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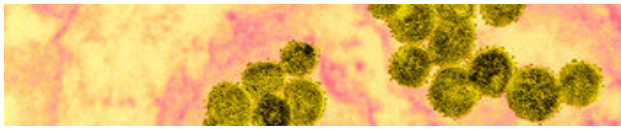
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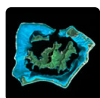
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
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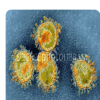
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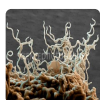
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New N-allylthiourea derivatives: Synthesis, molecular docking and in vitro cytotoxicity studies HTML (abstract.php?id=2233&aTitle=New N-allylthiourea derivatives: Synthesis, molecular docking and in vitro cytotoxicity studies) | Fulltext (../admin/12389900798187/2018_17_8_20.pdf)

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Apigenin exerts anticancer effects on human cervical cancer cells via induction of apoptosis and regulation of Raf/MEK/ERK signalling pathway HTML (abstract.php?id=2234&aTitle=Apigenin exerts anticancer effects on human cervical cancer cells via induction of apoptosis and regulation of Raf/MEK/ERK signalling pathway) | Fulltext (../admin/12389900798187/2018_17_8_21.pdf)

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Synergistic anticancer and antibacterial activities of cordycepin and selected natural bioactive compounds HTML (abstract.php?

Original Research Article

New N-allylthiourea derivatives: Synthesis, molecular docking and *in vitro* cytotoxicity studies

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Abstract

Purpose: To synthesise derivatives of N-allylthiourea and evaluate their anticancer activities against epidermal growth factor receptor (EGFR) using *in silico* and *in vitro* methods.

Methods: Four compounds were synthesized using the Schotten-Baumann reaction. The structures of the synthesized compounds were confirmed using infrared (IR), proton nuclear magnetic resonance (¹H-NMR), carbon nuclear magnetic resonance (¹³C-NMR) and electrospray ionization mass spectrometry (ESI-MS) methods. Molecular modeling was carried out with Molegro Virtual Docker version 5.5 through docking of the compounds onto the protein binding site of EGFR, with protein data bank (PDB) codes 1M17, 1XKK, and 3POZ. *In vitro* cytotoxicity was evaluated in MCF-7 cell lines using MTT assay.

Results: The synthesized compounds showed lower Rerank Scores, relative to N-allylthiourea and hydroxyurea. The low Rerank Score values implied stable molecular bonds, and hence higher biological activities. In addition, the derivatives showed cytotoxicities against MCF-7 cell line (IC₅₀: 0.21 – 0.38 mM) which were superior to those of N-allylthiourea (IC₅₀: 5.22 mM) and hydroxyurea (IC₅₀: 2.89 mM).

Conclusion: The predicted anticancer activities of the synthesized compounds are consistent with results from *in silico* studies and assays of cytotoxicity against MCF-7 cell lines. Thus, N-allylthiourea derivatives can potentially be developed as anticancer drugs.

Keywords: N-allylthiourea derivatives, *In silico*, Synthesis, Cytotoxicity, MCF-7, EGFR

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INTRODUCTION

Chemotherapy is one method of cancer treatment that works by inhibiting the growth of cancer cells or killing them. It is known that chemotherapy has many adverse side effects, such as hair loss, diarrhea, dry mouth, nausea,

vomiting, and fatigue [1]. Therefore, it is important to evolve newer, more effective and more selective anticancer agents [2,3]. In the present study, thiourea derivatives were developed as potential anticancer agents by modifying the structure of N-allylthiourea (ATU) [3-8]. The choice of N-allylthiourea was due to

its thiol group, a pharmacophore which is responsible for its biological activity. In addition, *N*-allylthiourea possesses a primary amine group (-NH₂). These groups allow for possible modifications that may lead to the development of ATU as an anticancer agent.

