Synthesis and anticancer evaluation of N-benzoyl-N'-phenyltiourea derivatives against human breast cancer cells (T47D)

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Synthesis and anticancer evaluation of *N*-benzoyl-*N*′-phenyltiourea derivatives against human breast cancer cells (T47D)

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Abstract: New anti-breast cancer compounds have been found and may prove to have stronger activity. To predict the activities of *N*-benzoyl-*N*′-phenylthiourea (BPTU) derivatives, namely *N*-(3-chloro)benzoyl-*N*′-phenylthiourea (3-Cl-BPTU) and *N*-(3,4-dichloro) benzoyl-*N*′-phenylthiourea (3,4-2Cl-BPTU) with Sirtuin 2 receptor (PDB code: 4I5I), molecular docking was conducted at the beginning of this study. The compounds were then synthesized from benzoyl chloride derivatives and *N*-phenylthiourea. Molecular structure was confirmed using FTIR, ^{1}H NMR, ^{13}C NMR and Mass Spectra, while the anticancer activity was tested *in vitro* against human breast cancer cells (T47D) using MTT assay. The results indicated that the anti-cancer activities of the test compounds were better than those of the hydroxyurea as the reference compound, evidenced by the Rerank Score (RS). Furthermore, cytotoxic effect of 3-Cl-BPTU (IC_{50}: 0.43 mM) and 3,4-dichloro-BPTU (IC_{50}: 0.85 mM) showed better result compared with hydroxyurea (IC_{50}: 4.58 mM). Therefore, we concluded that these compounds could possess termendous potential as the candidate for a new anticancer drug.

Keywords: *N*-(3-chloro)benzoyl-*N*′-phenylthiourea; *N*-(3,4-dichloro)benzoyl-*N*′-phenylthiourea; Anticancer; T47D cells; SIRT1

CLC number: R914 **Document code:** A **Article ID:** 1003–1057(2020)2–123–07

1. Introduction

The incidence and mortality of cancer are rapidly growing worldwide. The reasons are complex but may be attributed to both aging and growth of the population, as well as changes in the prevalence and distribution of the main risk factors for cancer, several of which are associated with socioeconomic development[1]. The types of cancers that cause major mortality every year are lung, stomach, colorectal, liver, and breast cancers. Among all those cancers, breast cancer becomes the most deadly cancer for women[2].

In response to that, hydroxyurea has been widely used for cancer treatment as an anticancer drug. Nevertheless, the research data show that the antitumor activity of this substance does not come up with satisfying result due to its hydrophilic properties, which leads to poor membrane penetration capability. Inevitably, it is crucial to develop a new anticancer drug of urea and thiourea derivative that is more lipophilic with better membrane penetration to obtain more potent activities[3–5]. In addition, Mc Charty[6] has synthesized and evaluated the anticancer activity of thiourea derivatives, 1-(4-acetamidophenyl)-3-(4-tert-butyl benzoyl) thiourea, which is later named Tenovin-1. These compounds are known to increase p53 protein levels *in vitro* and inhibit SIRT1. Widiandani[7] has also proven the anti breast-cancer activity of T47D cells of the *N*-(allylcarbamothioyl) benzamide compound.

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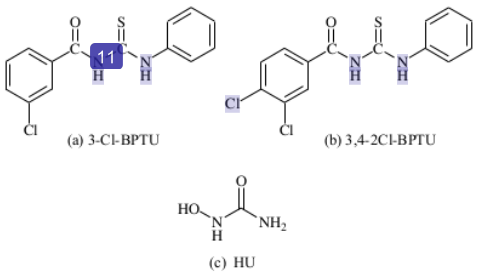


Figure 1. Structures of 3-Cl-BPTU (a); 3,4-2Cl-BPTU (b) and HU (c) compounds.

In the present study, the structure of *N*-benzoyl-*N*′-phenylthiourea (BPTU) compound was modified by adding chloro substituent to the benzoyl moiety. Two compounds were proposed, namely *N*-(3-chloro)benzoyl-*N*′-phenylthiourea (3-Cl-BPTU) and *N*-(3,4-dichloro) benzoyl-*N*′-phenylthiourea (3,4-2Cl-BPTU) (Fig. 1). Addition of phenyl groups and chloro-substituent at benzoyl moiety will improve the lipophilic and electronic properties of the compound. As a result, the binding affinity of the ligand to receptor will increase[8–10]. Previously, several BPTU compounds have been synthesized and shown their cytotoxic activity to T47D cells[11]. These breast cancer cells are used because they express the mutated p53 protein[12]. Within the present study, we performed the activity predictions by molecular docking of test compounds against Histon deacetylase SIRT1 inhibitor (PDB: 4I5I) using Molegro Virtual Docker 5.5[13]. This receptor plays an important role in the growth of tumor cells[14,15].

