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Synthesis, anticancer activity, and apoptosis mechanism of some chalcone derivatives

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Hery Suwito, Helda Dwi Hardiyanti, Kautsar ul Haq, Alfinda Novi Kristanti, Umrotul Furghoniyyah, Aprillia Noni Rahmawati, and Diwyareta Ristya Ayuningtyas

Synthesis, Anticancer Activity, and Apoptosis Mechanism of Some Chalcone Derivatives

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Abstract. The research for finding new cancer agents with good efficacy and low toxicity is still in demand because this disease is still counted as main cause of death worldwide. Chalcone derivatives are known as prospective sources to find potent anticancer agent. Some amino chalcone and coumarin chalcone derivatives have been successfully synthesized from the reaction of 4'-amino acetophenone, acetyl coumarin, and derivatives of benzaldehyde by Claisen-Schmidt reaction. The molecular structure of the prepared compounds was determined by spectroscopic evidence including IR, ESIMS, ^{1}H- and ^{13}C-NMR. Anti-proliferative activity of the prepared compounds is examined using MTT reagent. Apoptosis and cell cycle inhibition were determined by the flow cytometer. Double staining using orange acridine – etidium bromide was used to determine morphologically cancer cells underwent apoptosis. The IC_{50} value of anti-proliferative examination ranging from 30.4 µg/mL to more than 100 µg/mL toward T47D cells and from 27.5 µg/mL to more than 100 µg/mL toward HeLa cells. Compound **2** (*E*)-1-(4-aminophenyl)-3-(4-fluoro-phenyl)prop-2-en-1-one exhibited the most active anticancer activity through induction apoptosis mechanism. It caused cell cycle arrest at G0/G1 and G2/M phase both for HeLa cells and T47D cells. Additionally, it also blocks S phase for T47D cells.

INTRODUCTION

Cancer is a group of diseases indicated by uncontrolled cells growth and are still considered as one of main cause of death worldwide because it was responsible for 8.8 million deaths in 2015. Globally, nearly 1 in 6 deaths is due to cancer. Statistically 70% of deaths from cancer occur in low- and middle-income countries meanwhile it is estimated 1.7 million new cancer cases to occur in the South East Asia region. Breast and cervix cancer are the two most common cancer reported among women in the region [1]. Chemotherapy is one effective treatment method for cancer therapy. However, the problems arising in cancer chemotherapy are resistance of the cancer cells toward applied drugs, severe side effects, and necrosis. Therefore, finding new cancer agents possessing high efficacy but low toxicity is still in demand.

Chalcone (1,3-diaryl-2-propen-1-one) is considered as an important class of natural product, which has been known to possess wide spectrum of pharmacological activities, such as anticancer [2-6] and antitumor [7], antibacterial [8], antifungal [9], anti-inflammatory [10], antioxidant [11], and antimalarial [12,13]. Furthermore, some chalcone derivatives have also been reported to inhibit several enzymes working in cellular systems, such as protein tyrosine kinase [14] and xanthine oxidase [15]. Beside their various pharmacological activities, the interest to chalcone derivatives is also due to their simple synthetic method which is generally employing Claisen-Schmidt condensation [13,16].

Molecular hybridization is a new concept and strategy in drug design through combining pharmacophic moieties from different bioactive substances to obtain a new hybrid compound with enhancing activity and better property [17]. Various hybrid substances constructed from different origins have been designed and synthesized although an adequate expectation has not been achieved.

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The regulation of cell number is a crucial property of multicellular organisms. As a disease related to uncontrollable cell proliferation, therefore cancer is concerning with the regulation of cell number. Apoptosis as a universal and exquisitely cellular suicide pathway [18] are essential mechanism to control cell number. Therefore, identification of small molecule acting as regulator and inducer of apoptosis has boosted intense research in developing anticancer agents.

Chalcone derivatives are able to induce apoptosis in cancer cells through modulation of key element in cellular signal transduction pathway related to apoptosis [19]. Based on the potential anticancer activity of amino chalcone derivatives and application of molecular hybrid strategy, herewith we report and discuss synthesis some amino chalcone derivatives and coumarin-chalcone derivatives, evaluation of their anticancer activity toward breast cancer cells T47D and cervix cancer cells HeLa, and inducing apoptosis mechanism of the prepared compounds.