The chemical modification of the structure of *N*-allylthiourea was effected by reacting it with derivatives of benzoyl chlorides, resulting in generation of *N*-benzoyl-3-allylthiourea (**A** – **D**, Figure 1) using the Schotten-Baumann reaction [7]. In the first step, the amine group of *N*-allylthiourea reacted with the C-carbonyl of benzoyl chloride forming an amide, with the release of a proton and a chloride ion. The addition of the weak base, triethylamine (TEA) was necessary to neutralize the acidic proton formed, otherwise, the reaction would not have proceeded. Moreover, the addition of TEA blocked the protonation of the amine, a reaction which would have made it impossible for the base to react as a nucleophile [7].

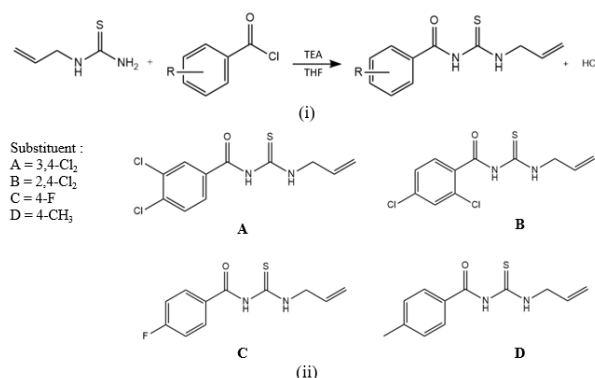


Figure 1: (i) Steps in the synthetic process according to the Schotten-Baumann procedure. (ii) Chemical structures of the four derivatives of *N*-allylthiourea: **A**. 3, 4-dichlorobenzoyl-3-allylthiourea; **B**. 2, 4-dichlorobenzoyl-3-allylthiourea; **C**. 4-fluorobenzoyl-3-allylthiourea; **D**. 4-methylbenzoyl-3-allylthiourea

Molecular modeling is usually conducted to examine the affinity of a ligand to its docking site through evaluation of the energy of drug-receptor binding. It has been shown that the evaluation of the interaction between a molecule and its docking protein involved in signal transduction may aid in identifying potential biological activity, as well as possible mechanisms of action [8,10,11]. Studies indicate that the 1M17, 1XKK, and 3POZ receptors are used as models of the epidermal growth factor receptor, EGFR [1,12]. The standard ligands for these receptors are erlotinib, lapatinib, and TAK-285, respectively (TAK-285 is a selective EGFR inhibitor) [12]. In addition, these receptors resemble thiourea derivatives (EGFR/HER-2 inhibitors) which act by inhibiting the tyrosine kinase receptor (RTKs) in

the intracellular region [13-15]. As inhibitors of EGFR, thiourea derivatives exhibit anti-proliferation activities against tumor cells, including human breast cancer cells [3,4,14].

One important parameter in molecular docking is the Rerank Score (RS). It is the energy of the ligand-receptor interaction, and a measure of bond energy between ligand and receptor [7,8,10]. The smaller the RS value, the more stable the bond between ligand and receptor. Therefore, a strong interaction implies a high biological activity [8].

In the present study, the cytotoxicities of *N*-allylthiourea and its derivatives against MCF-7 breast cancer cell line were investigated using MTT assay [6,16,18].

EXPERIMENTAL

Chemicals and reagents

N-Allylthiourea was purchased from Merck; 3, 4-dichlorobenzoyl chloride; 2, 4-dichlorobenzoyl chloride; 4-fluorobenzoyl chloride, and 4-methylbenzoyl chloride were products of Sigma-Aldrich. The reactions were monitored by Thin Layer Chromatography (TLC) carried out on silica gel 60 F₂₅₄ plates (Merck). Spot detection was performed at UV 254 nm [19]. Purification of the products was carried out by recrystallization [7,19].

