Green synthesis and inhibitory effect of novel quinoline based thiazolidinones on the growth of MCF-7 human breast cancer cell line by G2/M cell cycle arrest

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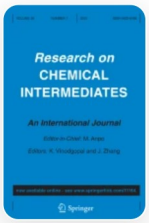

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Abstract

Searching for new active molecules against human breast cancer cell line MCF-7, novel quinoline based thiazolidinones has been efficiently synthesized under ultrasound irradiation. The newly synthesized compounds were tested against human breast cancer cell line MCF-7. Compounds P3, P4, and P6 were found to be promising inhibitors of MCF-7 characterized by

lower IC_{50} values in a dose-dependent mode with high specificity against MCF-7 (IC_{50} of 10 μM at 24 h). Among all the synthesized compounds, P3, P4, and P6 shows IC_{50} values 5.38, 5.12, and 0.73 μM, respectively, were considered as a potential lead. These lead molecules showed significant anti-cancer activity against human breast cancer cell line MCF-7. Additionally, induction of G2/M cell arrest within 24 h was discovered via flow cytometry analysis. Overall, our data suggest that potent compounds have an inhibitory effect on cell proliferation of MCF-7 through cell cycle arrest, giving it great potential as a future therapeutic reagent for cancers.

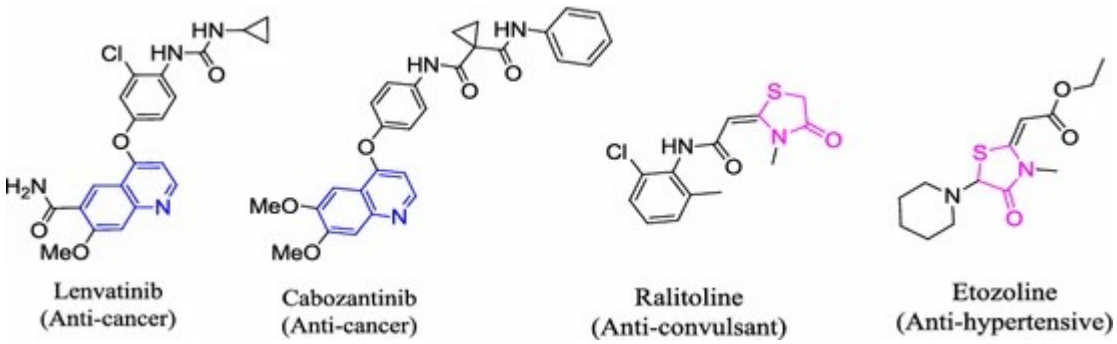
Introduction

Cancer is a life threatening disease characterized by abnormal growth of cells, the incursion of surrounding tissues and often invades other vital organs. The incidence and mortality of cancer patients has become a major issue across the world. According to a WHO report, cancer was responsible for 8.2 million deaths in 2012. The most common cancers implicated in cancer

mortality are lung, liver, stomach, and breast cancers [1]. Even though significant progress has been achieved with therapeutic techniques, it remains one of the greatest challenges to discover and develop more effective and less harmful targeted anticancer drugs. During recent years, researchers have focused on the development of potential anticancer agents with minimal side effects [2, 3]. Molecular hybridization, which combines two or more pharmacophores in single molecular framework is an effective strategy used for developing new chemotherapeutic agents.

Quinolines have a paramount importance in medicinal chemistry because of their wide spectrum of biological activities and their presence in naturally occurring compounds. They have been shown to possess anti-microbial [4], anti-inflammatory [5], antimalarial [6], antiviral [7], antibiotic [8], anticancer [9], antitubercular [10], and anti-HIV [11] properties. The quinoline unit is contained in the structure of anticancer agents such as lenvatinib, cabozantinib; see Fig. 1.

Fig. 1



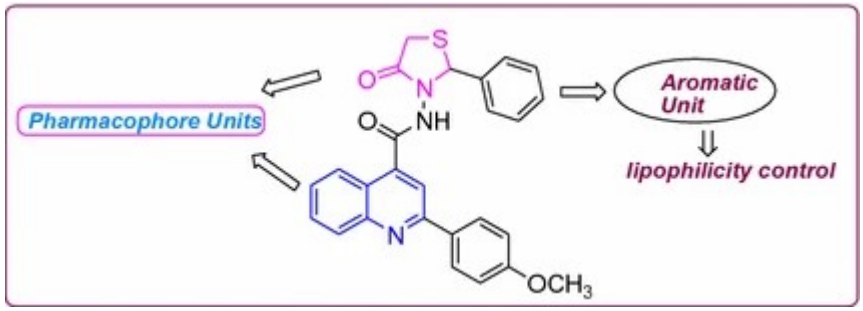
Representative drugs containing quinoline and thiazolidinone rings

