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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and evaluation of anticancer effect of a novel molecule based-on pillar[5]arene including multi quinoline units

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Abstract

In this study, pillar[5]arene containing ten terminal alkynyl-functional group was prepared and carried out an optimization procedure for target molecule with using 5-hydroxyquinoline molecule known with biological activity. The novel molecule was named as iso-QP[5] and characterized by FT-IR, melting point, NMR, elemental analysis, and mass spectroscopy. The aim was to evaluate the anticancer effects of iso-QP[5] on MCF7 human breast cancer cells. The IC_{50} dose of iso-QP[5] in MCF7 cells was found to be 25 µM for 24 h using XTT assay. Expressions of eight genes for apoptosis were determined by qPCR. The results showed a significant increase in the expression of *BAX*, *CASP3, CASP9*, *CYCS*, and *P53* genes after treatment with iso-QP[5] in MCF7 cells. However, iso-QP[5] treatment significantly decreased expression of *BCL2* and *CASP8* genes. It is concluded that novel molecule iso-QP[5] caused apoptosis by regulating genes that are important in apoptosis in human breast cancer cells.

Keywords Apoptosis · Cytotoxicity · Pillar[5]arene · Quinoline

Introduction

Cancer is a huge class of diseases determined by unrestrained and spread of the abnormal growth cells. The ratio of breast cancer is 24.2% in all cancer types and it is the most common diagnosed cancer in women worldwide. Moreover, this disturbing disease causes death in women, which ratio is 15.0% (Siegel et al. 2016; Verma et al. 2019; Vineis and Wild 2014). In the past decades, the treatment of cancer by drug molecules has evolved from general cytotoxic chemotherapy to using drugs matching the specific targets of a cancer kind (Eren et al. 2014; Nowak-Sliwinska et al. 2019; Min et al. 2019). Among these drug agents, macrocycles have the most important position owing to their multi-supramolecular interactions (Soor et al. 2018; Chen et al. 2019; Wintgens et al. 2019). The substitution of macrocycles with the organic groups having pharmacological functions plays a crucial role in the effective of anticancer agents. It was reported that new generation drug molecules including quinoline derivatives may act as anticancer agents through a variety of mechanisms such as cell cycle arrest in topoisomerase inhibition (Cheng et al. 2008), the G2 phase (Kim et al. 2005), inhibition of tyrosine kinases and tubulin polymerization (Alqasoumi et al. 2009) and inhibition of which is the most common mechanism (Mulvihill et al. 2008; Pannala et al. 2007; Nishii et al. 2010). Quinoline scaffolds on macrocycles were emerged as potent multi inhibitors of EGFR kinase and human Topo IIα activity at very low concentrations against several cancer cell lines comparable to erlotinib (Matsui et al. 2008; Kubo et al. 2005).

Pillar[n]arene macrocycles as novel key player of supramolecular chemistry are nominated to multi-disciplinary areas such as pharmacology, biochemistry, medicine, material science, etc. (Ogoshi et al. 2008; Xue et al. 2012; Ogoshi et al. 2016; Ma et al. 2011; Yu et al. 2012). Therefore, they may transform to excellent cages having symmetrical and gifted arms, 10 and 12 effective

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organic fragments for all these applications (Park and Kim 2015; Yao et al. 2017).

The fascinating host-guest properties of pillararenes have been reported as polymer nanocapsule for drug delivery system. Design of smart molecules for pharmacological applications has been growing to be a hot topic (Duan et al. 2013; Zhang and Zhao 2016; Chang et al. 2014; Huang et al. 2017). However, pillararene was not directly proposed as a drug molecule for the anticancer studies when they were first synthesized in 2008.

To the best of our knowledge, the anticancer properties of this new kind of macrocycle, pillar[n]arene, have not been investigated earlier. In here, pillar[5]arene derivative having ten quinoline units, which pharmacologically active, including suitable reaction conditions for this type of compounds was designed and the chemical synthesis of the precursors materials was conducted. Then, it was aimed to investigate anticancer effects of the iso-QP[5]in MCF7 human breast cancer cells. For this, the cytotoxic effect of pillar[5]arene derivative was primarily evaluated in MCF7 human breast cancer cells. The apoptotic effect of pillar[5] arene derivative was determined by evaluate expression levels of important some genes in apoptosis and annexin V apoptosis assay.