EXPERIMENTAL

Materials and Instruments

All chemicals were provided from commercial origin with pro synthesis or pro analysis grade. Melting point was determined by a Fisher-Johns melting point apparatus 220 VAC (Fisher Scientific, Waltham, MA, USA) and uncorrected. The reaction progress was monitored by thin layer chromatography on silica gel GF_{254} plate (E Merck, Darmstadt, Germany), and the spots were identified by UV lamp (λ 254 nm). The high resolution mass spectra was recorded on micrOTOF-Q II (Bruker, Billerica – MA, USA), while the ESI-mass spectrum was recorded on Triple Quadrupole Thermo Scientific TSQ Vantage (Waltham, MA – USA). FTIR spectra was recorded in KBr powder with Diffuse Reflectance method on spectrophotometer IRTracer100 (Shimadzu, Kyoto, Japan). NMR spectra (^{1}H, ^{13}C-APT) were recorded on JEOL JNM-ECS400 spectrometer (JEOL, Tokyo, Japan) using $CDCl_3$ as solvent and internal standard. Anticancer test was conducted using Benchmark Elisa microplate reader (Biorad, California – USA). Cell apoptosis induction test was determined using flow cytometer Becton Dickinson FACS Calibur (San Jose, California – USA)

Synthesis of Amino Chalcones

The mixture of 6 mmol benzaldehyde derivatives, 6 mmol 4'-amino acetophenone, and 30 mL ethanol were mixed in a round bottom flask, cooled under 10 °C. NaOH 40% (6 mL) solution was added to the reaction mixture dropped wise, and the temperature was kept under 10 °C for 1 hour, then the temperature was increased to room temperature for next 4 hours. The precipitate was then filtered off and recrystallized with aqueous-ethanol [13]. The purity of all target compounds were tested by TLC, and their melting points were determined. The structure of the prepared compounds were established by FTIR, ESI-MS, ^{1}H- and ^{13}C- NMR

Synthesis of 3-acetylcoumarin

5 mmol ethyl acetoacetate, 5 mmol salicylaldehyde, and 3 drops of triethylamine were put sequently into the round bottom flask and then was refluxed for 8 hours. The reaction progress was followed by TLC. The reaction was stopped when it was completed. The obtained precipitate was filtered off and recrystallized using ethanol.

Synthesis of Coumarin-chalcone Derivatives

The mixture of 1 mmol 3-acetylcoumarin, 1 mmol derivatives of benzaldehyde, and 0.2 mmol *p*TSA in 10 mL ethanol was refluxed for 6 hours. The reaction progress was monitored with TLC and stopped until completion. The precipitate was then filtered off and then subjected to column chromatography for purification using *n*-hexane : ethyl acetate (3:2) as antimobile phase.

In Vitro Anticancer Assay

The cervix cancer cells line HeLa and breast cancer cells line T47D were provided from the collection of the Laboratory of Parasitology – Faculty of Medicine, Gadjah Mada University, Yogyakarta. Cells were routinely

cultured with phenol-red free RPMI-1640 supplemented with 10% FBS, 100 U/mL penicillin, and 100 µg/mL streptomycin in a humidified incubator at 37 °C in an atmosphere of 5% CO_2.

The *in vitro* antiproliferative activity of the prepared compounds was determined by MTT reagent following the already available procedure [20]. The cancer cells were seeded in a 96 well plate at density of $1x10^4$ cells/well and maintained for 24 h. The cells were then treated with prepared compounds in different concentration or DMSO (as negative control) for 24 h. After addition of 0.5% MTT solution as 1/10 volume of medium in the well, incubation was continued for further 4 h at 37 °C /5% CO_2. An equal volume of stop solution (0.04 N HCl in isopropanol) was subsequently added to that each well of the culture medium, and then the absorbance at 570 nm (peak) and 630 nm (bottom) was measured after thorough pipetting to disperse the generated blue formazan. It was performed in triplicate. The IC_{50} value was then calculated using Probit Analysis (SPSS 17).

Cell Apoptosis and Cell Cycle Inhibition Analysis Using Flow Cytometry

Cell culture of T47D and HeLa (5×10^5 cells/well) in 2000 µL medium RPMI were subjected in 6 well plate, incubated for 24 hours in CO_2 incubator, the medium was washed out, then washed with PBS. The tested compounds then added to the well with concentration of IC_{50}, and further incubated for 24 hours. The sample was re-suspended into 1 mL PBS and added with 1 mL cold ethanol, and incubated for 30 min in refrigerator. After centrifugation, 100 µL reagent Annexin V-PI and 350 µL buffer were added, mixed and poured into flow cytometer tube and then subjected to flow cytometer.

For cell cycle determination, 400 µL the test solution for flow cytometer analysis was re-suspended until homogen, incubated at 37 °C for 10 min, poured into flow cyto-tube, and analyzed the cell cycle profile. To determine the cell cycle phase, data obtained from flow cytometer was read using cell quest program [21].

Orange Acridine and Etidium Bromide Double Staining

The cancer cells culture ($5x10^4$ cell/well in 1000 µL RPMI) was harvested and distributed into 24-well plate with coverslip. The cells were then incubated for 24 hours in a CO_2 incubator, followed by addition of the tested compound and then incubated for further 24 hours. Hereinafter the RPMI culture medium was taken carefully, washed using PBS, and then the cells were subjected onto glass object, added with 10 µL orange acridine-etidium bromide solution. The cell morphology was then observed using a fluorescence microscope [21].

