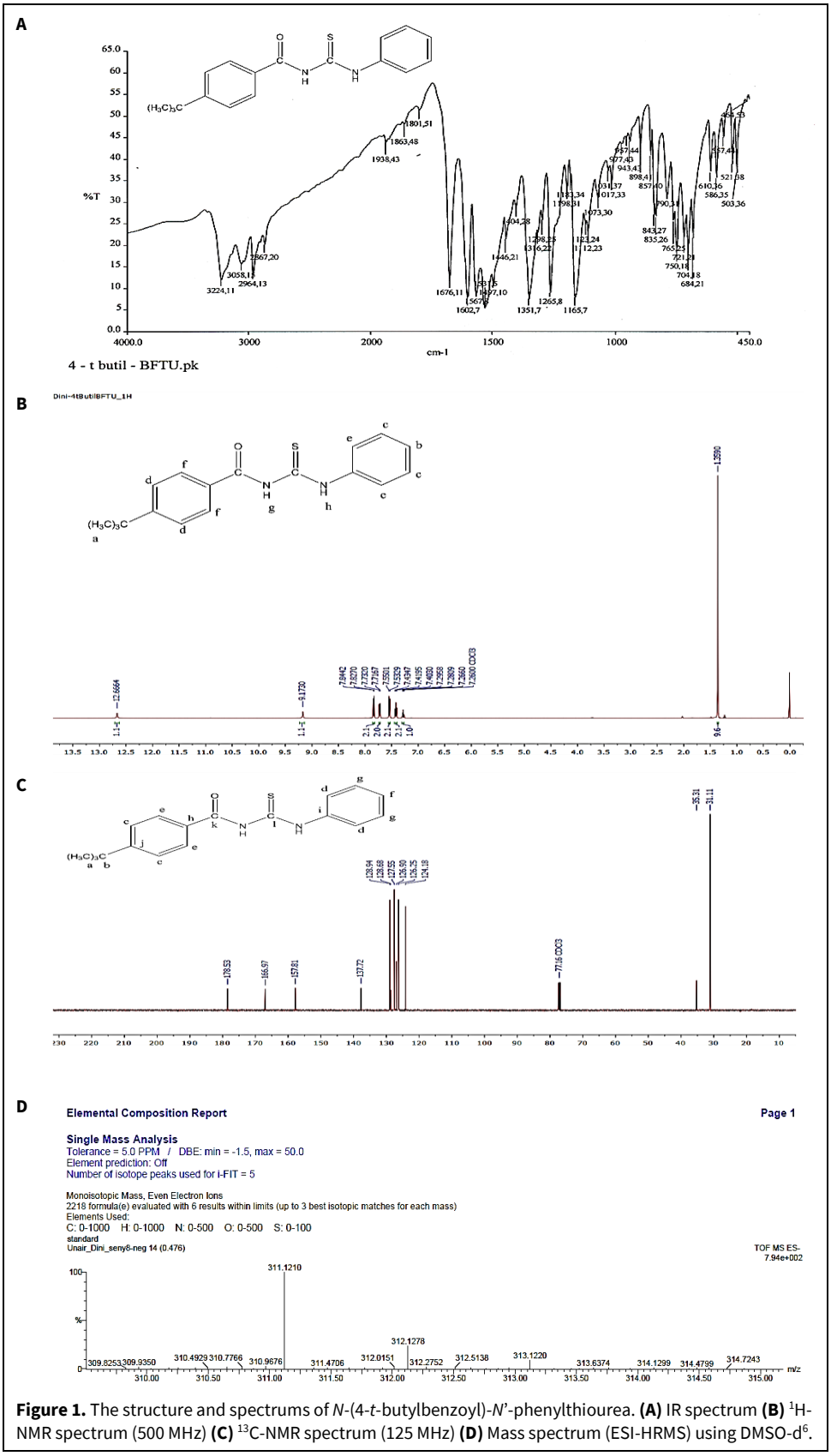


Figure 1. The structure and spectrums of *N*-(4-*t*-butylbenzoyl)-*N*'-phenylthiourea. **(A)** IR spectrum **(B)** ^{1}H-NMR spectrum (500 MHz) **(C)** ^{13}C-NMR spectrum (125 MHz) **(D)** Mass spectrum (ESI-HRMS) using DMSO-d^{6}.

Table 3. IC_{50} and SI of *N*-(4-*t*-butylbenzoyl)-*N*'-phenylthiourea, HU, and erlotinib against cancer and normal cells.