Materials and methods

Chemicals

The iso-QP[5] was prepared as a known synthesis steps (Kursunlu et al. 2017). The synthesis route of 1,4-bis(2-iodoethoxy)benzene, pillar[5]arene, and iso-QP[5] were given in Fig. 1 where all reactions were performed in nitrogen atmosphere. BF_3OEt_2, 4′-hydroxy-4-biphenylcarboxylic acid, carbon tetraiodide, 5-hyroxyquinoline, 1,4-Bis(2-hydro-xyethoxy) benzene, paraformaldehyde, triphenylphosphine, potassium carbonate, 1,2-dichloroethane, and toluene were purchased from Acros and Sigma-Aldrich. ^{13}C-NMR and ^{1}H-NMR spectra were recorded at r.t. on a Varian 400 MHz. The elemental analyses results were taken from a TruSpec Elemental Analyzer. The infrared measurements were performed on a Bruker Fourier Transform Infrared FTIR (ATR). Also, the tested compounds and all purchased reagents have to range between 95 and 100% purity. For assays of cell culture, RPMI-1640 medium and XTT [2,3-bis (2-methoxy-4-nitro-5-sulfophenyl) 2H tetrazolium-5-carboxanilide] kit were purchased from Biological Industries. Penicillin/streptomycin mixture and phosphate-buffered saline (PBS) were commercially obtained from Gibco. Fetal bovine heat-inactivated serum (FBS) and TRIzol reagent were purchased from Capricorn Scientific

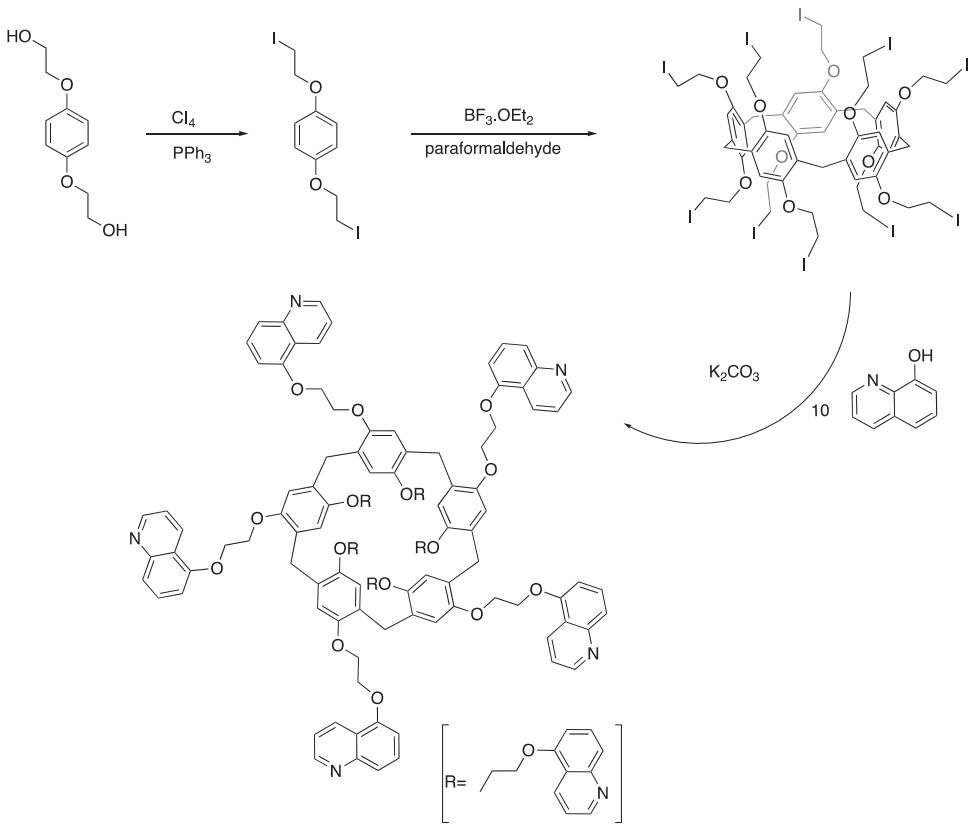

Fig. 1 Synthesis of pillar[5] arene (iso-QP[5]) and its functionalization with 5-hyroxyquinoline

and Invitrogen, respectively. Transcriptor first strand cDNA synthesis kit and SYBR® Green Supermix were commercially supplied from Bio-Rad. FITC Annexin V Apoptosis Detection Kit was purchased from BioLegend.