The test compounds were synthesized from *N*-phenylthiourea with benzoyl chloride derivatives (3-Cl and 3,4-2Cl) using acyl nucleophilic substitution reactions[16,17]. The structures of the synthesis compounds were identified using IR, ^{1}H NMR, ^{13}C NMR and mass spectrometers[18].

The anticancer activity of the test compound was determined through cytotoxic assay using MTT method (3-(4,5-dimetylthiazol-2-il)-2,5-diphenyltetrazolium bromide) *in vitro* on T47D breast cancer cells and Vero normal cells. The result of anticancer activity test on T47D cells was obtained as IC_{50} and compared with hydroxyurea, as well as observed in Vero normal cells[12,19].

It is expected to obtain a candidate of anticancer drug from the new class of thiourea derivatives that have potent anticancer activity on breast cancer cells T47D. This study will proceed with the synthesis of other *N*-benzoyl-*N*′-phenylthiourea (BPTU) derivatives to obtain QSAR equation and molecular mechanism test, before preclinical and clinical trials.

2. Materials and methods

2.1. Materials and tools

Materials for synthesis included *N*-phenylthiourea, benzoyl chloride derivatives (3-Cl and 3,4-2Cl) (Sigma Aldrich), tetrahydrofuran (THF), triethylamine (TEA), acetone, ethyl acetate, *n*-hexane, chloroform and ethanol, and those for activity test included 3-Cl-BPTU; 3,4-2Cl-BPTU and HU compounds, T47D and Vero cell cultures, culture media RPMI and M199, buffer saline phosphate (PBS), FBS (fetal bovine serum), tripsin, penicillin-streptomycin, fungizon, DMSO, MTT(3-(4,5-dimethyltiazole-2-yl)-2,5-diphenyltetrazolium bromide) 0.5 mg/mL, SDS 10% in HCl 0.01 N.

Corning Hot Plate P351, Fisher-John Electrothermal Mel-Temp, Jasco FT-IR 5300 Spectrophotometer, ^{1}H NMR Spectrometer and ^{13}C NMR Agilent 500 MHz with DD2 console system at 500 MHz (^{1}H) and 125 MHz (^{13}C), Mass Waters Spectrometer were used in the present study. Tool for cytotoxic test included 5% CO_2 incubator, LAF, micropipet, test tube, vortex, 96-well microplate, Conical tube, inverter microscope, hemocytometer, ELISA-reader. Tools for molecular modeling included ChemBioDraw Ultra 15.0, Molegro Virtual Docker (MVD) 5.5.

2.2. Methods

2.2.1. Molecular modeling

Activity prediction was conducted with molecular modeling of *N*-(3-chloro)benzoyl-*N*′-phenylthiourea and *N*-(3,4-dichloro)benzoyl-*N*′-phenylthiourea by docking with Histon deacetylase SIRT1 inhibitor PDB code: 4I5I followed by Software Molegro Virtual Docker 5.5., and hydroxyurea was used as reference compound.

2.2.2. Synthesis of 3-Cl-BPTU; 3,4-2Cl-BPTU compounds

Synthesis of *N*-(3-chloro)benzoyl-*N*′-phenylthiourea and *N*-(3,4-dichloro)benzoyl-*N*′-phenylthiourea compounds: In the round flask, *N*-phenylthiourea was mixed with tetrahydrofuran and TEA. Benzoyl chloride derivatives (3-Cl; 3,4-2Cl) solution was added to tetrahydrofuran, and the mixture was incubated in the ice bath. It was added gradually through a dropping funnel and stirred with a magnetic stirrer. The mixture was refluxed and stirred on top of a water bath. Just as a single spot appeared in the TLC , the reaction was terminated. THF was then completely evaporated on the rotary evaporator before recrystallization process started[7].

