Research Article

Synthesis, Characterization, and Anticancer Activity of New Benzofuran Substituted Chalcones

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Benzofuran derivatives are of great interest in medicinal chemistry and have drawn considerable attention due to their diverse pharmacological profiles including anticancer activity. Similarly, chalcones, which are common substructures of numerous natural products belonging to the flavonoid class, feature strong anticancer properties. A novel series of chalcones, 3-aryl-1-(5-bromo-1-benzofuran-2-yl)-2-propanones propenones (**3a–f**), were designed, synthesized, and characterized. *In vitro* antitumor activities of the newly synthesized (**3a–f**) and previously synthesized (**3g–j**) chalcone compounds were determined by using human breast (MCF-7) and prostate (PC-3) cancer cell lines. Antitumor properties of all compounds were determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cell viability assay for the tested chalcone compounds was performed and the log IC₅₀ values of the compounds were calculated after 24-hour treatment. Our results indicate that the tested chalcone compounds show antitumor activity against MCF-7 and PC-3 cell lines ($p < 0.05$).

1. Introduction

Cancer is one of the most important clinical problems worldwide. Among the wide range of compounds approved as potential anticancer agents, derivatives with functionalities as α,β -unsaturated Michael acceptor have attracted great interest [1, 2]. Previous studies have proposed that anticancer compounds such as alkylating agents bind directly to various cellular nucleophiles, thus lacking selectivity. However, Michael acceptors can be structurally modified so that they can react selectively with target nucleophiles [3]. Chalcones, the compounds having 1,3-diaryl-2-propen-1-one system, also have shown a broad spectrum of biological activities including anti-inflammatory [4–7], antimalarial [8], anti-invasive [9], antibacterial [10–12], and anticancer [13–16] activities. On the other hand, chalcones are capable of inducing apoptosis [17, 18]. Consequently, these compounds are recognized as promising anticancer agents [19–22]. A number of clinically useful anticancer drugs have genotoxic effects because of their interaction with the amino groups of nucleic acids. However, chalcones have been found not to show such undesired side effects [23]. Numerous reports

have been published on the interesting anti-breast cancer activity shown by chalcones [24–26]. Benzofuran derivatives are an interesting class of heterocyclic compounds. Benzofuran derivatives are of great interest in medicinal chemistry and have drawn remarkable attention due to their biological activities with chemotherapeutic properties [27]. Some benzofurans bearing various substituents at the C-2 position are greatly distributed in nature; for example, aianthoidol, a neolignan derivative, has been reported to have antiviral, antioxidant, and antifungal activities [28]. Furthermore, most of the compounds prepared from 2-acetylbenzofuran have antimicrobial, anticancer, antitumor, anti-inflammatory, and antitubulin activities and are also used for treatment of cardiac arrhythmias [29–32]. The use of the combinations of different pharmacological compounds in the design of new drugs may lead to finding novel drugs with interesting biological activity [33, 34]. Furthermore, no studies were found in the literature evaluating anticancer properties of benzofuran substituted chalcone derivatives. This encouraged us to synthesize benzofuran substituted chalcone compounds and to investigate anticancer properties of these compounds.

SCHEME 1: Structure of synthetic derivatives **3a–3j**.

In this study, we aimed at designing and synthesizing new compounds (**3a–f**) with both benzofuran and chalcone units in one molecule and examining anticancer activity of this newly synthesized chalcones (**3a–f**) and previously synthesized chalcones [35] (**3g–j**) bearing no substituent in the benzofuran ring as a different series against human breast cancer cell lines (MCF-7) and human prostate cancer cells (PC-3) (Scheme 1).

2. Materials and Methods

2.1. Materials. Chemical agents used in the present study included dimethyl sulfoxide (DMSO; Merck, Germany), penicillin-streptomycin, fetal bovine serum (FBS), and DMEM (Dulbecco's Modified Eagle Medium). Double-distilled water was used at all stages of the experiments. Samples of chalcone compounds for testing were prepared at 1, 5, 25, 50, and 100 μM concentrations.

2.2. Characterization Techniques. Melting points were measured using a differential scanning calorimeter (Shimadzu DSC-50) and were uncorrected. NMR spectra were determined on a Bruker AC 400 (400 MHz) spectrometer, with tetramethylsilane (TMS) as the internal standard in DMSO- d_6 or CDCl_3 as solvents. FT-Infrared (FT-IR) spectra were recorded as KBr pellets on a Perkin-Elmer Spectrum One FT-IR spectrometer.