RESULTS AND DISCUSSION

Chemical Structure

Chalcones used as research objects were 4'-amino chalcone (**1-3**) and coumarin chalcone (**4-5**) derivatives; and were synthesized using Claisen-Schmidt condensation following the protocol of Suwito *et al.* [13]. The catalyst used in the preparation of 4'-amino chalcone derivatives was NaOH 40% solution, whereas coumarin-chalcone derivative was *p*TSA. The use of NaOH 40% solution for the synthesis of coumarin-chalcone gave no reaction product. The reaction processes and the structure of the target molecules are displayed in Fig. 1.

From the data obtained, the yield of the prepared compounds is affected by the electronic factor of the substituent of derivative of benzaldehydes. Electron withdrawing substituent increased the product due to increasing of electrophilicity of aldehyde carbonyl group, whereas electron donating substituent decreased the product. The molecular structure of the prepared compounds was established by spectroscopic data those are FTIR, ESI-MS, ^{1}H- and ^{13}C-NMR.

(*E*)-1-(4-aminophenyl)-3-(2-methoxyphenyl)prop-2-en-1-one (**1**): yellow solid (0.981 g; 64.55%); m.p. = 104-106 ºC; R_f = 0.52 (*n*-hexane/ethyl acetate : 3/2); FT-IR (DRS, KBr, cm^{-1}) 3456.44 and 3346.5 ($-NH_2$), 3022.5 (C-H sp^2), 1627.9 (C=O), 1597.1 (C=C), 1338.6 (C-N), 1172.72 (C_{aryl}-O-C_{alkyl}); ESI-MS $[M+H]^+$ calculated 253.30 observed 254.012; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H (ppm): 8.09 (d, *J* = 15.8 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 15.8 Hz, 1H), 7.63 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.35 (dt, *J* = 7.7, 1.5 Hz, 1H), 6.98 (t, *J* = 8.2 Hz, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 8.7 Hz, 2H), 4.21 (s, 2H), 3.89 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C (ppm): 188.8 (C), 158.7 (C), 151.1 (C), 138.7 (CH), 131.4 (CH), 131.2 (CH), 129.1 (CH), 128.8 (C), 124.4 C, 122.9 (CH), 120.7 (CH), 114.0 (CH), 111.3 (CH), 55.6 (CH_3).

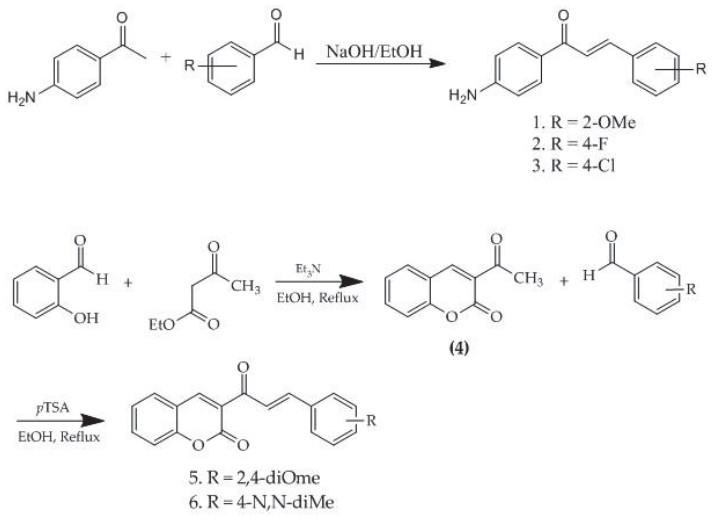

FIGURE 1. Reaction process and structure of target molecules.

(*E*)-1-(4-aminophenyl)-3-(4-fluorophenyl)prop-2-en-1-one (**2**) : yellow solid (1.281 g; 88.49%); m.p. = 142-144 ºC; R_f = 0.61 (n-hexane/ethyl acetate: 3/2); FT-IR (DRS, KBr, cm^{-1}) 3414.00, 3334.92 (-NH_2), 3049.46 (C-H sp^2), 1629.85 (C=O), 1593.20 (C=C), 1342.46 (C-N), and 1224.80 (C-F); ESI-MS $[M+H]^+$ calculated 241.27 and observed 241.99 ; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.92 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 15.6 Hz, 1H), 7.61 (dd, J = 8.6, 5.4 Hz, 2H), 7.47 (d, J = 15.6 Hz, 1H), 7.09 (t, J = 8.6 Hz, 2H), 6.69 (d, J = 8.7 Hz, 2H), 4.22 (s, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C (ppm): 188.0 (C), 163.9 (d, $^1J_{C\text{-}F}$ =252.5 Hz, C), 151.4 (C), 141.9 (CH), 131.6 (d, $^4J_{C\text{-}F}$ = 4.0 Hz, C), 131.2 (CH), 130.2 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, CH), 128.4 (C), 121.8 (CH), 116.1 (d, $^2J_{C\text{-}F}$ = 22.2 Hz, CH), 114.0 (CH).

