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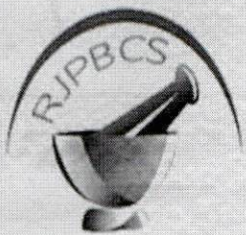
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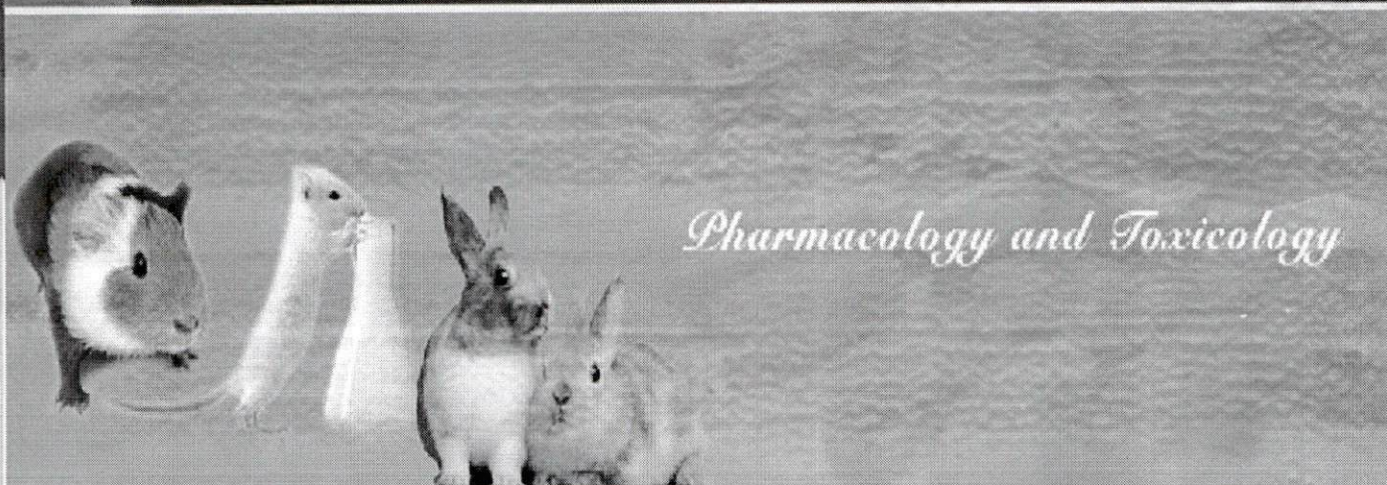
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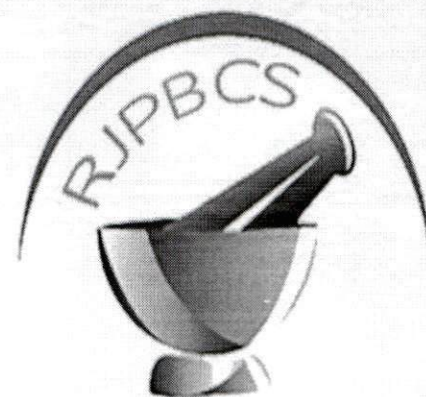
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Current Issue

RES J PHARM BIOL CHEM SCI
Volume 8, Issue 2, 2017 (March - April)