Synthesis of 1-(5-Bromo-1-benzofuran-2-yl)ethanone (D1). A mixture of 4-bromo salicylaldehyde (1g, 4.97 mmol) and potassium carbonate (0.69 g, 4.97 mmol) in dry acetone (10 mL) was stirred at 25°C for 1 h. Reaction mixture was cooled at $0-5^\circ\text{C}$, and then chloroacetone (4 mL, 4.97 mmol) was added dropwise. Reaction mixture was stirred at room temperature for ten minutes and then refluxed. Progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was poured on crashed ice. The precipitated solid was filtered, washed with water, and dried. The product

was crystallized from ethanol (yield 1.08 gr, 91%; mp: $117-119^\circ\text{C}$).

FT-IR (KBr, cm^{-1}). 1667 (C=O), 1542 (C=C); **$^1\text{H-NMR}$** (400 MHz, DMSO- d_6), ppm: 8.03 (s, 1H, 5-H), 7.82 (s, 1H, 7-H), 7.69 (dd, 1H, $J = 8.6$ Hz and $J = 8.2$ Hz, 3-H), 7.65 (d, 1H, $J = 8.8$ Hz, 2-H), 2.56 (s, 3H, methyl protons); **$^{13}\text{C-NMR}$** (400 MHz, DMSO- d_6): 188.40, 154.14, 153.46, 131.43, 129.46, 126.39, 116.63, 114.84, 113.83, 26.97; Anal. Calc.; % C, 50.24; H, 2.95. Found: % C, 50.21; H, 2.99.

General Procedure for Synthesis of Chalcones (3a–f). A solution of 1-(5-bromo-1-benzofuran-2-yl)ethanone (1g, 4.18 mmol) and one of the aldehyde derivatives (**2a–f**, 4.18 mmol) in MeOH (10 mL) was cooled at $0-5^\circ\text{C}$ and then 6 mL of aqueous NaOH (1 mol/L) was added to this solution and stirred at room temperature for 3 h. The reaction mixture was poured on crushed ice. The precipitated solid was filtered after neutralization with diluted HCl and was washed several times with water and then dried. The product was recrystallized from ethanol.

(2E)-1-(5-Bromo-1-benzofuran-2-yl)-3-phenylprop-2-en-1-one (3a). Yield: 70%; M.p. $145-147^\circ\text{C}$; **FT-IR** (KBr, cm^{-1}): 1655 (C=O), 1599 (C=C); **$^1\text{H-NMR}$** (400 MHz, DMSO- d_6), ppm: 8.27 (s, 1H, 5-H), 8.12 (s, 1H, 7-H), 7.92–7.84 (m, 4H, 13-H, 17-H, 10-H, 11-H), 7.84–7.65 (m, 2H, 3-H, 2-H), 7.65–7.40 (m, 3H, 16-H, 15-H, 14-H); **$^{13}\text{C-NMR}$** (400 MHz, DMSO- d_6): 178.96, 154.59, 154.55, 144.46, 134.76, 131.63, 131.46, 129.64, 129.50, 129.46, 126.49, 122.18, 116.77, 114.88, 114.56; Anal. Calc.; % C, 62.41; H, 3.39 Found: % C, 62.43; H, 3.43.

(2E)-1-(5-Bromo-1-benzofuran-2-yl)-3-(3-bromophenyl)prop-2-en-1-one (3b). Yield: 82%; M.p. $206-208^\circ\text{C}$; **FT-IR** (KBr, cm^{-1}): 1654 (C=O), 1604 (C=C); **$^1\text{H-NMR}$** (400 MHz, DMSO- d_6), ppm: 8.29 (s, 1H, 5-H), 8.15 (s, 1H, 7-H), 8.00–7.62 (m, 8H, 3-H, 2-H, 17-H, 16-H, 14-H, 13-H, 10-H, 11-H); **$^{13}\text{C-NMR}$** (400 MHz, DMSO- d_6): 178.90, 154.58, 154.52, 143.18, 134.04, 132.47, 131.78, 131.68, 131.43, 129.62, 126.59,

124.98, 122.87, 116.84, 114.98; Anal. Calc.; % C, 50.28; H, 2.48 Found: % C, 50.24; H, 2.50.