The identification of the structure of the synthesized compounds was performed based on the results of the examination: Infrared, ^{1}H NMR, ^{13}C NMR and HRMS[18].

2.2.3. Cytotoxicity test of MTT assay method

The test started with the distribution of T47D and M199 cells into 96-well plates 24 h prior to incubation in 5% CO_2 incubators, followed by adding test solutions, positive and negative controls in various concentration series. Each concentration was replicated for three times. Wells with no cells were filled with media as media controls and then re-incubated for 24 h. Before incubation ended, each well was added with 0.5 mg/mL of MTT up to 100 μL. The incubation proceeded for 3 h, and then the MTT reaction was discontinued by adding 100 μL SDS 10% in 0.01 N HCl to each hole. The microplate was wrapped in paper and incubated at 37 ºC for 24 h. The live cells converted MTT into a dark blue formazan. To identify the absorption at λ = 595 nm, ELISA reader was employed, and the IC_{50} values of the two test compounds as well as the reference compound were determined by using probit analysis[12].

3. Results and discussion

The RS values could describe drug activities *in silico* accordingly. On the basis of *in silico* test results as shown on Table 1, the RS of 3-Cl-BPTU compound was –120.4530. The RS of 3,4-2Cl-BPTU compound was –116.3190, and the RS of HU compound was –40.0237. The smaller the RS value is, the more stable the resulting drug-receptor interaction is, which corresponds to larger activity[20]. Table 2 and Figure 2 indicate the number and type of amino acids residues in the binding site. Based on the data, 3-Cl-BPTU compound had the largest number of hydrogen and steric bonds (van der Waals and Hydrophobic). This conclusion indicated that the anticancer activity of 3-Cl-BPTU compound was the best among the proposed compounds.

Two new compounds, namely: *N*-(3-chloro)benzoyl-*N*′-phenyltiourea and *N*-(3,4-dichloro) benzoyl-*N*′-phenyltiourea, were synthesized from benzoyl chloride derivatives with *N*-phenylthiourea in one step. The two compounds were yellow solids and insoluble in water. The structure of the compound was synthesized and identified by IR spectroscopy, ^{1}H NMR, ^{13}C NMR, and HRMS as follows:

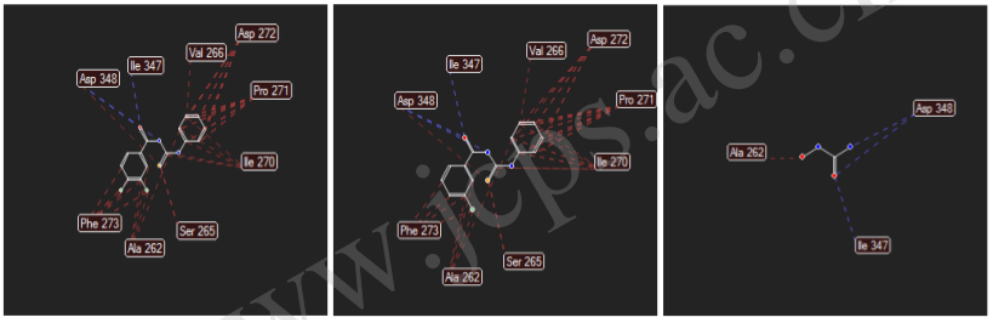
Table 1. Rerank score (RS) value.

Compounds	RS, PDB code: 4I51 (kcal/mol)
3-Cl-BPTU	−120.4530
3,4-2Cl-BPTU	−116.3190
HU	−40.0237

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

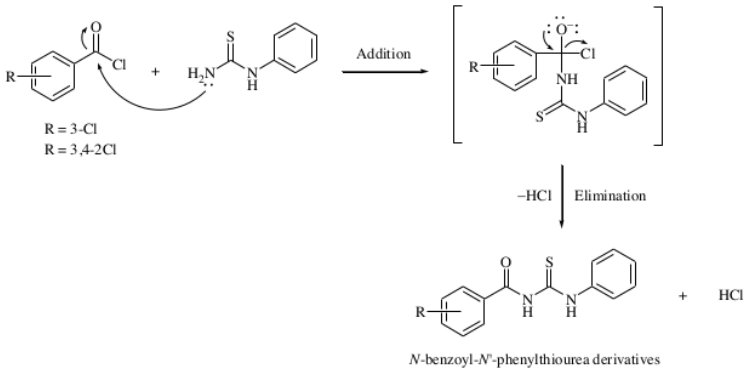
Compounds	Amino Acids								
	Ala262	Asp272	Asp348	Ile270	Ile347	Phe273	Pro271	Ser265	Val266
3-Cl-BPTU	4S	4S	1H/1S	5S	1H	5S	6S	1S	1S
3,4-2Cl-BPTU	3S	3S	1H/1S	5S	1H	4S	5S	1S	1S
Hydroxyurea	1S	–	2H	–	1H	–	–	–	–