1. A Rare Case of Reversible Dementia In Old Age
Aravindan R*, Noorul Ameen, Ramakrishnan, Abhishek, and Manikandan. [Download PDF](#)
2. Tracheal Agenesis
Vahini P*, and Johnson WMS. [Download PDF](#)
3. A Case of Asymmetrical Lateral Ventricles with Normal Variant.
Aravindan R*, Noorul Ameen KH, and Manikandan. [Download PDF](#)
4. Secure Data Search Using One To Many OPE In Cloud.
Ravi Shankar R*, Rajesh B, and Chandu PMSS. [Download PDF](#)
5. Improvement role of curcuma longa against oxidative stress by lithium carbonate in the male rat.
Haider Salih Jaffat*. [Download PDF](#)
6. An Assessment of Autonomic Function Tests in Female Migraine Patients with Aura During Interictal Period.
Durgavati Tak*, Jyotsna Shukla, Bajrang Tak, Pooja Shukla, Kapil Dev Mathur, and Amitabh Dube. [Download PDF](#)
7. Comparison between oral midazolam and oral clonidine as a pre-anaesthetic medication in a paediatric age group for general anaesthesia.
Vikram Thamilselvam*, and Sekaran NK. [Download PDF](#)
8. An in vitro study on Hemiscorpiuslepturus (scorpionida: Hemiscorpiidae) venom cytotoxicity effects on K562 cells.
Nazanin Fathi, Mehri Ghafourian Broujerdnia, Babak Vazirianzade, Golnaz Rashidi, Mohammad Rashno and Ali Khodadadi*. [Download PDF](#)
9. Optimization and Performance Characteristics of Methyl Esters Produced from Chicken Fat
Selva Ilavarasi Panneerselvam*, and Lima Rose Miranda. [Download PDF](#)
10. Physico-chemical studies, indirect band gap energy and antitumor assay of some selected oxaloyldihydrazones and their cobalt(II) complexes.
Ayman H. Ahmed*, Ali M. Hassan, Hosni A. Gumaa, Bassem H. Mohamed, Ahmed M. Eraky, and Ahmed A. Omran. [Download PDF](#)
11. EPR and Spectral Investigations on Edible Green Leafy Vegetables.
Venkata Subbaiah Kotakadia, Babu Singarapu, Susmila Aparna Gaddam, Sucharitha KV, Sai Gopal DVR, and Rao JL, [Download PDF](#)
12. Influence of Dielectric Constant of Medium on Chemical Speciation of Co(II), Ni(II) and Cu(II) Complexes with 5-Hydroxysalicylic acid in DMF-Water Mixtures.
Balakrishna M, Srinivasa Rao G*, Ramanaiah M, Ramaraju B, and Nageswara Rao G. [Download PDF](#)
13. Phytochemical Analysis and Acute Toxicity Studies Of Methanolic Extract Of Stem Of Dalbergia lanceolaria, Flowers Of Dendrobium normale And Bark Of Measa indica.
Narsimha Rao Y*, and Naveen Babu K. [Download PDF](#)