(2E)-1-(5-Bromo-1-benzofuran-2-yl)-3-(3-nitrophenyl)prop-2-en-1-one (**3c**). Yield: 87%; M.p. 202–204°C; FT-IR (KBr, cm^{-1}): 1666 (C=O), 1610 (C=C); ^1H -NMR (400 MHz, DMSO-d_6), ppm: 8.78 (s, 1H, 5-H), 8.37–8.27 (m, 13-H, 15-H, 17-H), 8.13 (s, 1H, 7-H), 8.08 (d, 1H, $J = 15.6$ Hz, 11-H), 7.92 (d, 1H, $J = 16$ Hz, 10-H), 7.78–7.68 (m, 3H, 3-H, 2-H, 16-H); ^{13}C -NMR (400 MHz, DMSO-d_6): 178.73, 154.67, 154.40, 148.95, 141.86, 136.66, 135.70, 131.87, 130.92, 129.57, 126.59, 125.43, 124.88, 123.51, 116.85, 115.39, 114.93; Anal. Calc.; % C, 54.86; H, 2.71; N, 3.76 Found: % C, 54.90; H, 2.76; N, 3.75.

(2E)-1-(5-Bromo-1-benzofuran-2-yl)-3-[4-(dimethylamino)phenyl]prop-2-en-1-one (**3d**). Yield: 70%; M.p. 179–181°C; FT-IR (KBr, cm^{-1}): 1646 (C=O), 1579 (C=C); ^1H -NMR (400 MHz, DMSO-d_6), ppm: 8.10 (s, 2H, 5-H, 7-H), 7.78–7.56 (m, 6H, 3-H, 2-H, 13-H, 17-H, 10-H, 11-H), 6.77 (d, 1H, $J = 2.8$ Hz, 14-H), 6.75 (d, 1H, $J = 3.6$ Hz, 16-H), 3.02 (s, 6H, CH_3); ^{13}C -NMR (400 MHz, DMSO-d_6): 178.52, 155.35, 154.31, 152.75, 145.69, 131.61, 131.10, 129.85, 126.24, 122.00, 116.64, 115.98, 114.83, 112.98, 112.22, 40.56–39.31; Anal. Calc.; % C, 61.64; H, 4.36; N, 3.78 Found: % C, 61.40; H, 3.31; N, 3.80.

(2E)-1-(5-Bromo-1-benzofuran-2-yl)-3-(2-furyl)prop-2-en-1-one (**3e**). Yield: 83%; M.p. 170–172°C; FT-IR (KBr, cm^{-1}): 1658 (C=O), 1596 (C=C); ^1H -NMR (400 MHz, DMSO-d_6), ppm: 8.03–7.96 (m, 3H, 5-H, 7-H, 15-H), 7.74–7.62 (m, 3H, 3-H, 2-H, 11-H), 7.55–7.40 (d, 1H, $J = 15.2$ Hz, 10-H), 7.14 (s, 1H, 13-H), 6.71 (s, 1H, 14-H); ^{13}C -NMR (400 MHz, DMSO-d_6): 178.56, 154.54, 154.41, 151.34, 147.15, 131.48, 130.78, 129.65, 126.37, 118.73, 118.50, 116.72, 114.85, 114.57, 113.77; Anal. Calc.; % C, 56.81; H, 2.86 Found: % C, 56.75; H, 2.90.

(2E)-1-(5-Bromo-1-benzofuran-2-yl)-3-(2-thienyl)prop-2-en-1-one (**3f**). Yield: 83%; M.p. 168–170°C; FT-IR (KBr, cm^{-1}): 1660 (C=O), 1602 (C=C); ^1H -NMR (400 MHz, DMSO-d_6), ppm: 8.17 (s, 1H, 5-H), 8.09 (s, 1H, 7-H), 8.02 (d, 1H, $J = 15.6$, 11-H), 7.91–7.67 (m, 4H, 3-H, 2-H, 15-H and 13-H), 7.51 (d, 1H, $J = 15.2$ Hz, 10-H), 7.23 (dd, 1H, 14-H); ^{13}C -NMR (400 MHz, DMSO-d_6): 178.54, 154.53, 154.48, 139.86, 137.27, 134.10, 131.64, 131.54, 129.69, 129.36, 126.42, 120.35, 116.76, 114.90, 114.05; Anal. Calc.; % C, 56.81; H, 2.86 Found: % C, 56.75; H, 2.90.