On the other hand, 4-thiazolidinone is an important and versatile scaffold that has occupied a prominent position in medicinal chemistry [12]. Further, the presence of the N–C–S linkage in the thiazolidines is also responsible for nematocidal, fungicidal, antibacterial, and antiviral activities [13]. 4-Thiazolidinones have been reported to possess diverse biological activities including anti-viral [14], antidiabetic [15], antimicrobial [16], antitumor [17], antihistamic [18], anti-inflammatory [19], antimalarial [20], anti-HIV [21], and anticonvulsant [22]

activity. The 4-thiazolidinone moiety is very versatile and is featured in many drugs; see Fig. 1.

Here, in continuation of the search for bioactive molecules, we coupled thiazolidinone with quinoline moiety in a single molecular framework; see Fig. 2. We designed and synthesized quinoline-based thiazolidinone derivatives under ultrasound irradiation and evaluated for their anticancer activity against breast cancer cell line MCF-7.

Fig. 2



The designed scaffold containing quinoline and thiazolidinone as a main backbone

Experimental section

Materials and methods

All reagents used for chemical synthesis were purchased from commercial suppliers and required no further purification. Dulbecco's Modified Eagle's Medium (DMEM), trysin-EDTA, fetal bovine serum (FBS), and antibiotics (penicillin/streptomycin) were purchased from Gibco. Methyl thiazolyltetrazolium (MTT) was purchased from Sigma-Aldrich. Propidium iodide was purchased from Invitrogen. All other reagents used in cell-based studies were of standard quality. Analytical thin-layer chromatography (TLC) was carried out using the Merck silica gel 60 F_{254} plates and visualized using UV light and iodine vapors as visualizing reagent. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Carry 600 Series FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE II 400 NMR spectrometer in $CDCl_3$ and/or DMSO-d_6 solution using tetramethylsilane as an internal standard. Chemical shift values are given in ppm

relative to TMS as internal reference and the coupling constant (*J*) in Hertz. The splitting pattern abbreviations are assigned as singlet (s), broad singlet (brs), doublet (d), double doublet (dd), triplet (t), and multiplate (m). Mass was recorded on a WATERS, Q-TOF micro mass equipped with an electron spin impact (ESI) source. For ultrasonic irradiation, Bandelin Sonorex (frequency 40 MHz, power 100 W) ultrasound bath was used and the reaction flask was located in the ultrasonic bath containing water.

General method for the synthesis of compounds (2a–h)

Conventional method

A mixture of equimolar quantities of 2-(4-methoxyphenyl)quinoline-4-carbohydrazide 1 (10 mmol) and substituted aldehydes (10 mmol) in methanol (30 mL) was stirred for 10–15 min. in the presence of few drops of glacial acetic acid. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured on ice cold water, the formed precipitate was filtered off, washed with water and crystallized from ethanol.

Non-conventional method

2-(4-methoxyphenyl) quinoline-4-carbohydrazide 1 (10 mmol) was added to a solution of substituted aldehydes (10 mmol) in methanol (30 mL) in the presence of a few drops of glacial acetic acid. The reaction mixture was irradiated under ultrasonication for 2–5 min at 65 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured on ice cold water, the formed precipitate was filtered off, washed with water and crystallized from ethanol.

(E)-N′-benzylidene-2-(4-methoxyphenyl)quinoline-4-carbohydrazides (2a)

Yellow solid; IR (KBr) υ: 3434, 3190, 3047, 1656, 1591 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ: 3.86 (s, 3H, OCH_3), 7.10 (d, 2H, *J* = 8.8 Hz, ArH), 7.19 (d, 1H, *J* = 4.4 Hz, ArH), 7.46–7.47 (m, 2H, ArH), 7.61 (ddd, 1H, *J* = 8.2, 6.9, 1.1 Hz, ArH), 7.79 (d, 2H, *J* = 7.7 Hz, ArH), 8.09–8.12 (m, 2H, ArH), 8.22 (d, 1H, *J* = 7.7 Hz, ArH), 8.26 (s, 1H, quinoline CH), 8.32 (d, 2H, *J* = 9.2 Hz, ArH), 8.38 (s, 1H, N=CH), 12.23 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): 55.1, 114.0, 116.6, 123.1, 125.0, 126.5, 126.6, 127.2, 128.4, 128.5, 128.6, 128.6, 129.4, 129.9, 130.1, 130.5, 133.9, 140.8, 144.7,

148.0, 148.7, 155.3, 160.8, 163.0; LCMS Anal. Calcd. For $C_{24}H_{19}N_3O_2$ $(M + H)^+$: 382.16. Found: 382.11.