(*E*)-1-(4-aminofenil)-3-(4-klorofenil)prop-2-en-1-one (**3**) : yellow solid (1.103 g; 71.33%); m.p. = 158-160 ºC; Rf = 0.54 (*n*-hexane/ethyl acetate: 3/2); FT-IR (DRS, KBr, cm^{-1}) 3460.30 and 3341.64 (-NH_2), 3051,39 (C-H sp^2), 1629.85 (C=O), 1571(C=C), 1346.31 (C-N), and 1178.51 (C-Cl); ESI-MS $[M+H]^+$ calculated for 257.72 and observed 257.91; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H (ppm): 7.92 (d, J = 8.7 Hz, 2H), 7.72 (d, J = 15.6 Hz, 1H), 7.55 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 15.6 Hz, 1H), 7.37 (d, J = 8.5 Hz, 2H), 6.69 (d, J = 8.7 Hz, 2H), 4.18 (s, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C (ppm): 187.9 (C), 151.4 (C), 141.8 (CH), 136.0 (C), 134.0 (C), 131.2 (CH), 129.5 (CH), 129.3 (CH), 128.5, 122.6 (CH), 114.1 (CH).

(*E*)-3-(3-(2,4-dimethoxyphenyl)acryloyl)-2H-chromen-2-one (**4**): yellow-orange solid (yield = 44%), R_f = 0.52 (*n*-hexane:ethyl acetate = 3:2); FTIR (DRS, KBr, cm^{-1}) 3093 (C-H sp^2), 1714 and 1654 (C=O), 1604 (C=C), 1174 (C_{aryl}-O-C_{alkyl}); HRESI-MS $[M+Na]^+$ calculated 359.0896 and observed 359.08915 for $C_{20}H_16O_5$; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H (ppm): 8.54 (s, 1H), 8.17 (d, J = 15.8 Hz, 1H), 7.89 (d, J = 15.8 Hz, 1H), 7.64 (d, J = 8.6 Hz, 3H), 7.65 (m, 2H), 7.38 (d, J = 8.2 Hz, 1H), 7.34 (dt, J = 7.8, 1.1 Hz, 1H), 6.53 (dd, J = 8.6, 2.4 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C (ppm): 186.9 (C), 163.6 (C), 160.8 (C), 155.2 (C), 147.5 (CH), 140.9 (CH), 134.0 (CH), 131.3 (CH), 130.0 (CH), 126.6 (C), 126.1 (C), 125.0 (CH), 122.0 (CH), 118.8 (C), 117.2 (C), 116.8 (CH), 105.6 (CH), 98.5 (CH), 55.7 (CH_3), 55.7 (CH_3).

(*E*)-3-(3-(4-(dimethylamino)phenyl)acryloyl)-2H-chromen-2-one (**5**): red solid (yield = 29%), R_f = 0.54 (*n*-hexane: ethyl acetate = 3:2); FTIR (DRS, KBr, cm^{-1}) 3072 (C-H sp^2), 2916 (C-H sp^3), 1735 and 1645 (C=O), 1606 (C=C); HRESI-MS $[M+Na]^+$ calculated 342.1106 and observed 342.11035 for $C_{20}H_{17}NO_3$; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H (ppm): 8.56 (s, 1H), 7.87 (d, J = 15.5 Hz, 1H), 7.73 (d, J = 15.5 Hz, 1H), 7.65 (t, J = 6.9 Hz, 1H), 7.62 (dd, J = 6.9, 1.4 Hz, 1H), 7.58 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.3 Hz, 1H), 7.33 (t, J = 8.3 Hz, 1H), 6.69 (d, J = 8.7 Hz, 2H), 3.05 (s, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ_C (ppm): 186.1 (C), 159.6 (C), 155.1 (C), 147.3(CH), 146.5 (CH), 133.8 (CH), 131.2 (CH), 129.9 (CH), 126.1 (C), 124.9 (CH), 118.8 (C), 118.8 (CH), 116.7 (CH), 111.9 (CH), 40.3 (CH_3).

Anticancer Activity

The effect of the prepared chalcones on cell proliferation was examined using MTT assay. As shown in Fig. 2, the chalcone derivatives suppressed cell proliferation in concentration dependent manner, the higher the concentration of the prepared compounds the higher anticancer activity. The IC_{50} values of each compound are presented in Table 1.

As shown in Table 1, the IC_{50} value ranging from 30.4 µg/mL to more than 100 µg/mL toward T47D cells, and from 27.5 µg/mL to more than 100 µg/mL toward HeLa cells. Among the tested compounds, compound **2** showed the most active compound. The presence of fluor atom as substituent is necessary for the anticancer activity. In addition the importance of amino group for the anticancer activity [3] is described in this experiment, where only amino chalcone derivatives exhibited anticancer activity, whereas coumarin-chalcone derivatives were inactive (IC_{50} > 100 µg/mL). The most active compound was then selected for further study of induction apoptosis test and cell cycle analysis using flow cytometry at concentration of IC_{50}.