Synthesis of 1,4-bis(2-iodoethoxy)benzene

1,4-bis(2-iodoethoxy)benzene was prepared as a known synthesis procedure (Kursunlu et al. 2017). The white flake-like crystals were dried in a desiccator (4.25 g, 83%), purity: 99% and characterized as ^{1}H-NMR (400 MHz, chloroform-d, r. t.) δ (ppm): 6.94 (s, 4H), 4.31 (*t*, $J = 5.2$ Hz, 4H), 3.53 (*t*, $J = 5.7$ Hz, 4H). ^{13}C-NMR (100 MHz) δ (ppm): 150.44, 116.15, 75.22, 4.29.

Synthesis of pillar[5]arene having ten iodine units

Pillar[5]arene was also prepared as a known synthesis procedure (Kursunlu et al. 2017) using column chromatography (SiO_2; petroleum ether/CH_2Cl_2, 1:1) gave product (0.90 g, 31%). Purity: 98% purity^{1}H-NMR (400 MHz, chloroform-d, r. t.) δ (ppm): 6.93 (s, 10H), 4.31 (*t*, $J =$ 5.4 Hz, 20H), 3.85 (s, 10H), 3.53 (*t*, $J = 5.4$ Hz, 20H). ^{13}C-NMR (100 MHz) δ (ppm): 149.82, 125.89, 116.40, 67.41, 29.72, and 3.91. Elemental analysis calcd: $C_{55}H_{60}I_{10}O_{10}$: C, 30.72; H, 2.81; found: C, 30.56; H, 3.08.

Synthesis of iso-QP[5]

Iso-QP[5] was synthesized by using a previously reported procedure (Kursunlu et al. 2017). K_2CO_3 (1.6 g, 12 mmol) was added to a solution of pillar[5]arene having ten iodine units (0.86 g, 0.4 mmol) and 5-hydroxyisoquinoline (0.608 g, 2.1 mmol) in acetonitrile/DMF (100 mL/6 mL) and the mixture was refluxed for 120 h. Column chromatography (SiO_2; eluent-CH_2Cl_2) gave iso-QP[5] as a pale-brown solid (0.376 g, 81%). Mp: 110–112.0 °C. Purity: 95%.^{1}H-NMR (400 MHz, chloroform-d, room temperature) δ (ppm): 8.88 (bs, 10H), 8.51 (bs, 10H), 7.35–7.10 (m, 40H), 6.93 (bs, 10H), 3.86 (m, 40H), 3.69 (bs, 10H). ^{13}C-NMR (100 MHz) δ (ppm): 166.12, 155.21, 147.32, 145.11, 139.46, 137.14, 133.26, 128.99, 128.31, 125.16, 123.42, 112.42, 106.32, 68.21, 66.37, 29.91. Elemental analysis calcd $C_{145}H_{120}N_{10}O_{20}$: C, 74.98; H, 5.21; N, 6.03; found: C, 74.54; H, 5.56; N, 5.97. m/z calcd for $[M + H]^+$, 2323.6; found 2324.6.

Cell culture

MCF7 (ATCC® HTB-22™) human breast cancer cell line was obtained from ATCC. Cells were proliferated in a cell culture incubator including 37 °C, 5% CO_2 atmosphere, humidified 95% air in RPMI-1640 medium containing 2 mM L-glutamine, 10% FBS, and 1% penicillin/streptomycin mixture. MCF7 cells were treated with 25, 50, 75, 100, and 150 µM iso-QP[5]during 72 h, time- and dose-dependent manner.

Cytotoxicity assay

Cytotoxic effect of iso-QP[5] in MCF7 cells were determined by using XTT assay as indicated in manufacturer's instruction. The iso-QP[5] was dissolved in dimethylsulfoxide (DMSO) and the final concentration of DMSO did not exceed 0.1%. Briefly, MCF7 cells were seeded in 96-well plates at a number of 1×10^3 cells/well and incubated for 24 h. Then, cells were treated with various concentrations (0–150 µM) of iso-QP[5] and incubated for 24, 48, and 72 h. After the incubations, cell viability was determined by using XTT mixture as recommended by supplier. After XTT mixture was added to wells, plates were re-incubated for 4 h. Then, amount of cell viability was determined with absorbance at wavelength 450 nm (reference wavelength 630 nM) using a microplate reader. Viability was calculated using the background-corrected absorbance as follows: Viability (%) = A of experiment well/A of control well × 100.