(E)-N′-(4-fluorobenzylidene)-2-(4-methoxyphenyl)quinoline-4-carbohydrazide (2b)

Yellow solid; IR (KBr) υ: 3428, 3168, 3030, 1665, 1570 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ: 3.86 (s, 3H, OCH_3), 7.11 (d, 2H, J = 8.8 Hz, ArH), 7.28 (t, 2H, J = 8.8 Hz, ArH), 7.62 (ddd, 1H, J = 1.1, 7.1, 8.3 Hz, ArH), 7.80 (ddd, 1H, J = 1.3, 6.9, 8.3 Hz, ArH), 7.86 (dd, 2H, J = 5.5, 8.8 Hz, ArH), 8.11 (d, 1H, J = 5.9 Hz, ArH), 8.24 (d, 1H, J = 7.7 Hz, ArH), 8.27(s, 1H, quinoline CH), 8.33 (d, 2H, J = 9.2 Hz, ArH), 8.41 (s, 1H, N=CH), 12.26 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): 55.2, 114.1, 115.7, 115.9, 116.7, 123.1, 125.0, 126.7, 128.6, 128.7, 129.3, 129.4, 130.1, 130.0, 130.5, 140.9, 142.9, 143.6, 147.6, 148.0, 155.4, 160.9, 162.1, 163.0; LCMS Anal. Calcd. For $C_{24}H_{18}FN_3O_2$ $(M + H)^+$: 400.1461. Found: 400.1228.

General method for the synthesis of compounds (3a–h)

Conventional method

Mercaptoacetic acid (3 mmol) was added to a solution of hydrazones (2a–h) (1 mmol) in acetic acid. The contents were refluxed for 5–6 h until completion of reaction. Excess of solvent was removed under reduced pressure and the residue was treated with saturated solution of $NaHCO_3$, extracted with ethyl acetate, dried with Na_2SO_4 , and solvent was distilled off. The residue on recrystallization afforded the pure product.

Non-conventional method

Mercaptoacetic acid (3 mmol) was added to a solution of hydrazones (2a–h) (1.5 mmol) in acetic acid. The reaction mixture was then sonicated for 20–25 min at 65 °C. After completion of the reaction (monitored by TLC), the reaction mixture was poured into ice cold water, filtered to give the crude product, and further purified by crystallization from ethanol, which afforded the pure product.

2-(4-methoxyphenyl)-N-(4-oxo-2-phenylthiazolidin-3-yl)quinoline-4-carboxamide (3a)

Yellow solid; IR (KBr) υ: 3487, 3156, 2984, 1665, 1593 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ: 3.85 (s, 3H, OCH_3), 3.88–3.90 (m, 2H, thiazol CH_2), 6.08 (s, 1H, thiazol CH), 7.05 (d, 2H, J = 8.8 Hz, ArH), 7.39–7.44 (m, 3H, ArH), 7.48 (td, 1H, J = 1.1, 7.7 Hz, ArH), 7.58 (dd, 2H, J = 1.8, 7.7 Hz, ArH), 7.70–7.73 (m, 1H, ArH), 7.75 (s, 1H, quinoline CH), 7.93 (d, 1H, J = 8.1 Hz, ArH), 8.03 (d, 1H, J = 8.4 Hz, ArH), 8.10 (d, 2H, J = 8.8 Hz, ArH), 11.02 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): 29.66, 55.07, 61.96, 114.00, 116.53, 122.63, 124.76, 126.54, 128.15, 128.41, 128.42, 128.44, 129.13, 129.14, 129.20, 129.87, 129.88, 130.34, 137.32, 139.51, 147.82, 155.12, 155.13, 160.80, 165.42, 168.62; LCMS Anal. Calcd. For $C_{26}H_{21}N_3O_3S$ $(M + H)^+$: 456.14. Found: 456.09.