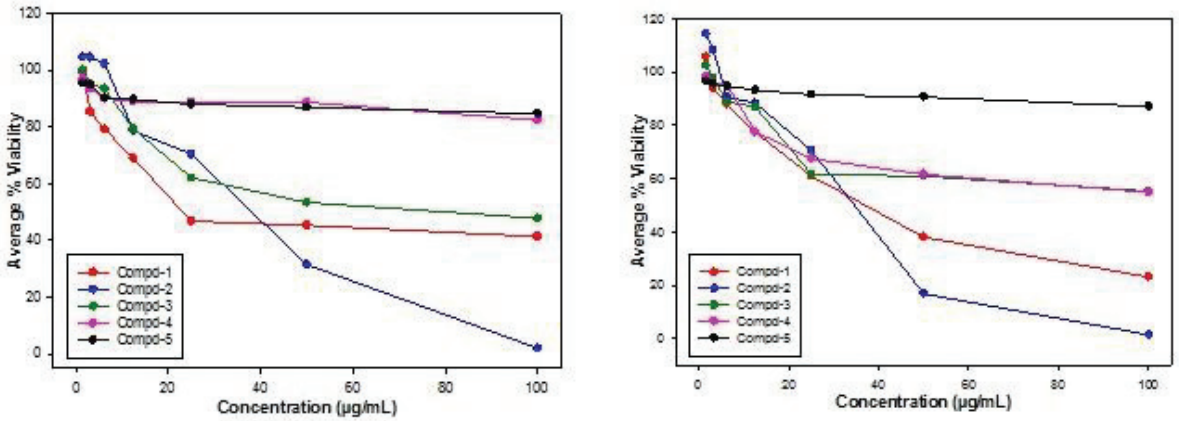

FIGURE 2. The effect of concentration of the prepared compounds toward cell proliferation: (a) T47D cells, (b) HeLa cells

TABLE 1. Value of IC_{50} of the tested compounds against T47D and HeLa cancer cells

Compound	IC_{50} (µg/mL)	
	T47D	HeLa
1	36.8	34.6
2	30.4	27.5
3	63.7	92.4
4	>100	>100
5	>100	93.6
Doxorubicin	0.11	1.19

Analysis of Apoptosis and Cell Cycle

Apoptosis analysis with flow cytometry using Annexin-V/PI as staining reagent was performed to determine early apoptotic, late apoptotic and necrotic cells following compound **2** treatment to T47D and Hela cells quantitatively. Annexin-V and propidium iodide act selectively to bind intact or fragmented cells. The cytograms are presented in Fig. 3, while the quantitative results are presented in Table 2.

The flow cytometry analysis data showed that compound **2** underwent 1.09% early apoptosis and 2.35% late apoptosis for HeLa cells. However, T47D cells underwent 18.14% early apoptosis and 48.73% late apoptosis after treatment with compound **2** at concentration of IC_{50}. This data prove that compound **2** causes cancer cells death through induction of apoptosis mechanism. The morphological alteration of HeLa and T47D cells due to apoptosis after treatment with compound **2** at concentration of IC_{50} is also observed with a phase-contrast microscope and presented in Fig. 4.

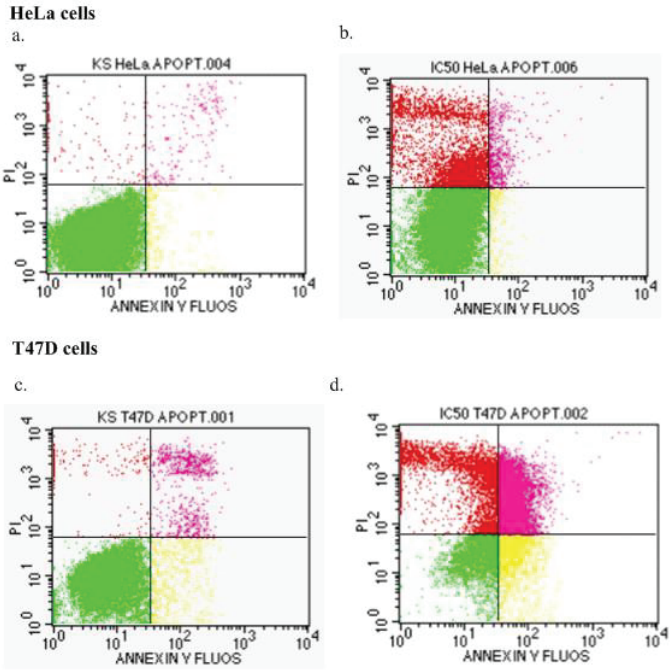

FIGURE 3. Apoptosis analysis using flow cytometry: HeLa cells: (a) control cells, (b) after treatment with compound **2**. T47D cells, (c) control cells, (d) after treatment with compound **2**