- Monalisa Das, Moumita Das*, and Ambarish Mukherjee. [Download PDF](#)
209. **Docking and Cytotoxicity Test on Human Breast Cancer Cell Line (T47d) of N-(Allylcarbamothioyl)-3-chlorobenzamide and N-(Allylcarbamothioyl)-3, 4-dichlorobenzamide.**
Siswandono, Tri Widiandani*, and Suko Hardjono. [Download PDF](#)
210. **Antibacterial Effect of Gaseous Ozone In Infected Root Canal. In-Vivo Study.**
Nexhmije Ajeti, Teuta Pustina-Krasniqi*, Sonja Apostolska, Violeta Vula, Tringa Kelmendi, and Lindihana Emini. [Download PDF](#)
211. **Bioethanol Production Using Alginate from Sargassum binderi as an Immobilization Matrix for Saccharomyces cerevisiae D.01 cells in a Batch Reactor with Circulation.**
Yumechris Amekan*, and Guntoro. [Download PDF](#)
212. **Pharmacognostical with preliminary phytochemical studies of Iraqi Aswagandha (withania somniferaL.) plant.**
Ibrahim S. Aljubory, Thamer Mouhi jasiem*, Iman S. Jaafar, and Ameera A. Radhi. [Download PDF](#)
213. **Risk Factors Analysis of Social Media Networks.**
Bala Sundara Ganapathy N*, and Mohana Prasad K. [Download PDF](#)
214. **Analysis of Diesel Engine Characteristics with Selective Vegetable Oil Biodiesel.**
L. Karikalan*. [Download PDF](#)
215. **International Wheat Trade-- Proteinor Gluten?**
Agapkin AM, Karagodin VP, and Yurina OV*. [Download PDF](#)
216. **Formation Of The Yield And Grain Quality Of Winter Wheat Depending On Application Of Terraflex, A Water Soluble Complex Fertilizer.**
V7 Isaychev, VI Kostin, NN Andreev. [Download PDF](#)
217. **The Formation Of Crop Yield And Grain Quality In Winter Wheat In Dependence To Application Of Mineral Fertilizers And Growth Regulators**
VA Isaychev, NN Andreev*, VG Polovinkin, and SV Antonova. [Download PDF](#)
218. **Alternative Antibiotic Assessment Against Isolated Pathogenic Salmonella Typhi From Water Resources.**
El Dougdoug, KA; Nahed, MEI Aiate; Fatehi, A Khalifa and Nashwa, HA*. [Download PDF](#)
219. **Abundance of Paederus Sp, Micraspis Sp, Austrogomphus Sp, And Orthetrum Sp. In Paddy Field Using Cowpea and Mung Beans As Shelter At Paddy Dikes.**
Tamrin Abdullah*. [Download PDF](#)
220. **Molecular Phylogenetic Affinities of Endangered Trombidium Grandissim Using Mitochondrial 16S RDNA Sequence.**
Ramakrishna Y, Chittaranjan J, Krupanidhi S, and Jalaja N*. [Download PDF](#)
221. **Clinicopathological Profile of Breast Cancer Patients in Tertiary Hospital, Medan, Indonesia.**
Yolanda Sitompul, Sumaryati Syukur, Syafrizayanti, Edy Fachrial, and Endang Purwati*. [Download PDF](#)
222. **Probabilistic Standardized Risk Differences in Formation of Certain Disease Groups Among Adolescents.**
Valeeva ER*, Serazetdinova FI, Nigmatullina NA, Stepanova NV, Ziyatdinova AI, and Yusupova NZ. [Download PDF](#)
223. **Laxative effects of sea tangle (Laminaria japonica) snack in rats with low-fiber diet-induced constipation.**
Ki-Woong Kim, Choel-Woo Kim, Dong-Soo Kang, and Sun Hee Cheong*. [Download PDF](#)
224. **Clinicopathological Changes in Sera of Broiler Chicken Given Antibacterial and Or Prebiotics.**
Khaled Mohamed Elbayoumi*, Zelnab MS Amin Girh, Aziza M Amer, Eman R Hassan, and MM Amer. [Download PDF](#)
225. **An Insight Into Measuring Conductivity Of Solutions With Ease: A Review.**
Ali Abd Ali, Dhuha H. Fadhil, Emad Yousif*, Zainab Hussain, Sabah Abdul-Wahab, and Dheaa Zageer. [Download PDF](#)
226. **Electrical Resistivity: Concept And Measurement.**
Ali Abd Ali, Dhuha H. Fadhil, Emad Yousif*, Zainab Hussain, Ahmed Al-Hussin, Dheaa Zageer, and Salam Mohammed. [Download PDF](#)
227. **A Comprehensive Study of Conductive Polymer Matrix Composites: A Review.**
Ali Abd Ali, Dhuha H. Fadhil, Emad Yousif*, Zainab Hussain, and Sabah Abdul-Wahab. [Download PDF](#)



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Docking and Cytotoxicity Test on Human Breast Cancer Cell Line (T47d) of *N*-(Allylcarbamoithiopl)-3-chlorobenzamide and *N*-(Allylcarbamoithiopl)-3, 4-dichlorobenzamide.

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ABSTRACT

The specific objective of this research is to investigate the biological activity of thiourea derivatives by *in silico* study and the cytotoxicity test on human breast cancer cell lines. In this present study, the molecular docking of the new compound *N*-(allylcarbamoithiopl)-3-chlorobenzamide (BATU-02) and *N*-(allylcarbamoithiopl)-3,4-dichlorobenzamide (BATU-04) were evaluated on EGFR (1M17.pdb) using MVD v5.5 and showed that the re-rank scores of BATU-02 and BATU-04 are smaller than 5-fluorouracil (5-FU). From the docking result, we can predict that the compounds have a higher biological activity. The cytotoxicity test were evaluated on human breast cancer cell lines (T47D) using MTT assay. Relevant result showed that these compounds (BATU-02 and BATU-04) demonstrated are more potent compared to 5-FU as the commercial anticancer drug, with respective IC_{50} were 128 $\mu\text{g}/\text{mL}$ (BATU-02); 86 $\mu\text{g}/\text{mL}$ (BATU-04); and 213 $\mu\text{g}/\text{mL}$ (5-FU). It can be concluded that the modification compounds of thiourea can be further developed as a potential anticancer drug.

Keywords: Docking, thiourea, cytotoxicity, T47D, 1M17

*Corresponding author



INTRODUCTION

Cancer is one of the leading causes of death in the world and it is becoming a severe problem in the world of wellness. The success of cancer treatment is a challenge in the 21st century, so it underlines the most urgent to develop novel and safe chemotherapeutic agents with greater anticancer [1].