N-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)-2-(4-methoxyphenyl)quinoline-4-carboxamide (3b)

Yellow solid; IR (KBr) υ: 3454, 3118, 2926, 1634, 1572, 1084 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ: 3.85 (s, 3H, OCH_3), 3.91–3.99 (m, 2H, thiazol CH_2), 6.12 (s, 1H, thiazol CH), 7.10 (d, 2H, J = 9.2 Hz, ArH), 7.25 (t, 2H, J = 8.8 Hz, ArH), 7.51–7.55 (m, 1H, ArH), 7.68 (dd, 2H, J = 5.5, 8.8 Hz, ArH), 7.77 (ddd, 1H, J = 1.3, 6.8, 8.4 Hz, ArH), 7.82 (s, 1H, quinoline CH), 7.98 (d, 1H, J = 8.4 Hz, ArH), 8.07 (d, 1H, J = 8.4 Hz, ArH), 8.15 (d, 2H, J = 8.8 Hz, ArH), 11.04 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): 29.47, 55.20, 61.12, 114.21, 115.30, 115.51, 116.43, 122.62, 124.79, 126.74, 128.52, 129.28, 130.19, 130.27, 130.49, 130.58, 133.89, 133.92, 139.73, 147.79, 155.13, 160.88, 161.36, 163.81, 165.34, 168.59; LCMS Anal. Calcd. For $C_{26}H_{20}FN_3O_3S$ $(M + H)^+$: 474.1288. Found: 474.0835.

N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-2-(4-methoxyphenyl)quinoline-4-carboxamide (3c)

Yellow solid; IR (KBr) υ: 3476, 3109, 2953, 1619, 1526, 1123 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ: 3.41 (s, 3H, OCH_3), 3.88–4.01 (m, 2H, thiazol CH_2), 6.11 (s, 1H, thiazol CH), 7.08 (d, 2H, J = 8.8 Hz, ArH), 7.48 (d, 2H, J = 8.4 Hz, ArH), 7.53 (t, 1H, J = 7.7 Hz, ArH), 7.64 (d, 2H, J = 8.1 Hz, ArH), 7.77 (t, 1H, J = 7.5 Hz, ArH), 7.81 (s, 1H, quinoline CH), 7.97 (d, 1H, J = 8.4 Hz, ArH), 8.07 (d, 1H, J = 8.4 Hz, ArH), 8.14 (d, 2H, J = 8.4 Hz, ArH), 11.04 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): 29.48, 55.16, 61.12, 114.17, 116.46, 122.62, 122.63, 124.79, 124.80, 126.67, 128.50, 128.53, 128.54, 129.27, 130.09, 130.10, 130.27, 130.28, 134.08, 136.70, 139.64, 147.80, 155.12, 160.86, 165.35, 168.53; LCMS Anal. Calcd. For $C_{26}H_{20}ClN_3O_3S$ $(M + H)^+$: 490.0992. Found: 490.0784.

N-(2-(4-bromophenyl)-4-oxothiazolidin-3-yl)-2-(4-methoxyphenyl)quinoline-4-carboxamide (3d)

Yellow solid; IR (KBr) υ: 3446, 3175, 2935, 1675, 1534, 1196 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ: 3.85 (s, 3H, OCH_3), 3.91–3.98 (m, 2H, thiazol CH_2), 6.09 (s, 1H, thiazol CH), 7.08 (d, 2H, J = 8.8 Hz, ArH), 7.50–7.54 (m, 1H, ArH), 7.55–7.62 (m, 4H, ArH), 7.74–7.77 (m, 1H, ArH), 7.79 (s, 1H, quinoline CH), 7.97 (d, 1H, J = 7.7 Hz, ArH), 8.06 (d, 1H, J = 8.4 Hz, ArH), 8.14 (d, 1H, J = 8.8 Hz, ArH), 11.03 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): 29.49, 55.13, 61.22, 114.14, 116.47, 122.62, 124.78, 124.79, 126.64, 128.47, 129.27, 129.28, 130.04, 130.05, 130.29, 13.0.36, 130.37, 131.45, 13.46, 137.10, 139.58, 147.82, 155.11, 160.84, 165.34, 168.49; LCMS Anal. Calcd. For $C_{26}H_{20}BrN_3O_3S$ $(M + H)^+$: 534.0487. Found: 534.0448.