Infrared spectra were measured using a Perkin-Elmer Spectrum One spectrophotometer and major absorptions were listed in cm⁻¹. ¹H-NMR (600 MHz) and ¹³C-NMR (150 MHz) spectra were measured on JEOL JNM-ECS 600 instrument with DMSO-d₆ as solvent and chemical shifts reported in ppm on the δ-scale. Positive ion HR-ESI-MS was accomplished by an Applied Biosystems QSTAR XL Nanospray™ system. *In silico* studies were carried out using Molegro® Virtual Docker version 5.5; 1M17, 1XKK, and 3POZ receptors were obtained from Protein Data Bank (www.pdb.org). The 2-D and 3-D structures of *N*-allylthiourea derivatives and the ligand were measured using ChemBio® Office Ultra 11.0 and MMFF94 for minimization of the energy [8,11].

Cell culture

MCF-7 cell lines were obtained from the Laboratory of Gene Regulation at Graduate School of Biological Sciences, Nara Institute of Science and Technology (NAIST), Japan. The cells were grown on high-glucose Dulbecco's modified Eagle's medium (DMEM; Nacalai

Tesque, Japan) containing 10 % fetal bovine serum (FBS) (Sigma, USA) and 1 % penicillin-streptomycin (Sigma, USA). The cells were harvested from culture dish using Trypsin-EDTA 0.25 % (Sigma, USA). The MTT reagent (5 mg/ml) was prepared by dissolving MTT (Nacalai, Japan) in phosphate-buffered saline (PBS).

Docking

Receptor and ligand were downloaded from Protein Data Bank. The ligand-receptor complexes were measured in the cavity. The 3-D structures of derivatives of *N*-allylthiourea were replaced to the fixed cavity. The ligands were docked towards the 1M17, 1XKK, and 3POZ receptors [12]. In the next step, Docking Score, Rerank Score, RMSD value, and the state of the environment of each compound derivative, such as hydrogen bonds, hydrophobic interactions, and electronic bonds, were determined [11,16,20].

Synthesis of *N*-allylthiourea derivatives

N-Allylthiourea (0.025 moles) was dissolved in 20 mL of tetrahydrofuran. Benzoyl chloride derivatives (1 eq) and triethylamine (7 mL) were slowly added to the solution, stirred for 30 min at room temperature, and refluxed for 3 - 4 h. Thereafter, the mixture was evaporated and washed with saturated aqueous sodium bicarbonate solution. The crude product was purified using column chromatography, with hexane: acetone (3:2); chloroform: hexane (5:2) and chloroform: hexane: ethyl acetate (1:6:2) as mobile phases at the indicated volume ratios. Recrystallization was done using ethanol: water at a volume ratio of 1:1 [7].

EVALUATION OF CYTOTOXICITY

The cytotoxic effects of the derivatives against MCF-7 cells were evaluated using MTT assay. The cells were seeded into 96-well plates at a density of 8×10^3 cells/well and incubated at 37 °C for 24 h in an atmosphere containing 5 % CO₂. The synthesized compounds were applied to the wells separately at different concentrations. After a 24-h incubation, MTT (5 mg/mL in PBS) was added to each well, and incubation was continued for 4 h at 37 °C to allow for formation of formazan crystals. Then, the reaction in each well was stopped by addition of the stopper reagent, a solution of 10 % sodium dodecylsulphate (SDS, Merck) in 0.01 N HCl (Merck), which also served to solubilize the formazan crystals. The plates were kept overnight in the dark at room temperature, after

which the absorbance of the formazan solution in each well was read at 570 nm in an ELISA plate reader [2,17,18].