2.3. In Vitro Antitumor Activity

2.3.1. Cell Culture. The cell lines of human breast cancer (MCF-7) and human prostate cancer (PC-3) were employed in our study. The PC-3 and MCF-7 cell lines were retrieved from American Type Culture Collection (ATCC). MCF-7 and PC-3 cells were fed with DMEM medium (supplemented with 4500 mg/L glucose, 10% FBS, 100 U/mL penicillin, and 0.1 mg/mL streptomycin added) in 75 cm^2 culture flasks and RPMI-1640 medium (supplemented 10% FBS, 100 U/mL penicillin, and 0.1 mg/mL streptomycin added), respectively. A humidified carbon dioxide incubator (5% $\text{CO}_2 + 95\% \text{O}_2$;

Panasonic, Japan) was used to keep all cells at 37°C during the experiments. Before the treatment of chalcone compounds, the viability ratios of the cells were identified by 0.4% trypan blue. If the viability ratios were under 90%, we did not initiate the experiments [36].

2.3.2. MTT Assay. The synthetic chalcone derivatives were tested for their antitumor activities against different type cancer cell lines (PC-3 and MCF-7) using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay method. The pale-yellow tetrazolium salt, MTT, was transformed by active mitochondria to form a dark blue formazan that was determined by a microplate reader [37]. The MTT method provides a simple way to detect living and growing cells without using radioactivity.

When the cells were confluent, they were removed from the flasks using trypsin-EDTA solution and were seeded in 96-well plates such that there were 15×10^3 cells in each well. The plates were incubated for 24 h at 37°C. After treatment of these cancer cells with DMSO (for positive control group) and different concentrations (1, 5, 25, 50, and 100 μM) of chalcone compounds (**D1**, **3a–j**) in DMSO, the cells then were incubated for 24 h at 37°C in 5% CO_2 humidified incubator. MTT solution (0.5 mg/mL) was prepared from the MTT stock solution in sterile PBS and was added to each well and the plates were then incubated for 3 h after the incubation for 24 h with chalcone compounds. After that, DMSO and the optical density of the cells were determined by an ELISA reader (Synergy HT, USA) at 550 nm wavelength. The averages of the absorbance values were recorded by reading the control wells that were considered as 100%. The values of absorbance achieved from chalcone compounds and solvent (DMSO) added wells were proportioned to the control values, and the percentages of cell viability were determined. The tests were reiterated ten times at several days [38].

2.4. Statistical Analyses. Quantitative data are expressed as mean $\pm$ standard deviation (SD). Normal distribution was confirmed using Kolmogorov-Smirnov test. Quantitative data were analyzed using Kruskal-Wallis H test following Mann-Whitney U test with Bonferroni adjustment as a *post hoc* test. All p values < 0.05 were considered as statistically significant. All analyses were done by IBM SPSS Statistics 22.0 for Windows. The log IC_{50} values were determined by using % cell viability values of compounds by GraphPad Prism 6 program.

3. Results and Discussion

The new 1-(5-bromo-1-benzofuran-2-yl)ethanone was obtained from the reaction of 5-bromosalicylaldehyde and 1-chloroacetone. A series of chalcones (**3a–f**) were synthesized by condensation of 1-(5-bromo-1-benzofuran-2-yl)ethanone and various aromatic aldehydes (**2a–f**) (Scheme 2). For the synthesis of chalcones, the most common route is the base-catalyzed Claisen-Schmidt reaction involving condensation

SCHEME 2: General synthesis of benzofuran ketone (**D1**) with chalcone derivatives (**3a-j**). Reagents and conditions (i). K₂CO₃, acetone, reflux; (ii). NaOH, MeOH, rt.

of a benzaldehyde derivative with an acetophenone derivative in methanol with sodium hydroxide catalyst [39–41].

The benzofuran substituted chalcone derivatives (**3a-f**) were characterized by elemental analysis, FT-IR, ¹H, and ¹³C-NMR spectroscopy techniques.