N-(2-(4-(trifluoromethyl)phenyl)-4-oxothiazolidin-3-yl)-2-(4-methoxyphenyl)quinoline-4-carboxamide (3e)

Yellow solid; IR (KBr) υ: 3467, 3175, 2927, 1692, 1537, 1076 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ: 3.85 (s, 3H, OCH_3), 3.93–4.01 (m, 2H, thiazol CH_2), 6.23 (s, 1H, thiazol CH), 7.08 (d, 2H, J = 8.8 Hz, ArH), 7.51 (t, 1H, J = 7.7 Hz, ArH), 7.64–7.68 (m, 1H, ArH), 7.74–7.76 (m, 2H, ArH), 7.83 (s, 1H, quinoline CH), 7.93 (d, 1H, J = 8.1 Hz, ArH), 7.97–8.00 (m, 2H, ArH), 8.07 (d, 1H, J = 8.1 Hz, ArH), 8.14 (d, 2H, J = 8.8 Hz, ArH), 11.10 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): 29.47, 55.15, 61.15, 114.12, 116.34, 122.50, 122.60, 124.71, 124.84, 125.21, 125.84, 125.89, 126.65, 128.47, 129.29, 129.53, 129.85, 130.11, 130.26, 132.29, 139.44, 139.69, 147.81, 155.12, 160.88, 165.39, 168.62; LCMS Anal. Calcd. For $C_{27}H_{20}F_3N_3O_3S$ $(M + H)^+$: 524.1256. Found: 524.0791.

2-(4-methoxyphenyl)-*N*-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)quinoline-4-carboxamide (3f)

Yellow solid; IR (KBr) υ: 3486, 3177, 2976, 1643, 1538 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ: 3.84 (s, 3H, OCH_3), 3.94–4.10 (m, 2H, thiazol CH_2), 6.25 (s, 1H, thiazol CH), 7.07 (d, 2H, J = 8.8 Hz, ArH), 7.54 (t, 1H, J = 7.5 Hz, ArH), 7.75–7.79 (m, 1H, ArH), 7.85 (s, 1H, quinoline CH), 7.91 (d, 2H, J = 8.8 Hz, ArH), 8.06 (dd, 2H, J = 4.8, 8.4 Hz, ArH), 8.14 (d, 2H, J = 8.8 Hz, ArH), 8.29 (d, 2H, J = 8.8 Hz, ArH), 11.15 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): 29.31, 55.18, 60.67, 114.18, 116.48, 122.59, 123.67, 124.78, 126.76, 126.77, 128.52, 129.30, 129.31, 129.32, 129.33, 129.35, 130.20, 130.21, 130.25, 139.52, 145.78, 147.84, 155.13, 160.87, 165.50, 168.74; LCMS Anal. Calcd. For $C_{26}H_{20}N_4O_5S$ $(M + H)^+$: 501.1233. Found: 501.1000.

2-(4-methoxyphenyl)-N-(4-oxo-2-p-tolylthiazolidin-3-yl)quinoline-4-carboxamide (3g)

Yellow solid; IR (KBr) υ: 3464, 3133, 2949, 1673, 1546 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ: 2.34 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.89 (s, 2H, thiazol CH_2), 6.08 (s, 1H, thiazol CH), 7.06 (d, 2H, J = 8.8 Hz, ArH), 7.24 (d, 2H, J = 8.1 Hz, ArH), 7.48 (d, 2H, J = 8.1 Hz, ArH), 7.76 (s, 1H, quinoline CH), 7.96 (d, 1H, J = 8.1 Hz, ArH), 8.04–8.09 (m, 2H, ArH), 8.12 (d, 2H, J = 8.8 Hz, ArH), 8.25 (d, 1H, J = 8.8 Hz, ArH), 10.99 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): 20.83, 29.62, 55.11, 61.75, 114.07, 116.53, 122.65, 123.11, 124.82, 126.57, 128.22, 128.45, 128.60, 129.05, 129.23, 129.98, 130.34, 130.63, 134.31, 138.81, 139.62, 140.67, 147.81, 155.11, 160.82, 165.32, 168.58; LCMS Anal. Calcd. For $C_{27}H_{23}N_3O_3S$ $(M + H)^+$: 470.1538. Found: 470.1216.

N-(2-(4-hydroxy-3-methoxyphenyl)-4-oxothiazolidin-3-yl)-2-(4-methoxyphenyl)quinoline-4-carboxamide (3h)

Yellow solid; IR (KBr) υ: 3467, 3245, 3175, 2927, 1692, 1537 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ: 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.86 (s, 2H, thiazol CH_2), 6.04 (s, 1H, thiazol CH), 6.84 (d, 1H, J = 8.1 Hz, ArH), 6.99 (dd, 1H, J = 2.2, 8.1 Hz, ArH), 7.09 (d, 2H, J = 8.8 Hz, ArH), 7.16 (s, 1H, ArH), 7.51 (t, 1H, J = 7.7 Hz, ArH), 7.73 (s, 1H, quinoline CH), 7.75–7.79 (m, 1H, ArH), 8.06 (d, 1H, J = 8.4 Hz, ArH), 8.12 (d, 2H, J = 9.2 Hz, ArH), 8.25 (d, 1H, J = 8.8 Hz, ArH), 9.34 (brs, 1H, OH), 10.92 (brs, 1H, NH); ^{13}C NMR (100 MHz, DMSO): 29.71, 55.15, 55.53, 62.08, 11.76, 114.19, 114.90, 116.46, 121.51, 122.65, 124.83, 126.62, 127.36, 128.44, 128.62, 129.23, 130.06, 130.25, 139.91, 140.74, 147.73, 147.81, 155.09, 155.30, 160.84, 165.24, 168.42; LCMS Anal. Calcd. For $C_{27}H_{23}N_3O_5S$ $(M + H)^+$: 502.1437. Found: 502.1249.