RESULTS

Derivatives synthesized from *N*-allylthiourea

The desired derivatives were synthesized through nucleophilic substitution of *N*-allylthiourea with benzoyl chloride derivatives i.e. 3, 4-dichlorobenzoyl chloride; 2, 4-dichlorobenzoyl chloride; 4-fluorobenzoyl chloride, and 4-methylbenzoyl chloride, yielding compounds **A**, **B**, **C** and **D**, respectively (Figure 1). The detailed physicochemical and spectral data of the compounds are described below:

Compound (**A**) was obtained as a white crystal (49 % yield) with the following spectral characteristics: IR (cm⁻¹) = 1672; 3467; 1548; and 1447; ¹H-NMR δ_H (ppm, *J* in Hz) = 4.30 (t, *J* = 5.2, 2H), 5.20 (d, *J* = 12, 1H), 5.25 (d, *J* = 3, 1H), 6.00 - 5.93 (m, 1H), 7.88 (d, *J* = 6, 2H), 7.89 (d, *J* = 6, 2H), 8.21 (s, 1H), 10.83 (s, 1H), and 11.61 (s, 1H); ¹³C-NMR δ_C (ppm) = 46.86, 116.69, 128.81, 130.57, 130.63, 131.18, 132.71, 132.96, 135.64, 165.80, and 180.09; HR-ESI-MS *m/z* = 288.9222 [M + H]⁺ (calculated value for C₁₁H₁₂ON₂Cl₂S = 288.9262). These spectral data agreed with the structure of 3,4-dichlorobenzoyl-3-allylthiourea (**A**).

The synthesized compound (**B**) was a white crystal obtained at a yield of 75 %. Its spectral data were: IR (cm⁻¹) = 1684, 3467, 1585 and 1425; ¹H-NMR δ_H (ppm, *J* in Hz) = 11.81 (s, 1H), 10.64 (s, 1H), 7.75 (d, *J* = 2, 1H), 7.62 (d, *J* = 8.3, 1H), 7.54 (d, *J* = 5.1, 1H), 6.02-5.92 (m, 1H), 5.25 (d, *J* = 10.3, 1H), 5.20 (d, *J* = 1.6, 1H), and 4.29 (t, *J* = 3.6, 2H); ¹³C-NMR δ_C (ppm) = 180.24, 167.09, 136.17, 133.88, 133.45, 131.66, 131.03, 129.54, 127.80, 117.33 and 47.31; HR-ESI-MS *m/z* = 288.9966 [M + H]⁺ (calculated value for C₁₁H₁₁ON₂Cl₂S = 288.9969). These spectral data agreed with the structure of 2,4-dichlorobenzoyl-3-allylthiourea (**B**).

Compound (**C**) was a white crystalline salt (48 % yield) with the following spectral data: IR (cm⁻¹) = 1674; 3429; 1568 and 1449; ¹H-NMR δ_H (ppm, *J* in Hz) = 4.30 (t, *J* = 12, 2H), 5.20 (d, *J* = 12, 1H), 5.26 (d, *J* = 18, 1H), 6.00-5.94 (m, 1H), 7.36 (t, *J* = 18Hz, 2H), 8.03 (t, *J* = 12, 2H), 10.93 (s, 1H), and 11.43 (s, 1H); ¹³C-NMR δ_C (ppm) = 46.83, 115.42, 116.65, 128.73 and 131.55 (2C); 133.05, 164.00, 166.99, 180.30; HR-ESI-MS *m/z* = 239.0650 [M + H]⁺ (calculated value for C₁₁H₁₂ON₂FS = 239.0654). These spectral data

agreed with the structure of 4-fluorobenzoyl-3-allylthiourea (**C**).

The derivative compound (**D**) was a white crystal (35 % yield). Its spectral features were: IR (cm^{-1}) = 1663, 3467, 1609 and 1448; $^1\text{H-NMR}$ δ_{H} (ppm, J in Hz) = 11.26 (s, 1H), 11.00 (s, 1H), 7.87 (d, J = 8.2, 2H), 7.33 (d, J = 7.9, 2H), 6.02-5.93 (m, 1H), 5.28 (d, J = 42, 1H), 5.20 (d, J = 12, 1H), 4.30 (t, J = 3.6, 2H), and 2.39 (s, 3H); $^{13}\text{C-NMR}$ δ_{C} (ppm) = 180.176, 166.847, 144.736, 131.941, 129.929, 128.861 (2C), 127.574 (2C), 117.801, 48.160, 21.769. HR-ESI-MS m/z = 235.0900 [$\text{M} + \text{Na}$] $^+$ (calculated value for $\text{C}_{12}\text{H}_{15}\text{ON}_2\text{S}$ = 235.0905). These were consistent with the structure of 4-methylbenzoyl-3-allylthiourea (**D**).