RNA isolation, cDNA synthesis, and qPCR analysis

Total RNA from MCF7 cells was extracted with TRIzol reagent. cDNA synthesis was conducted using the Transcriptor first strand cDNA synthesis kit according to the manufacturer's instructions. The primer sequences of target and reference genes (Table 1) used in the qPCR were previously reported elsewhere (Eroğlu et al. 2018). Briefly, qPCR mix for each gene was set up in 10 µL final volume containing 5 µL 2X SYBR Green Supermix, 5 pMol of forward and reverse primer, and 2 µL cDNA. PCR profile was consist of an initial denaturation at 95 °C for 30 s, followed by 40 cycles of denaturation at 95 °C for 5 s and annealing/extension at 60 °C for 30 s.

Cell apoptosis assay

Apoptotic effect of iso-QP[5] in MCF7 cells was detected using the FITC Annexin V Apoptosis Detection Kit (BioLegend, BioLegend Inc., San Diego) according to the manufacturer's instructions. MCF7 cells were seeded in six-well plates at density of 1×10^6 cells per well in 2 mL of complete RPMI and incubated at 37 °C in a 5% CO_2 humidified atmosphere for 24 h. After treating with iso-QP [5] for 24 h, the cells were trypsinized and then washed three times with cold PBS. The cells centrifuged and the pellets were resuspended in Annexin V Binding Buffer at a concentration of 1×10^6 cells/mL. Subsequently, 5 µL of

Table 1 Primers sequences used qPCR analysis

Gene	Primer sequence	PCR product size (bp)
GAPDH	F:5-TGAACGGGAAGCTCACTGG-3 R:5-TCCACCACCCTGTTGCTGTA-3	307
BAX	F:5-GGAGCTGCAGAGGATGATTG-3 R:5-GGCCTTGAGCACCAGTTT-3	151
BCL2	F:5-GTGGATGACTGAGTACCTGAAC-3 R:5-GAGACAGCCAGGAGAAATCAA-3	125
CASP3	F:5-GAGCCATGGTGAAGAAGGAATA-3 R:5-TCAATGCCACAGTCCAGTTC-3	162
CASP7	F:5-CGAAACGGAACAGACAAAGATG-3 R:5-TTAAGAGGATGCAGGCGAAG-3	169
CASP8	F:5-GCCCAAACTTCACAGCATTAG-3 R:5-GTGGTCCATGAGTTGGTAGATT-3	160
CASP9	F:5-CGACCTGACTGCCAAGAAA-3 R:5-CATCCATCTGTGCCGTAGAC-3	153
CYCS	F:5-GGAGAGGATACACTGATGGAGTA-3 R:5-GTCTGCCCTTTCTTCCTTCTT-3	102
P53	F:5-GAGATGTTCCGAGAGCTGAATG-3 R:5-TTTATGGCGGGAGGTAGACT-3	129

FITC Annexin V and 7AAD added to 100 µL of cell suspension and then cells incubated for 15 min at the room temperature in the dark. Then, 400 µL of Annexin V Binding Buffer was added to each tube. Obtained cell suspensions were examined using the Becton Dickinson Canto II (BD Biosciences, Heidelberg, Germany) flow cytometry devices. The data analyses were performed using FACSDiva software (version 6.1.3, BD Biosciences).

Statistical analysis

Statistical analysis of the data was previously described (Eroğlu et al. 2018). Briefly, the qPCR analysis was conducted with the ΔΔCT method. The comparisons of the control and dose groups were performed with "Volcano Plot" analysis in "RT^{2}Profiles^{TM}PCR Array Data Analysis", which was assessed statistically using the "Student *t* test". Moreover, other analyses were done using the "Student *t* test" in SPSS 20.0 statistical analysis program. If $p < 0.05$ or less, was reported as statistically significant difference.