Biological methods

Cell viability assay

The human breast cancer cell line MCF-7 was grown in DMEM containing 10% foetal bovine serum and 0.7% antibiotics. Cells were seeded into 96-well microtiter plates in 100 µL of media at plating density of 5000 cells/well. Seeded cells were incubated at 37 °C, 5% CO_2, 95% air and 100% humidity for 24 h. At 24 h, old media was changed to fresh media followed by treatment with each compound at 10, 1, and 0.1 µM. After 24 h treatment, cell viability was

assessed by 3-(4,5-dimethylthiazol)-2,5- diphenyltetrazolium bromide (MTT), cell were incubated with 20 µL of MTT (5 mg/mL) in PBS for 4 h at 37 °C. The medium was removed and form azan crystal was dissolved in DMSO. MTT reduction was quantified by measurement of absorbance at 570 nm using a multimode reader, Synergy Mx of BioTek.

Cell cycle analysis

Cell cycle progression was evaluated using a flow cytometer, BD LSR Fortessa with software FACS Diva Version 6.2. In brief, MCF-7 human breast cancer cells were incubated for 24 h with given compounds, each at two concentrations closer to IC_{50} values, obtained during the cell viability assay. After 24 h of treatment, cells were harvested, washed with PBS and fixed in ice cold 70% ethanol for overnight in 4 °C. The next day, all samples were centrifuged at 3000 RPM for 4 min and stained with propidium iodide (PI) (5 mg/mL) followed by addition of RNase and analyzed.

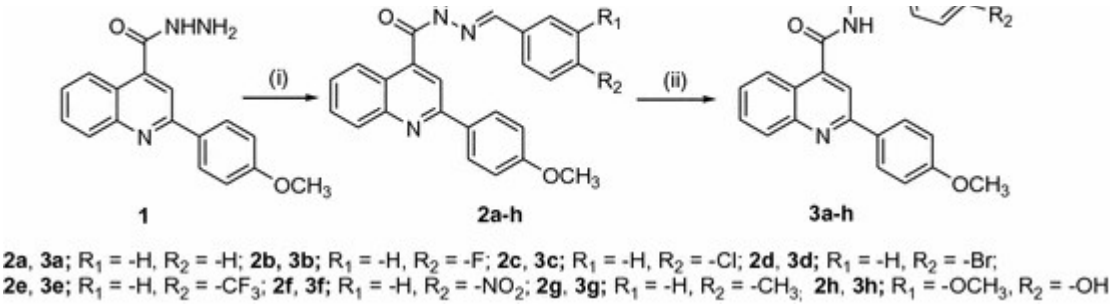
Results and discussion

Chemistry

Over the last three decades, ultrasound-irradiated reactions have become increasingly popular and widely used methodologies in organic synthesis [23]. Compared to the traditional methods, these reactions are known to be faster, convenient and high-yielding process. We, therefore, decided to explore the use of ultrasound irradiation as a green protocol for the synthesis of the target analogues.

The synthetic route of the title compounds 3a–h is shown in Scheme 1. The starting material 2-(4-methoxyphenyl) quinoline-4-carbohydrazide 1 was synthesized according to the previously reported method [24]. We have synthesized and optimized hydrazone derivatives 2a–h, as well as thiazolidinone derivatives 3a–f under conventional and ultrasound irradiation method (Table 1).