TABLE 2. Results of apoptosis analysis using flow cytometry

	Cell population (%)			
	Living cell	Early apoptosis	Late apoptosis	Necrosis
HeLa				
- Control	95.59	1.89	0.92	0.64
- IC_{50}	74.30	1.09	2.35	22.48
T47D				
- Control	91.88	3.52	3.33	1.30
- IC_{50}	11.30	18.14	48.73	22.61

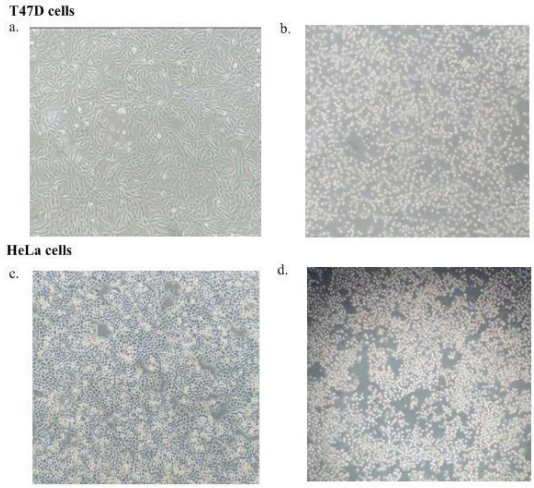

FIGURE 4. The morphological changes of the cancer cells after exposure of the compound **2**. T47D cells: (a) control cells, (b) after treatment with compound **2** (30.37 µg/mL). HeLa cells: (c) control cells, (d) after treatment with compound **2** (27.46 µg/mL).

Moreover, this observation is supported by the results of qualitative analysis through double staining test using orange acridine-ethidium bromide and presented in Fig. 5.

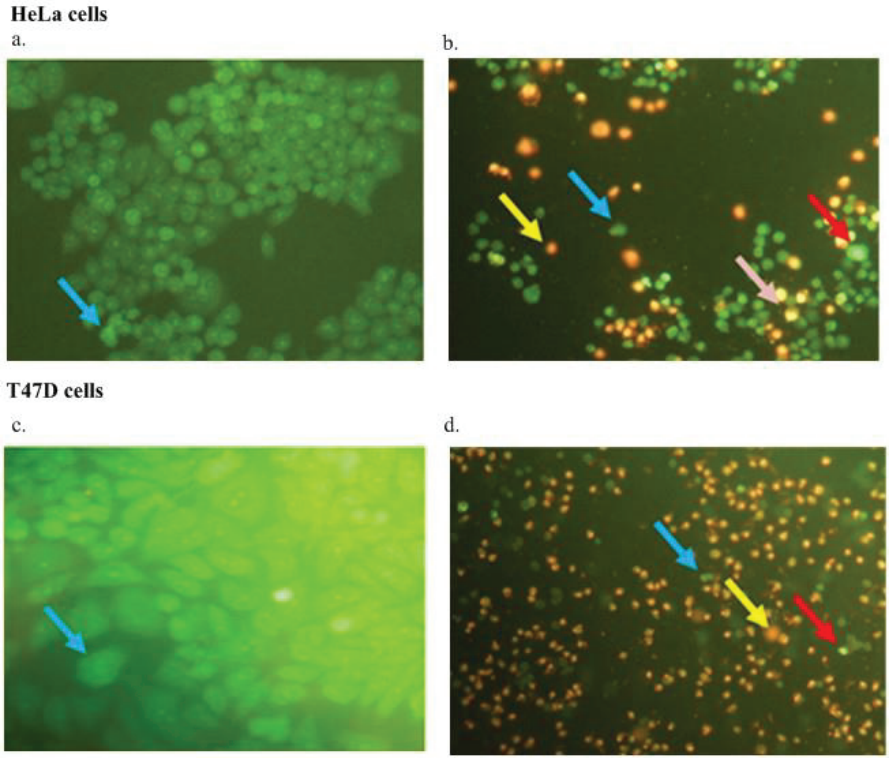

FIGURE 5. Results of double staining experiment of compound **2**. HeLa cells: (a) control cells, (b) after treatment with compound **2** (27.46 µg/mL). T47D cells: (c) control of, (d) after treatment with compoud **2** (30.37 µg/mL).

Legend: living cells early apoptosis late apoptosis Necrosis

To investigate whether compound **2** shows an effect on the cell cycle regulation, we measured its effect on cell cycle distribution using flow cytometry after staining with PI. The results are presented in Fig. 6. As shown in Fig. 6 and Table 3, concomitant with grow inhibitory effects, treatment of compound **2** induced cell cycle arrest at different phase for both cancer cells. Compound **2** induced cell cycle arrest of HeLa cells and T47D cells at G_0/G_1 and G_2/M phase due to decreasing of cell population at those phases. In addition it blocks also the DNA replication during S phase in T47D cells.