Results and discussion

Characterization of compounds

The NMR (^{1}H & ^{13}C-NMR) spectra of the prepared compounds were given in SI. The protons of 1,4-bis(2-iodoethoxy)benzene were observed at 6.92 ppm (singlet), 4.33 ppm (triplet), and 3.52 ppm (triplet). Following to the transformation of 1,4-bis(2-iodoethoxy)benzene to pillar[5]arene having ten iodine units, the methylene bridge protons appeared at 3.86 ppm. In ^{1}H-NMR iso-QP[5], the proton signals were observed 8.88, 8.51, 7.35–7.10, and 6.93 for aromatic groups, 3.86 and 3.69 (bs, 10H) for the aliphatic fragments, respectively. The $-CH_2$ protons of pillar[5]arene having ten iodine units give a singlet peak asserting that there is no barrier to through-the annulus-rotation. After the reaction of pillar[5]arene having ten iodine units with 5-hydroxyisoquinoline, led to the broadened singlet peaks in ^{1}H-NMR iso-QP[5]. Actually, these differences are known that previous literatures support to understand why this happens that they split at higher or lower temperatures. The steric implications of the conformation, the intermolecular interactions such as hydrogen bonds and aggregation had been reported as the causing of these changes (Kursunlu et al. 2017).

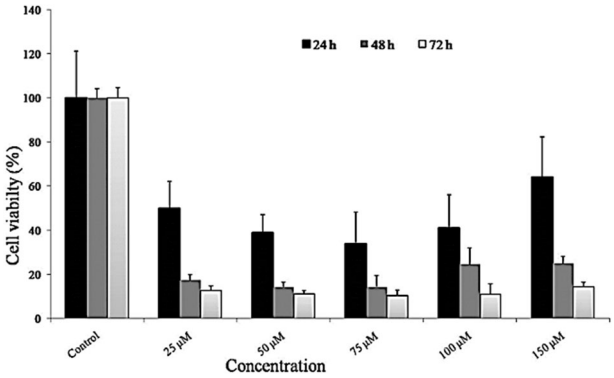

Fig. 2 Effect of iso-QP[5] on the viability in the MCF7 cells. The cells were treated with iso-QP[5] and at different concentrations and time intervals and antiproliferative effect was evaluated by XTT assay. IC_{50} dose of iso-QP[5] in MCF7 cell line was found to be 25 µM. Data are the average results of three independent experiments

Antiproliferative effect of iso-QP[5] in MCF7 cells

The effect of iso-QP[5] on proliferation of MCF7 cell line was determined by XTT assay. As shown in Fig. 2, iso-QP[5] inhibited the cell viability of MCF7 breast cancer cells time- and dose-dependent manner. The IC_{50} dose of iso-QP[5] in MCF7 cells was found to be 25 µM for 24 h. In the following experiments, dose of 25 µM, which inhibited 50% of the cells, was used for in MCF7 cells.

By advantage of the multi-arms and bidirectional of pillar[5]arenes, we prepared a new macrocycle by quinoline moieties having outstanding biological efficiency and good activity in cell lines. A number of studies were reported using of pillar[n]arenes having multi-arms in the drug delivery system owing to famous property with host–guest. Guo et al. showed that water-soluble pillar[5]arene-cationic poly(glutamamide) has negligible effect on the cell viability using concentrations ranging from 5.0 to 20 µg/mL in normal and

cancer cells (Guo et al. 2017). Chang et al. reported that a charge-reversal amphiphilic pillar[5]arene bearing ten charge-reversal head groups selectively destroyed cancer cells by targeting the cancer cell membrane both in vitro and in vivo (Chang et al. 2019). In this study, introduction of flexible chains into bidirectionally bounded from *para* positions of benzene fragments of pillar[5]arene (five-down and five-up chains) of the quinoline nucleus improved the water solubility features in living cell applications. The cunning modification of pillar[5]arene by our research group has led to the discovery of a potential next-generation anticancer agent iso-QP [5]. In a continuing effort to improve new drug molecule including quinoline derivatives endowed with better bioactivity in recent investigations. Venkatarao et al. (2019) designed and synthesized ten novel molecules of chalcone fused quinoline derivatives. Moreover, their anticancer activity was evaluated in some cancer cell lines using MTT assay. Especially six of the newly synthesized molecules exhibited more potent activity at very low doses in MCF7 (breast), A549 (lung), and A375 (melanoma) cancer cells. In these cells, IC_{50} dose range of newly synthesized molecules was 0.11–8.56 µM (Venkatarao et al. 2019). Thirunavukkarasua et al. synthesized quinoline based palladium (II) complexes and found cytotoxic effect in A549 human lung cancer and MCF7 breast cancer cell lines. It was reported that IC_{50} dose of palladium complex 1 synthesized was found to be 30 and 26 µM in A549 and MCF7 cells, respectively. IC_{50} doses of palladium complex 2 were found to be 31 µM (A549) and 29 µM (MCF7) in these cancer cells. Complexes showed cytotoxic effects at low concentrations (Thirunavukkarasu et al. 2018). In the present study, IC_{50} dose of iso-QP[5], a pillar[5]arene derivative having to quinoline units, was found to be 25 µM for 24 h in MCF7 cells.