Scheme 1



Reagents and conditions: (i) substituted aromatic aldehyde, cat. AcOH, EtOH, US, 65 °C, 2–5 min; (ii) mercaptoacetic acid, AcOH, US, 65 °C, 20–25 min

Table 1 Ultrasound-promoted synthesis of hydrazone and thiazolidinone derivatives 2a–h and 3a–h

As mentioned in Scheme 1, 2-(4-methoxyphenyl) quinoline-4-carbohydrazide 1 was stirred in ethanolic solution with substituted aldehydes in the presence of a few drops of acetic acid under ultrasound irradiation to obtain substituted (*E*)-*N*′-benzylidene-2-(4-methoxyphenyl) quinoline-4-carbohydrazide 2a–h. Further, intermediate quinoline hydrazones 2a–h treated with mercaptoacetic acid in acetic acid under ultrasound irradiation afforded 2-(4-methoxyphenyl)-*N*-(4-oxo-2-phenylthiazolidin-3-yl)quinoline-4-carboxamide derivatives 3a–h. The structures of compounds 3a–h were confirmed by FTIR, ^{1}H and ^{13}C NMR, and mass spectral analysis.

Cell viability assay

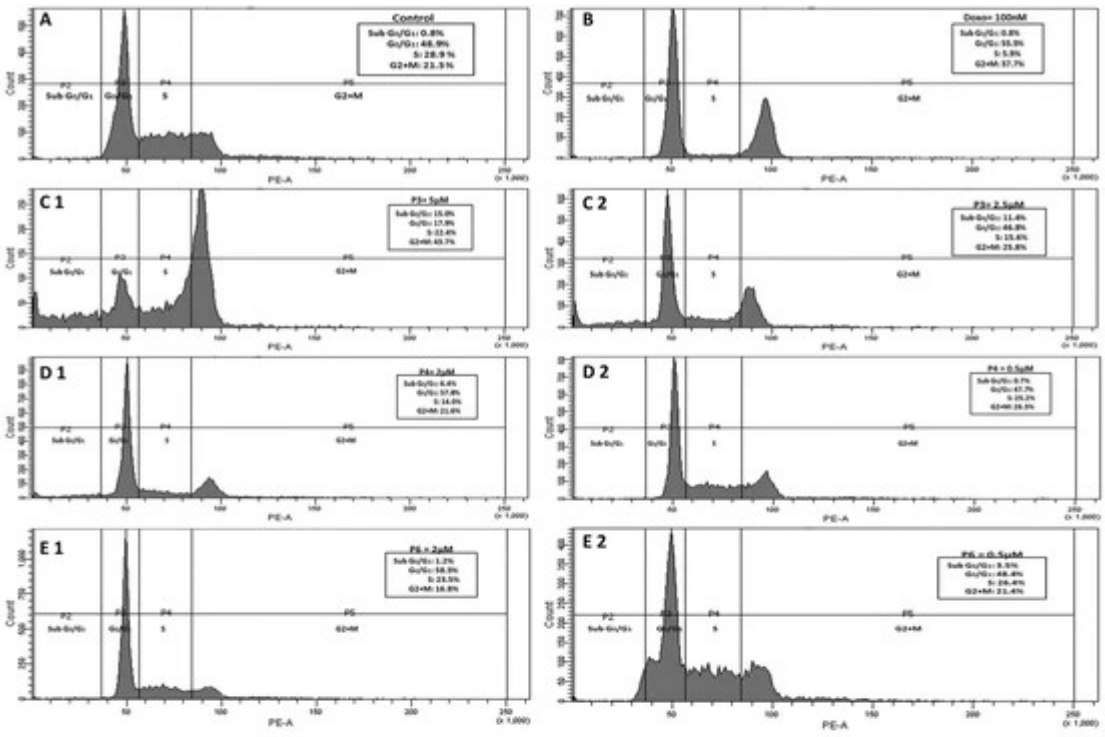
Based on MTT assay Table 2, out of 16 compounds from 2a–h (P series) and 3a–h (R Series), three compounds P3, P4, and P6 have shown inhibition at IC_{50} values of 5.38, 5.12, 0.73 µM, respectively. Others compounds of these series have not attended IC_{50} values, but has growth inhibition at varying degree shown in Table 2. These three compounds P3, P4, and P6 have been taken further for cell cycle analysis.

Table 2 Effect of compounds from P & R series on MCF-7 cells at 24 h of treatment