TABLE 3. Results of Cell cycle analysis using flow cytometry

HeLa cells					
	Cell population				
	M1	G_0/G_1	S	G_2/M	M5
Control	3.57	55.20	10.83	17.41	13.61
Compd **2** (IC50)	12.20	50.71	12.07	12.44	12.91
T47D cells					
Control	11.57	29.25	21.99	26.17	11.80
Compd **2** (IC50)	75.05	11.04	4.47	6.65	3.11

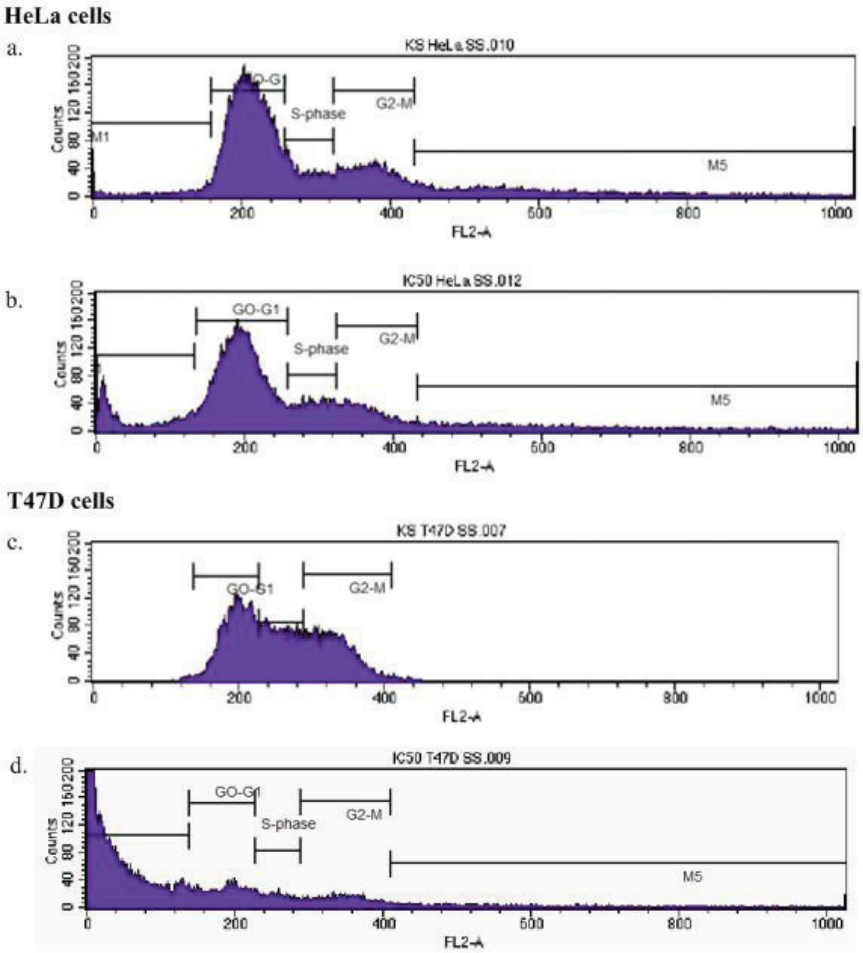

FIGURE 6. Cell cycle analysis after treatment of HeLa cells and T47D cells with compound **2.** HeLa cells: (a) control cells, (b) after treatment with compound **2** at IC_{50}; T47D cells: (c) control cells, (d) after treatment with compound **2** at IC_{50}

CONCLUSIONS

In conclusion, we have successfully synthesized some amino chalcone and coumarin chalcone derivatives using Claisen-Schmidt reaction. The prepared chalcones showed anticancer activity toward T47D cells and HeLa cells. Compound **2** [(*E*)-1-(4-aminophenyl)-3-(4-fluoro-phenyl)prop-2-en-1-one] showed the most active anticancer activity through induction apoptosis mechanism and induced cell cycle arrest at G_0/G_1 and G_2/M phase for HeLa cells and T47D cells and blocks S phase for T47D cells.