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



(a) 3,4-2Cl-BPTU (b) 3-Cl-BPTU (c) HU

Figure 2. Ligand interaction with amino acids at the EGFR binding site where hydrogen bonds are indicated by blue dashed-lines and steric interruptions shown by red dashed-lines (a) 3,4-2Cl-BPTU compound, (b) 3-Cl-BPCT compound and (d) HU reference compound.



N-benzoyl-*N*'-phenylthiourea derivatives

Figure 3. Reaction on the synthesis of *N*-benzoyl-*N*'-phenylthiourea or *N*-(phenylcarbamothioyl)-benzamide derivatives.

3.1. *N*-(3-chloro)benzoyl-*N'*-phenyltiourea (3-Cl-BPTU)

Yellow crystal, m.p. 119 ºC. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.24 (t, J = 7.2 Hz, 1H, Ar-H); 7.39 (dd, J_1 = 7.2 Hz, J_2 = 8.0 Hz, 2H, Ar-H); 7.52 (t, J = 8.0 Hz, 1H, Ar-H); 7.66 (d, J = 8.0 Hz, 1H, Ar-H); 7.67 (d, J = 8.0 Hz, 2H, Ar-H); 7.88 (d, J = 8.0 Hz, 1H, Ar-H); 7.99 (s, 1H, Ar-H); 11.75 (s, 1H, O=C-NH-C=S); 12.46 (s, 1H, S=C-NH-Ar). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 124.84 (1C, Ar); 126.90 (2C, Ar); 127.95 (1C, Ar); 129.01 (1C, Ar); 129.22 (2C, Ar); 130.86 (1C, Ar); 133.29 (1C, Ar); 133.66 (1C, Ar); 134.76 (1C, Ar); 138.49 (1C, Ar); 167.42 (1C, C=O); 179.47 (1C, C=S). IR (KBr), ν maks (cm^{-1}): 1672 (C=O amide); 1672, 1451 (C=C Ar); 3219, 1592 (NH strech sec.amides); 1085, 811 (C=S). HRMS (*m/z*) $C_{14}H_{10}N_2OSCl$: $(M-H)^-$: 289.0200, Calc. Mass: 289.0202. δ *m/z* = 0.0002<0.005.

3.2. *N*-(3,4-dichloro)benzoyl-*N'*-phenyltiourea (3,4-2Cl-BPTU)

Yellow crystal, m.p. 140 ºC. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.30 (t, J = 7.4 Hz, 1H, Ar-H); 7.43 (t, J = 7.4 Hz, 2H, Ar-H); 7.63 (d, J = 8.3 Hz, 1H, Ar-H); 7.69 (d, J = 7.4 Hz, 2H, Ar-H); 7.72 (dd, J_1 = 8.3 Hz, J_2 = 2.2 Hz, 1H, Ar-H); 8.02 (d, J = 2.2 Hz, 1H, Ar-H); 9.06 (s, 1H, O=C-NH-C=S); 12.40 (s, 1H, S=C-NH-Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 124.28 (2C, Ar); 126.42 (1C, Ar); 127.28 (1C, Ar); 129.13 (1C, Ar); 129.96 (2C, Ar); 131.41 (1C, Ar); 131.49 (1C, Ar); 134.26 (1C, Ar); 137.51 (1C, Ar); 138.75 (1C, Ar); 164.88 (1C, C=O); 178.04 (1C, C=S). IR (KBr), ν maks (cm^{-1}): 1644 (C=O amide); 1608, 1496 (C=C Ar); 3216, 1608 (NH strech sec.amides); 1083, 816 (C=S). HRMS (*m/z*) $C_{14}H_9N_2OSCl_2$: $(M-H)^-$: 322.9818, Calc. Mass: 322.9813. δ *m/z* = 0.0005<0.005.