Docking results

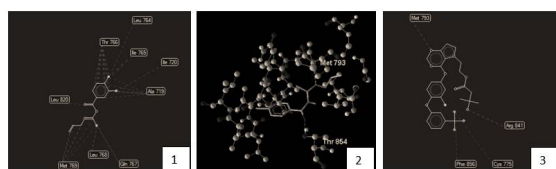


Figure 2: The amino acids involved in the interaction process between ligands in epidermal growth factor receptor. (1) 2-D interaction of compound A with 1M17; (2) H-bond interaction with 1XKK in 3-D illustration; and (3) 2-D interaction of ligand standard TAK-285 with 3POZ

The interaction between the synthesized compounds (ligands) and amino acid residues are shown in Table 1 and illustrated in 2D in Figure 2.

The docking scores with respect to interaction with epidermal growth factor receptors were obtained using the Molegro Virtual Docker as shown in Table 2.

Cytotoxicity of compounds A - D

The cytotoxic activities of the four derivatives were assessed using MTT assay, and the results are shown in Table 2. The viabilities of the cells obtained from the measurement of the absorbance of formazan formed after treatment with MTT reagent, and representative morphologies of MCF-7 cell line after treatment are shown in Figure 3.

DISCUSSION

In drug development and discovery, it is important to ensure that the drug-like physicochemical properties are maintained as described by Lipinsky's rule [9]. Most orally-administered drugs are relatively small and moderately lipophilic molecules.

Table 1: Interactions between the synthesized compounds (ligands) and amino acid residues in the EGFR receptor

Code	1M17		3POZ		1XKK	
	H-bond	Steric bond	H-bond	Steric bond	H-Bond	Steric bond
A	Met769	Met769, Thr766, Leu820, Leu768, Ile765, Gln767, Ala719	Met793, Thr854	Met793, Gly796, Gln791, Thr790, Val726, Ile744, Ala743, Ile789, Leu788	Met793, Thr854	Leu792, Thr790, Gln791, Ala743, Ile744, Ile789, Gly796, Met793
B	Met769	Met769, Thr766, Leu820, Leu768, Leu764, Ile765, Ile720, Gln767, Ala719	Met793, Thr854	Met793, Gly796, Gln791, Thr790, Val726, Ile744, Ala743, Ile789, Leu788	Met793, Thr854	Leu792, Leu788, Thr790, Gln791, Ala743, Ile789, Gly796, Met793
C	Met769	Met769, Thr766, Leu820, Leu764, Leu768, Ile765, Gln767, Ala719	Met793, Thr854	Met793, Gly796, Gln791, Thr790, Ala743, Ile789, Leu788	Met793, Thr854	Leu788, Thr854, Thr790, Gln791, Ala743, Ile789, Gly796, Met793
D	Met769	Met769, Thr766, Leu820, Leu764, Leu768, Ile765, Gln767, Ala719	Met793, Thr854	Met793, Gly796, Gln791, Thr790, Ala743, Ile789, Leu788	Met793, Thr854	Leu788, Thr854, Thr790, Gln791, Ala743, Ile789, Gly796, Met793
ATU	-	Met769, Leu768, Gln767, Leu820	-	Met793, Thr790, Gln791, Leu844	-	Met793, Thr790, Gln791, Leu844
HU	-	Met769, Leu768, Gln767	-	Met793, Gln791	-	Met793, Thr790, Gln791
SL	Met769	Met769, Gln767, Gly772, Pro770, Asp831	Met769, Arg841	Phe856, Cys775	Met793	Gln791, Arg776, Thr790, Leu788, Asp800, Cys797