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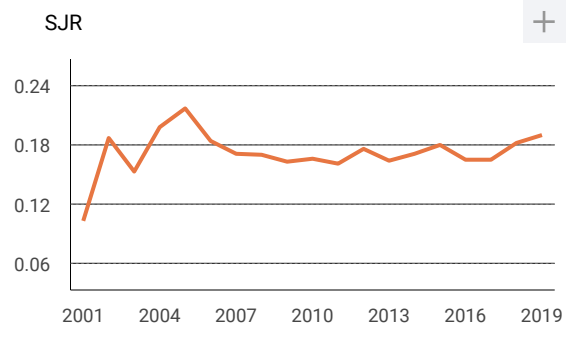

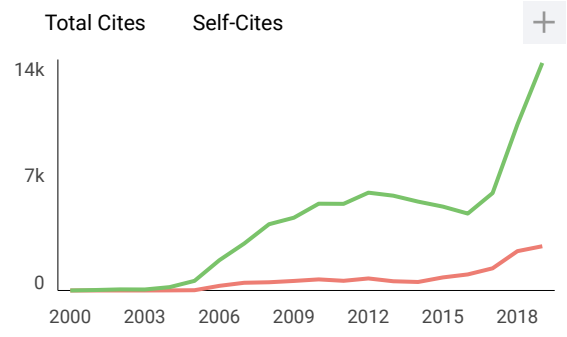

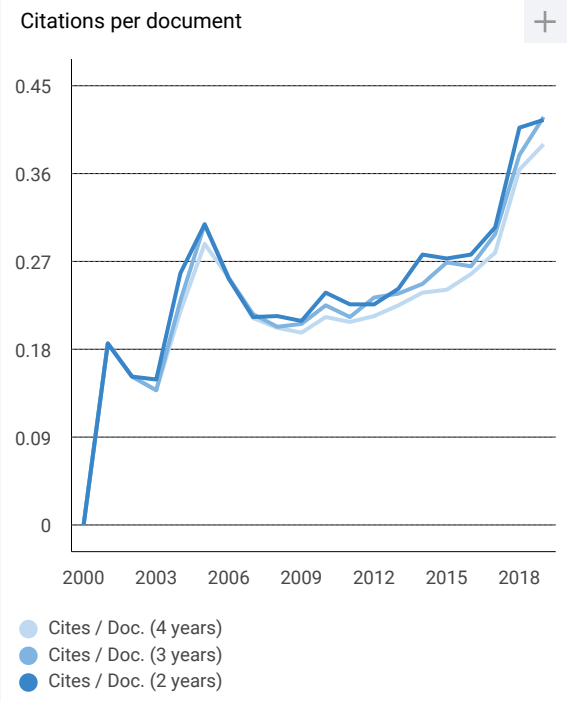

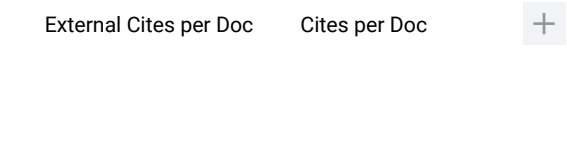

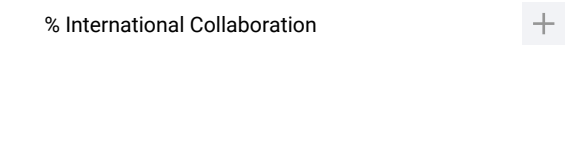

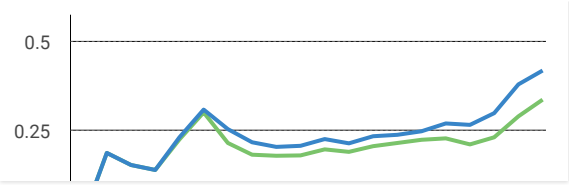

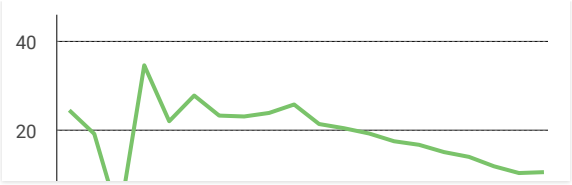

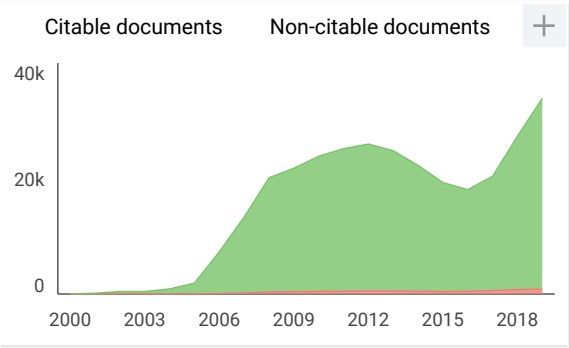

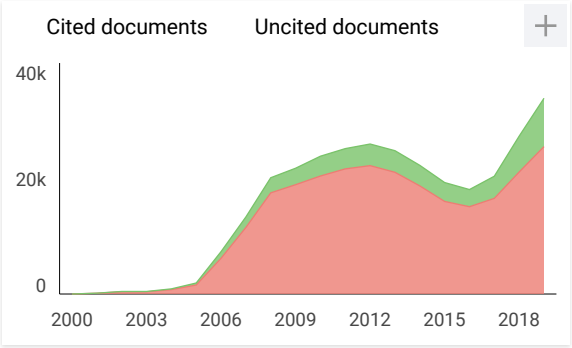

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