In the development of anticancer drugs, especially to obtain a better activity, it is performed modification of the structure of thiourea derivatives [2-4]. Thiourea derivatives constitute one class of anticancer promising for further development. This derivative work as inhibitors of EGFR to inhibit receptor tyrosine kinases (RTKs) in the intracellular region [5]. In addition, thiourea can also serve as a conjugate of the anti-EGFR monoclonal antibody [6,7].

In this study, the compounds have been made by reacting allylthiourea with benzoyl chloride derivatives (3-chloro and 3,4-dichloro) to form the compound *N*-(allylcarbamothioyl)-3-chlorobenzamide (BATU-02) and *N*-(allylcarbamothioyl)-3,4-dichlorobenzamide [9]. To predict the anticancer activity of the compounds, it is conducted in silico (docking) test using Molegro Virtual Docker version 5.5 that uses epidermal growth factor receptor (EGFR) kinase with pdb code 1M17, i.e. a receptor model of erlotinib constituting EGFR a receptor inhibitor [5,10].

The BATU-02 and BATU-04 are investigated for cytotoxicity activity in human breast cancer cell line (T47D) [12, 15]. The cytotoxicity test is determined through MTT method or 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide. IC₅₀ is determined based on 50% T47D cells alive. For comparability, it is used 5-fluorouracyl, an anticancer compound that has been used clinically for the treatment of cancer.

MATERIALS AND METHODS

In Silico

Materials: A computer (HP, core i7), Epidermal Growth Factor Receptor (1M17.pdb).

Method: The docking method is using Molegro Virtual Docker version 5.5. The docking began with a preparation on EGFR receptor with 1M17 code taken from the Protein Data Bank. The test ligand was prepared by making the 2-D and the 3-D structure of the compound using ChemBioOffice program Ultra 11.0 and its energy was minimized using MMF94. The result in Rerank Score describing the minimal energy required by the compound in interaction with the receptor [9].

In Vitro

Materials: (*N*-(allylcarbamothioyl)-3-chlorobenzamide (BATU-02), *N*-(allylcarbamothioyl)-3,4-dichlorobenzamide (BATU-04), 5-fluorouracyl (Sigma, USA); DMSO (Sigma, USA); *Rosewell Park Memorial Institute* (RPMI) 1640; 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide]= MTT (Sigma, USA); *Fetal Bovine Serum* (FBS) 10% (Gibco, USA).

Method: The Cytotoxicity assay was determined in vitro using cell lines T47D using the MTT method. This method required four test groups, namely the compound (A), a positive control (B), a control cell (C), and a control medium (D). It was prepared seven concentrations obtained from stratified dilution with RPMI medium (1000; 500; 250; 125; 62.5; 31.25; 15.625) µg/mL. T47D cell culture was prepared in the microplate of 96 wells, with a density of 5×10^3 cells/well.

MTT assay

The assay was carried out following Mossman method [16] with modification in stopper reagent. T47D cells were distributed into 96 well plates, then were incubated for 24 hours under CO₂. Test solutions in the series of concentrations were added, then the mixtures were incubated again for 24 hours. At the final stage of incubation, to each well was added MTT in PBS, then incubation was continued for 4 hours at 37 °C until formazan was formed. MTT reaction was stopped by addition of stopper reagent (SDS 10% in 0.01N HCl)

followed by overnight incubation at room temperature. Absorbance was read with an ELISA reader at 595 nm. The absorbance was converted to percentage of living cells (cell viability) [17].

RESULTS AND DISCUSSION

Docking

The result of preparing the structure of 2-Dimensional and 3-Dimensional of the *N*-(allylcarbamothioyl)-3-chlorobenzamide (BATU-02), *N*-(allylcarbamothioyl)-3,4-dichlorobenzamide (BATU-04) using ChemBio3D Ultra 11.0 program is shown in Figure 1 [12].