Note: ATU = Allylthiourea; HU = hydroxyurea; SL = standard ligand

Table 2: Docking (RS) and IC₅₀ data

Compound	Substituent	Docking Score (kcal/mol)*			IC ₅₀ (mM) ±SD
		1M17	1XKK	3POZ	MCF-7
A	3,4-Cl ₂	-94.7885	-90.8922	-81.6869	0.213±1.61
B	2,4-Cl ₂	-94.1892	-88.2606	-75.4107	0.231±1.34
C	4-F	-91.2717	-89.1355	-80.7994	0.261±1.92
D	4-CH ₃	-68.5424	-84.8147	-76.6435	0.230±1.05
ATU	-	-42.2023	-55.9170	-56.4322	5.219±1.81
HU	-	-44.2384	-44.2922	-41.3393	2.793±1.66

*Rerank Score is the value of energy after re-ranking by considering RMSD factor and chemical bonds involved [15].

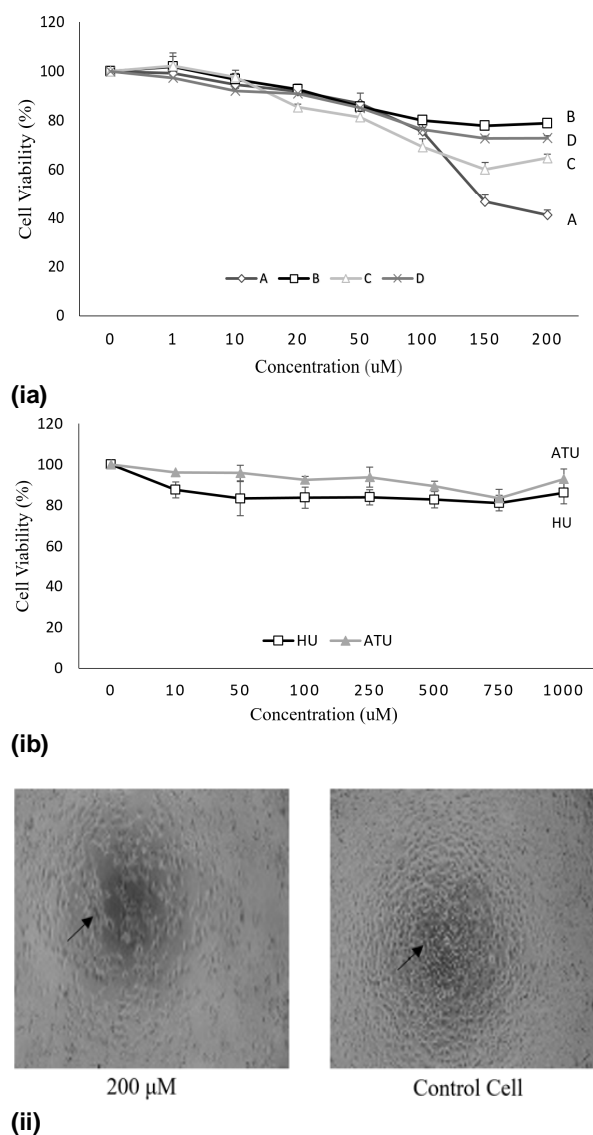


Figure 3: (i) Effect of compounds A-D on viability of MCF-7 cells. (1a): Hydroxyurea (HU) and *N*-allylthiourea (ATU); (1b) Effect on serial concentrations of HU and ATU on viability of MCF-7 cells; (ii) Effect of compound A (200 μM) on viability of MCF-7 cells, relative to control cells. Treatment with the synthesized compounds changed the morphology of MCF-7 cell line after 24-h incubation. Cell morphology was observed using an inverted microscope at a magnification of x100.