4. Conclusions

This study showed that two new compounds of *N*-benzoyl-*N'*-phenylthiourea (BPTU) derivatives, namely: *N*-(3-chloro)benzoyl-*N'*-phenylthiourea (3-Cl-BPTU) and *N*-(3,4-dichloro)benzoyl-*N'*-phenylthiourea (3,4-2Cl-BPTU) were successfully synthesized and showed higher *in vitro* anticancer activity against human breast cancer cells (T47D) compared with hydroxyurea anticancer drugs (Fig. 4). Furthermore, *in silico* study indicated that better inhibitory activity was related to a higher affinity with SIRT1 binding sites. The value of IC_{50} in *N*-(3-chloro)

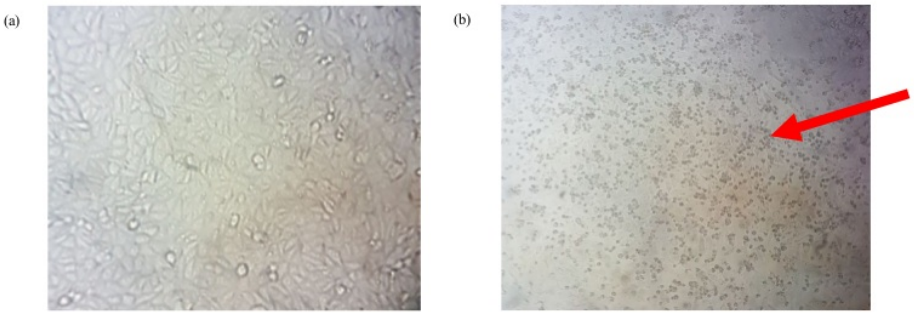


Figure 4. T47D cells before administration of a test compound: living cells condition (a) and red arrow shows: T47D cells after administration of a test compound (3-Cl-BPTU) with a dose of 500 µg/mL: the presence of dead cells after administration of a test compound (3-Cl-BPTU) (b).

Table 3. RS, IC_{50} T47D dan Vero cells value of 2 test compounds and reference.

Compounds	RS (kcal/mol)	IC_{50} T47D Cell Line (mM)	IC_{50} Vero Cell Line (mM)
3-Cl-BPTU	−120.4530	0.43	35.76
3,4-2Cl-BPTU	−116.3190	0.85	103.33
HU	−40.0237	4.58	–

benzoyl-*N'*-phenylthiourea was 0.43 mM and in *N*-(3,4-dichloro)benzoyl-*N'*-phenylthiourea was 0.85 mM, which was more active than the value in hydroxyurea (4.58 mM) (Table 3). These two new compounds were more compatible to binding enzymes compared with hydroxyurea, as they illustrated better inhibitory activities. It was predicted that the activities of these two new compounds were cell-targetted because they had toxic effects on cancer cells but were not toxic to Vero normal cells. Collectively, it is necessary to examine the molecular mechanisms of these two new compounds.

Acknowledgements

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References

[1] World Health Organization. Global Health Observatory. Geneva: World Health Organization. who.int/gho/database/en/. Accessed May 14, 2019. **2018**.

[2] Ministry of Health RI. Infodatin: Stop Cancer, Center for Data and Information Ministry of Health, (online). (accessible 14-05-2019). **2018**.

[3] Avendaño, C.; Menéndez, J.C. Drug targeting in anticancer chemotherapy. *Med. Chem. Anticancer Drugs.* **2015**, 595–653.

[4] Barosi, G.; Besses, C.; Birgegard, G.; Briere, J.; Cervantes, F.; Finazzi, G.; Gisslinger, H.; Griesshammer, M.; Gugliotta, L.; Harrison, C.; Hasselbalch, H.; Lengfelder, E.; Reilly, J.T.; Michiels, J.J.; Barbui, T. A unified definition of clinical resistance/intolerance to hydroxyurea in essential thrombocythemia: results of a consensus process by an international working group. *Leukemia*. **2007**, *21*, 277–280.

[5] Tibes, R.; Mesa, R.A. Blood consult: resistant and progressive essential thrombocythemia. *Blood.* **2011**, *118*, 240–242.