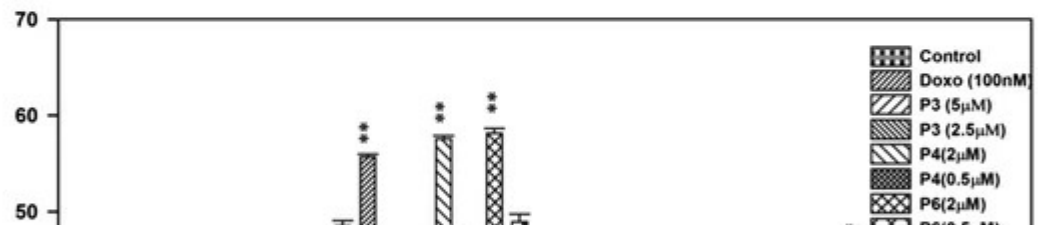
Cell cycle analysis

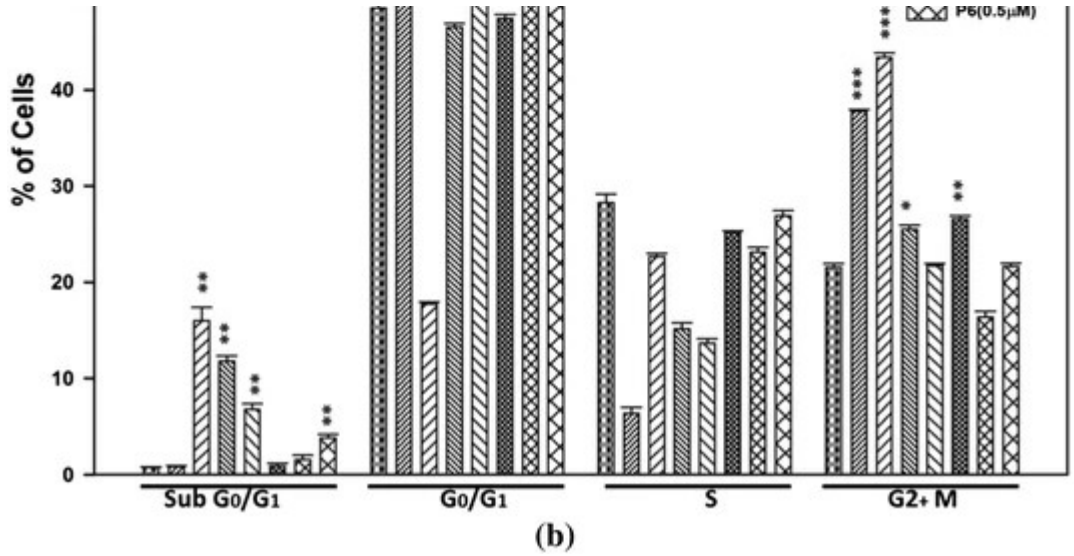
Targeting the cell cycle of tumor cells has been recognized as a promising strategy for cancer therapy [25]. In Fig. 3, compound P3 shows dose-dependent arrest of the cell cycle at G2/M phase, along with the decrease of cells at the G0/G1 phage. Further, increase in the sub G0/G1 population compared to control indicates apoptotic death in the treatment. Compound P4 has shown G0/G1 cell cycle arrest in comparison with control; this has also had an increase in the sub G0/G1 population as an indicator for apoptotic death of cells. Compound P6 has shown G0/G1 arrest and apoptotic cell death.

Fig. 3



(a)





Flow cytometrycell cycle analysis of control and compounds of 2a–h series treated MCF-7 cells. a Histogram analysis showing the effect of compounds from 2a–h series on cell cycle progression of MCF-7 cells. *A* Control (with 0.1% DMSO), *B* treated with doxorubicin (100 nM), *C1* treated with *P3* (5 μM), *C2–P3* (2.5 μM), *D1 – P4* (2 μM), *D2–P4* (0.5 μM), *E1–P6* (2 μM), and *E2–P6* (0.5 μM). b Bar chart showing a comparative analysis of the percentage of cells in each phage of cell cycle during different compound treatments in a dose dependent manner at 24 h. Statistical analysis was performed using Graph Pad Prism software version 6. Values are mean ± SD of three individual experiments (* < 0.05; ** < 0.001; *** < 0.0001 versus controls)

Conclusions

In conclusion, we have synthesized novel quinoline based thiazolidinone derivatives under ultrasound irradiation and evaluated for their anti-cancer activity. Among all the synthesized compounds, P3, P4, and P6 shows potent anti-proliferative activity (IC_{50} values 5.38, 5.12, and 0.73 μM, respectively). Further, these compounds inhibited cell proliferation in a dose-dependent manner. Flow cytometry analysis showed potent compounds significantly induces cell cycle arrest at G2/M on MCF-7 cells. From the result of anticancer activity, it can be concluded that the quinoline nucleus is important for the activity rather than the thiazolidinone nucleus. Thus suggesting that compounds P3, P4, and P6 can be further optimized and developed as a lead molecule.

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Electronic supplementary material

Below is the link to the electronic supplementary material.

Supplementary material 1 (DOC 8359 kb)

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