Chemdraw[®] is a helpful tool for predicting the lipophilicity of organic compounds [8]. The log P values of *N*-benzoyl-3-allylthiourea, *N*-allylthiourea and hydroxyurea are 2.0450, 0.0799, and -1.8000, respectively [7]. The higher the log P value, the more lipophilic the compound. Based on this parameter, the derivatives of *N*-allylthiourea are more lipophilic than *N*-allylthiourea and hydroxyurea. Thus, theoretically, the derivatives of *N*-allylthiourea can penetrate the cell membrane more easily, and so possess higher biological activities than the parent compound. The infrared spectra of the synthesized compounds **A-D** showed peaks above 1663 - 1684 cm⁻¹, indicating the presence of C=O carbonyl groups in their structures. Furthermore, the chemical structures of compounds **A-D** were confirmed through several parameters such as ratio of protons as seen from integrations and splitting patterns of the peaks in ¹H-NMR spectra, number of peaks in ¹³C-NMR spectra, and the exact mass of molecular ion measured by HR-MS.

Based on *in silico* studies on the interactions between the ligands and EGF receptor, compound **A** interacted with amino acid residues such as Met769, Met793, and Thr854 through steric bonds and H-bonds. The interactions of other compounds (**B, C and D**) followed a similar pattern. The synthesized compounds exhibited the same ATP binding site for the H-bond binding of the amino acid residues Met793 and Met769 to the EGFR. However, *N*-allylthiourea and hydroxyurea bound amino acid residues only through steric bonds: H-bonds were not involved.

The presence of the lipophilic benzoyl group in *N*-benzoyl-3-allylthiourea resulted in enhanced biological activity due to stabilization of the ligand-receptor bond. This is consistent with the Rerank Score values of the *N*-allylthiourea derivatives (compounds **A - D**) which were lower than those of *N*-allylthiourea (lead compound) and hydroxyurea (clinically-used anticancer drug). The addition of substituents with certain lipophilic, electronic and steric properties improves the stability of ligand-receptor bonds.

The variation of substituents on *N*-benzoyl-3-allylthiourea caused differences in the number of interaction with amino acids. However, it did not bring about significant differences in Rerank Score values. From the results of *in silico* studies, some derivatives of *N*-allylthiourea were predicted to have greater anticancer activities than hydroxyurea. The results of *in vitro* cytotoxicity performed on MCF-7 cell lines using the MTT method revealed that the IC₅₀ of compounds **A - D** (0.21 – 0.38 mM) were less than that of *N*-allylthiourea (IC₅₀ = 5.22 mM). These results indicate that the four derivatives of *N*-allylthiourea were more cytotoxic than the lead compound, *N*-allylthiourea. In addition, cytotoxicity studies revealed that all derivatives of *N*-allylthiourea were more cytotoxic against MCF-7 cell lines when compared to the commercial anticancer drug, hydroxyurea (IC₅₀ = 2.79 mM).

CONCLUSION

Molecular docking data have predicted that *N*-allylthiourea derivatives are epidermal growth factor receptor inhibitors. This is supported by results from cytotoxicity studies using MCF-7 cancer cell lines. Therefore, *N*-allylthiourea derivatives possess potential anticancer properties that can be harnessed for the development of new anticancer drugs.