No.	Test and reference compounds	IC_{50} MCF-7 cells (mM)	IC_{50} T47D cells (mM)	IC_{50} HeLa cells (mM)	IC_{50} Vero cells (mM)	SI of compound against to MCF-7 cells	SI of compound against to T47D cells	SI of compound against to HeLa cells
1.	4-*t*-butyl-BFTU	0.24	0.80	0.49	429.64	1790	537	876
2.	Hydroxyurea	9.76	4.58	8.42	369.88	37	80	43
3.	Erlotinib	0.90	0.78	0.20	300.67	334	385	1503

CONCLUSION

The compound *N*-(4-*t*-butylbenzoyl)-*N*'-phenylthiourea show cytotoxic activity against breast and cervical cancer cells, making it a candidate for anticancer medicine.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Contribution	Kesuma D	Kirtishanti A	Makayasa CHA	Sumartha IGA
Concepts or ideas	x	x		
Design	x			
Definition of intellectual content	x	x	x	x
Literature search	x	x	x	x
Experimental studies			x	x
Data acquisition	x	x		x
Data analysis	x	x		x
Statistical analysis	x			
Manuscript preparation		x	x	
Manuscript editing		x	x	
Manuscript review	x	x	x	x

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15.- Original Article

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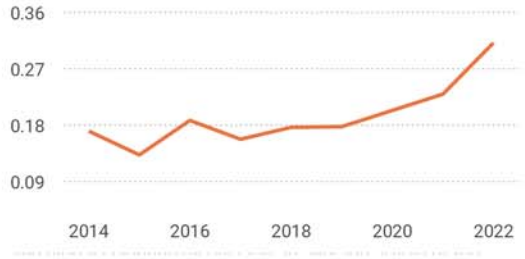

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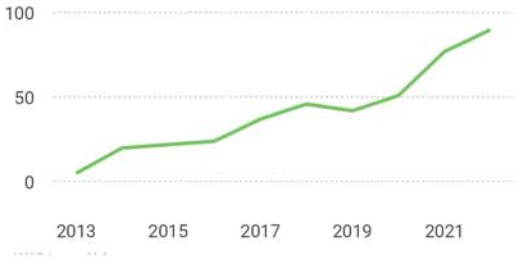

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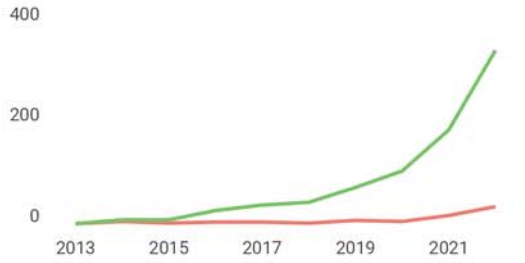

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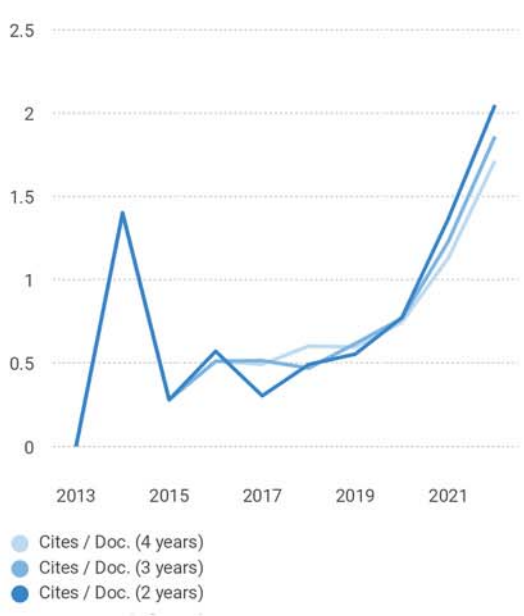

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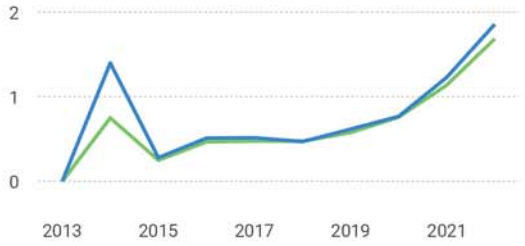

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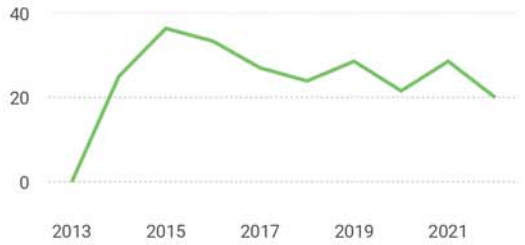

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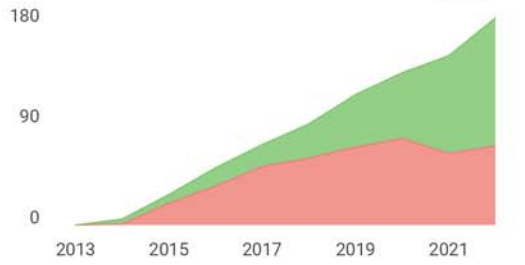

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