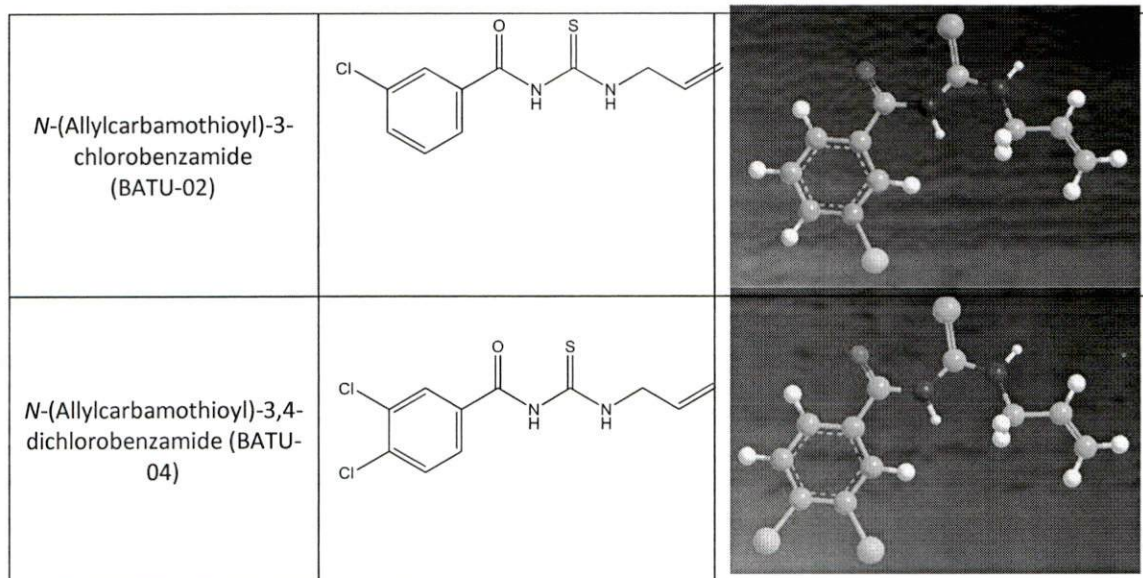


Figure 1: The structure of 2-Dimensional and 3-Dimensional of the *N*-(allylcarbamothioyl)-3-chlorobenzamide (BATU-02), *N*-(allylcarbamothioyl)-3,4-dichlorobenzamide (BATU-04) of which the energy has been minimized using MMFF94.

Docking results of 5-FU and BATU-02 and BATU-04 on EGFR kinase (1M17.pdb) can be seen in Table 1 [13].

Table 1: Docking Results of 5-FU and BATU Derivatives

Compound Code	Rerank Score
BATU-02	-94.4187
BATU-04	-93.1137
5-FU	-48.9354

From the docking results, the Rerank Score of all BATU derivatives is smaller than the Rerank Score of 5-FU. This suggests that the modified compound has smaller bond energy and so that the binding is more stable [14]. Thus, the modified compound can be expected to have greater biological activity by in silico test.

The overview of the amino acids involved in the interaction process of compounds between BATU-02 and BATU-04 versus EGFR is presented in Figure 2 [13].

Cytotoxicity Assay

Cell viability is converted from the absorbance of formazan formed after MTT treatment. Percentage of living cells (cell viability) after treatment of test compounds in different concentrations are presented in Table 2.

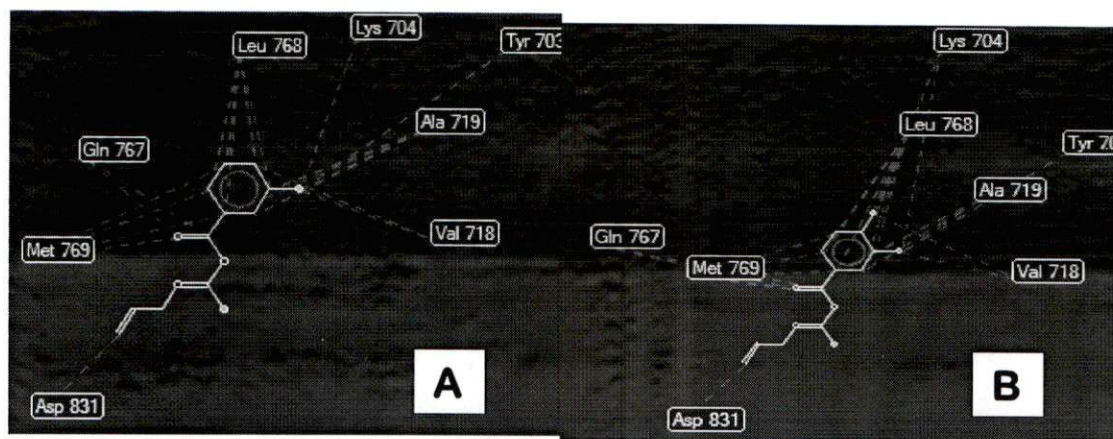


Figure 2: The amino acids involved in the interaction process of compounds between BATU-02 (A) and BATU-04 (B) and EGFR kinase (1M17)