DECLARATIONS

Acknowledgement

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities

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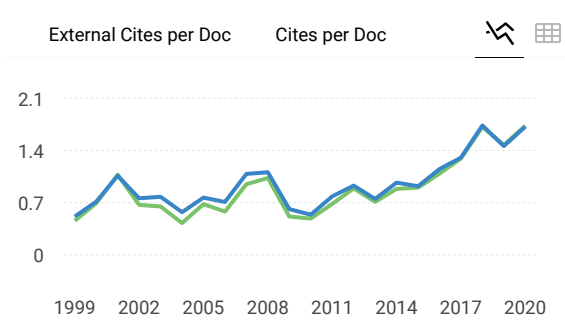
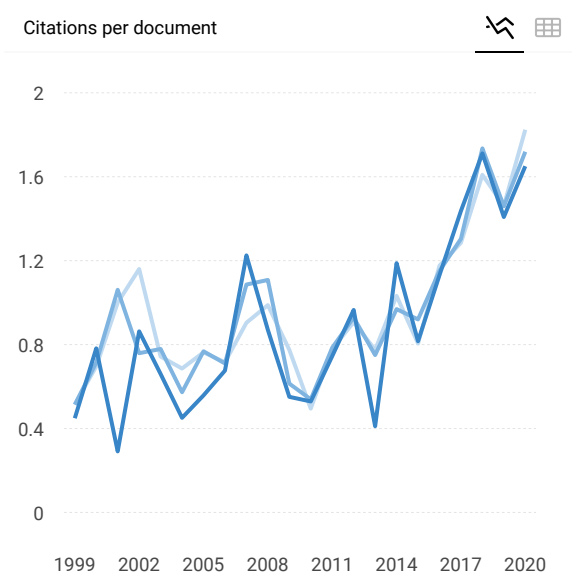
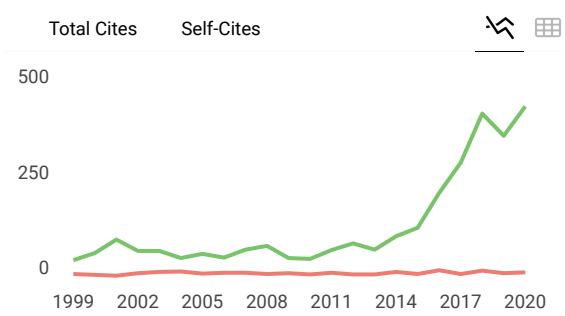
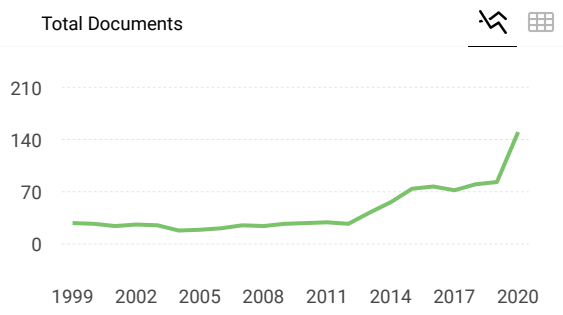
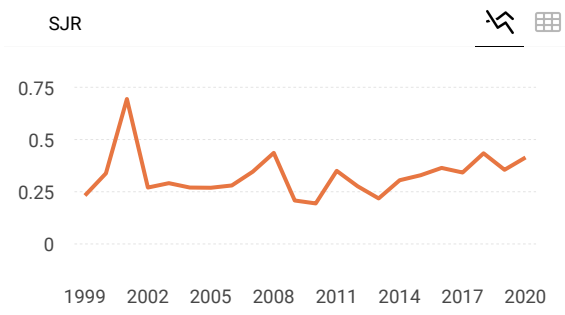
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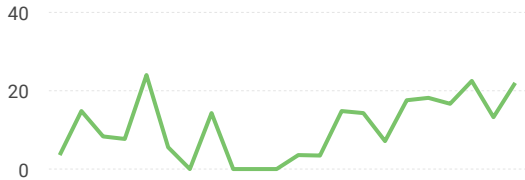


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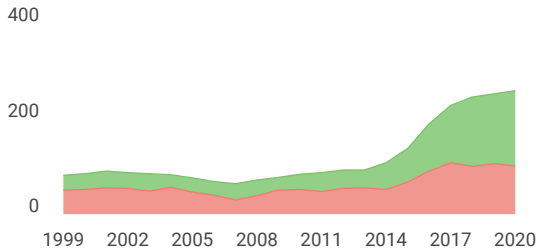
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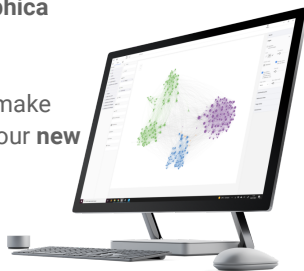
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