Anticancer activity against MCF-7 and PC-3 was investigated in both these newly synthesized chalcones (**3a-f**) and previously synthesized chalcone derivatives (**3g-j**).

3.1. Structural Characterization. In the FT-IR spectra of 1-(5-bromo-1-benzofuran-2-yl)ethanone, C=O stretching vibration was observed at 1667 cm⁻¹. The synthetic chalcones **3a-f** showed characteristic bands between 1646 and 1666 cm⁻¹ (C=O stretching at chalcone) and between 1579 and 1610 cm⁻¹ (C=C stretching at chalcone).

The most characteristic signals in ¹H-NMR spectra of the benzofuran substituted chalcones were observed at 8.29–8.03 ppm (B3-H at benzofuran ring) and at 7.80–7.40 ppm (α-H and β-H of chalcone moiety) with a coupling constant about 15 Hz which characterized the transconfiguration of the alkene moiety. The signal of β-H was found downfield at a lower field than that of α-H due to resonance of π-electrons between α-carbons and β-carbons with carbonyl group. The carbonyl carbon was observed at about 178 ppm in the ¹³C-NMR spectra of **3a-f**.

3.2. Anticancer Activity. The benzofuran substituted chalcone compounds synthesized were tested for their *in vitro* anticancer activity against two cancer cell lines including MCF-7 and PC-3 at five different concentrations (1, 5, 25, 50, and 100 μM) by MTT assay. The cell viability percentages of tested benzofuran substituted chalcone compounds were

TABLE 1: Evaluation of the cytotoxicity and log IC₅₀ values (μM) of chalcone compounds and docetaxel (reference chemotherapeutic drug) of two cancer cell lines. log IC₅₀ is the concentration of drug that reduces cell growth by 50%.

Compound	MCF-7	PC-3
	log IC ₅₀ (μM)	log IC ₅₀ (μM)
D1	2.12	1.54
3a	1.89	1.67
3b	1.45	1.24
3c	5.01	6.31
3d	5.79	1.81
3e	0.42	0.67
3f	2.30	2.47
3g	4.43	6.11
3h	2.55	2.57
3i	6.28	6.30
3j	−0.21	0.92
Docetaxel (reference drug)	−0.48	−0.52

determined. Figures 1 and 2 show the effects of the benzofuran substituted chalcones on cell viability measured at 24 h after exposure.

log IC₅₀ values of compounds **3a-j** were calculated by using inhibition percentage values by GraphPad Prism 6 program on a computer. log IC₅₀ results of this compound are given in Table 1.

The benzofuran substituted chalcones showed anticancer activity on PC-3 and MCF-7 cell lines (*p* < 0.05). All the compounds at 100 μM concentrations significantly reduced the viability percentage of PC-3 and MCF-7 cells (*p* < 0.001).

FIGURE 1: The relative cell viability (%) of MCF-7 cells following the exposure of various concentrations of all the compounds (D1 and 3a-j) and untreated control cell for 24 h (* $p < 0.05$; ** $p < 0.001$).

Structure activity relationships between these chalcone derivatives and starting material (D1) demonstrated that benzofuran substituted chalcones showed more potent activities than the starting material bearing only an unsubstituted benzofuran ring.

Among the synthesized chalcones, compounds 3a, 3h, and 3i were found to be the most potent against MCF-7 and PC-3 cell lines. In general, chalcone derivatives show anticancer activity. We have not run across any study in literature on the synthesis and anticancer properties of

FIGURE 2: The relative cell viability (%) of PC-3 cells following the exposure of various concentrations of all the compounds (D1 and 3a-j) and untreated control cell for 24 h (* $p < 0.05$; ** $p < 0.001$).

the chalcone compounds containing benzofuran ring. In this study we have firstly synthesized the chalcone compounds containing benzofuran ring. And also we have firstly studied on the anticancer properties of these compounds. We have studied only MCF-7 and PC-3 cells. These results suggested that benzofuran substituted chalcones could be used as lead compounds to develop novel potent anticancer agents.

4. Conclusions

Synthetic benzofuran chalcone compounds were evaluated *in vitro* for their anticancer activity by MTT assay. The benzofuran substituted chalcone derivatives showed high antitumor activity against MCF-7 and PC-3 cell lines ($p < 0.001$). These results displayed that chalcone derivatives bearing benzofuran ring may be useful in the future for anticancer drug development.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

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