[6] McCarthy, A.R.; Pirrie, L.; Hollick, J.J.; Ronseaux, S.; Campbell, J.; Higgins, M.; Staples, O.D.; Tran, F.; Slawin, A.M.Z.; Lain, S.; Westwood, N.J. Synthesis and biological characterisation of sirtuin inhibitors based on the tenovins. *Bioorg. Med. Chem.* **2012**, *20*, 1779–1793.

[7] Widiandani T.; Arifianti L.; Siswandono. Docking, Synthesis, and Cytotoxicity Test Human Breast Cancer Cell Line T47D of *N*-(Allylcarbamothioyl)benzamide, *Int. J. Pharm. Clin*. **2016**, *8*, 372–376.

[8] Kesuma, D.; Siswandono., Purwanto, B.; T., Rudyanto, M. Synthesis of *N*-(phenylcarbamothioyl)-benzamide derivatives and their cytotoxic activity against MCF-7 cells. *J. Chin. Pharm. Sci*. **2018**. *27*, 696–702.

[9] Siswandono, Development of New Drugs. Surabaya: Airlangga University Press. **2014**.

[10] Kar, A. *Medicinal Chemistry*, 4th ed. New Delhi: New Age International Ltd Publishers. **2007**, 794–810.

[11] Kesuma, D.; Siswandono.; Purwanto, B.T.; Rudyanto, M. Docking, Synthesis and Cytotoxic Test On Human Breast Cancer Cell Line T47D of *N*-(Phenylcarbamothioyl)-benzamide. *World J. Pharm. Res*. **2018**, *7*, 70–78.

[12] Cancer Chemoprevention Research Center Faculty of Pharmacy UGM (CCRC-UGM), Fixed procedure Cytotoxic Test Method MTT. **2012**.

[13] *Manual Software Molegro Virtual Docker*. http://www.molegro/mvd-technology.php. downloaded 7/8/2015. **2011**.

[14] Li, H.Q.; Yan, Y.; Shi, L.; Zhou, C.F.; Zhu, H. Synthesis and structure-activity relationships of *N*-benzyl-*N*-(X-2-hydroxybenzyl)-*N'*-phenylureas and thioureas as antitumor agents. *Bioorg. Med. Chem.* **2010**, *18*, 305–313.

[15] Huhtiniemi, T.; Suuronen, T.; Rinne, V.M.; Wittekindt, C.; Lahtela-Kakkonen, M.; Jarho, E.; Wallén, E.A.A.; Salminen, A.; Poso, A.; Leppänen, J. Oxadiazole-carbonylaminothioureas as SIRT1 and SIRT2 inhibitors. *J. Med. Chem.* **2008**, *51*, 4377–4380.

[16] Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*, 2nd ed. New York: Oxford University Press. **2012**, 279–289.

[17] McMurry, J.M. *Fundamental of Organic Chemistry*, 7th ed., Belmont: Brooks/Cole. **2011**, 349.

[18] Pavia, D.L.; Lampman, G.M.; Kriz, G.S.; James R.; Vyvyan, J.R. *Spectroscopy.* 4th ed. Belmont: Brooks/Cole. **2009**, 851–886.

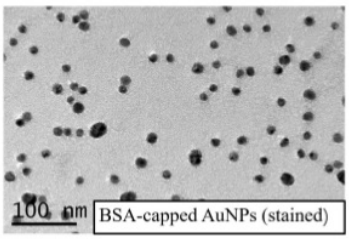
[19] Song, D.Q.; Du, N.N.; Wang, Y.M.; He, W.Y.; Jiang, E.Z.; Cheng, S.X.; Wang, Y.X.; Li, Y.H.; Wang, Y.P.; Li, X.; Jiang, J.D. Synthesis and activity evaluation of phenylurea derivatives as potent antitumor agents. *Bioorg. Med. Chem.* **2009**, *17*, 3873–3878.

[20] Hinchliffe, A. *Molecular Modelling for Beginners*, 2nd ed., Chichester: John Wiley and Sons Ltd. **2008**.

Author correction:

The authors regret to find that there is an error in the Figure 3(E) of their previously published paper (The adsorption of cellular proteins affects the uptake and cellular distribution of gold nanoparticles. **2016**, *25* (9): 651–659) due to the negligence in the process of assembling pictures. Although it does not affect the conclusion of the study, it is an obvious mistake. The authors have now modified the Figure 3(E) as below:

3 (E)



The authors would like to apologize for any inconvenience caused.

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