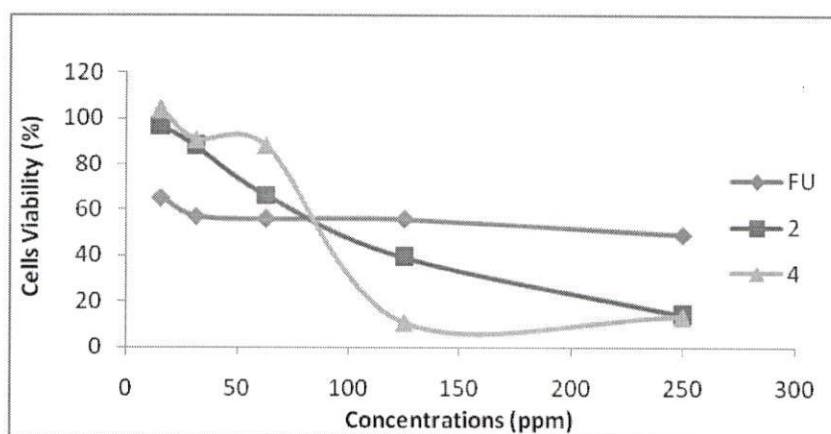


Figure 3: The cells viability overlay profile of 5-FU and BATU-02 and BATU-04

To provide clearer pictures on the influence of different concentrations of 5-FU and BATU-02 and 04 on cell viability, the data is plotted as profiles of cell viability as can be seen in Figure 3. It is obvious that cell viability is getting decreased as the concentration of 5-FU and BATU-02 and BATU-04 increased.

Table 2: T47D cells viability (%) after treatment at various concentrations

Compound	The percentage of living cells T47D (%) at various concentrations						
	15.625 $\mu\text{g/mL}$	31.25 $\mu\text{g/mL}$	62.5 $\mu\text{g/mL}$	125 $\mu\text{g/mL}$	250 $\mu\text{g/mL}$	500 $\mu\text{g/mL}$	1000 $\mu\text{g/mL}$
BATU-02	96.86 \pm 1.26	88.23 \pm 2.67	82.86 \pm 13.89	50.29 \pm 31.49	30.94 \pm 13.02	12.10 \pm 1.98	14.19 \pm 2.61
BATU-04	103.97 \pm 9.35	90.73 \pm 1.96	88.22 \pm 4.97	10.84 \pm 0.48	13.42 \pm 1.43	13.17 \pm 0.11	16.82 \pm 1.92
FU	61.70 \pm 7.98	54.23 \pm 4.07	52.91 \pm 2.66	52.85 \pm 4.58	46.58 \pm 4.96	39.41 \pm 2.19	27.28 \pm 1.05

Table 3: IC₅₀ of the test compounds on T47D

Compound	IC ₅₀ ($\mu\text{g/mL}$)
BATU-02	128 \pm 11.0
BATU-04	86 \pm 3.6
FU	213 \pm 2.2



The results of probit analysis to obtain the score of IC_{50} BATU-02; 04 and 5-FU as a comparison can be seen in Table 3.

Based on the cytotoxicity results on IC_{50} , it has been known that *N*-(allylcarbamoithiyl)-3-chlorobenzamide (BATU-02) and *N*-(allylcarbamoithiyl)-3,4-dichlorobenzamide (BATU-04) have higher cytotoxicity activity compared with 5-fluorouracyl. This result is linear with *in silico* approach. Therefore, these compounds are feasible to be developed as a potential anticancer drug.

CONCLUSION

Based on the results of this study can be concluded that the new compounds of thiourea derivatives (BATU-02 and BATU-04) can be further developed as a potential anticancer drug.

ACKNOWLEDGEMENTS

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