Gene expression analysis with qPCR

After total RNA isolation was conducted from control and iso-QP[5]-treated cell groups, cDNA synthesis was performed using the Transcriptor first strand cDNA synthesis kit. The changes in expression of *BAX, BCL2, CASP3, CASP7, CASP8, CASP9, CYCS*, and *P53* genes that play an important role in apoptosis relative to the control group after treatment with 25 µM iso-QP[5] in MCF7 cells were evaluated with qPCR analysis. It was observed that iso-QP[5] in MCF7 cells compared with the control group cells caused a significant increase in the expression of *BAX* (1.32 fold), *CASP3* (1.04 fold), *CASP9* (1.53 fold), *CYCS* (1.86 fold) and *P53* (2.78 fold) genes, and a significant decrease in the expression of *BCL2* (2.92) and *CASP8* (1.52) genes (Fig. 3, $p < 0.05$). In the iso-QP[5]-treated MCF7 cells compared with the control group cells was observed a decrease in *CASP7* gene expression, however it was not statistically significant.

Apoptosis, defined by Kerr et al. in 1972, is natural form of programmed cell death (Kerr et al. 1972). Moreover, it is also an induced important cell death pathway in cancer therapy such as chemotherapy and radiotherapy. Apoptosis can occur via intrinsic pathway triggered by intracellular stressors or extrinsic pathway induced with the activation of death receptors. Cytochrome c release from mitochondria is important process in the intrinsic pathway. Bcl-2 protein family (like proapoptotic protein BAX and antiapoptotic protein BCL2) plays an important role in release cytochrome c to cytosol from mitochondria by changing mitochondrial membrane permeabilization in this process. Furthermore, tumor suppressor protein p53 activates proapoptotic genes such as BAX in case of DNA damage in the cells. Cytochrome c forms a complex with Apaf-1 protein in cytosol and this complex cleaves initiator caspase-9. Then, executioner caspases 3, 6, and 7 are activated to induce cell death. However, activation of death ligands and death receptors on the cell surface is important in the extrinsic pathway (Wuest et al. 2019). Expression levels of important genes for apoptosis were analyzed by qPCR in this study. According to qPCR results, it was observed a significant increase in the expression of *BAX*, *CASP3, CASP9*, *CYCS*, and *P53* genes, after treatment with 25 µM iso-QP[5] in MCF7 cells. However, treatment of 25 µM iso-QP[5] caused a significantly decrease in expression of *BCL2* and *CASP8* genes. Although CASP7 gene expression was downregulated, this finding was statistically insignificant. It was seen that iso-QP[5] can cause apoptosis by regulating these genes that are important in apoptosis in MCF7 cells.

Apoptotic effect of iso-QP[5] in MCF7 cells

Annexin V and 7AAD were used to evaluate the apoptotic effect of iso-QP[5] in MCF7 cells. Only annexin V positive

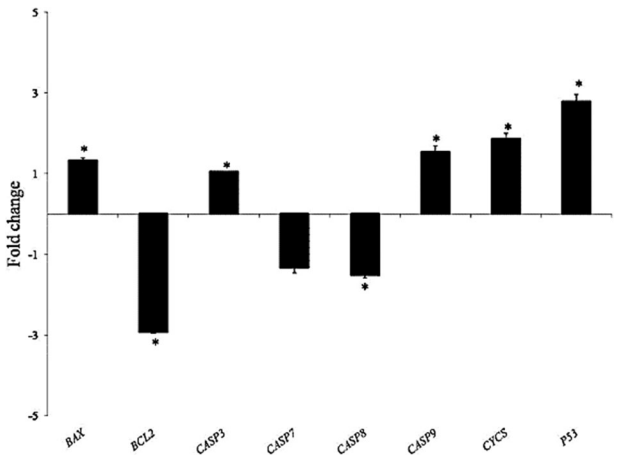

Fig. 3 The changes in expression of genes that play an important role in apoptosis relative to the control group after iso-QP[5] treatment in MCF7 cells. An asterisk indicates statistically important ($p < 0.05$) difference

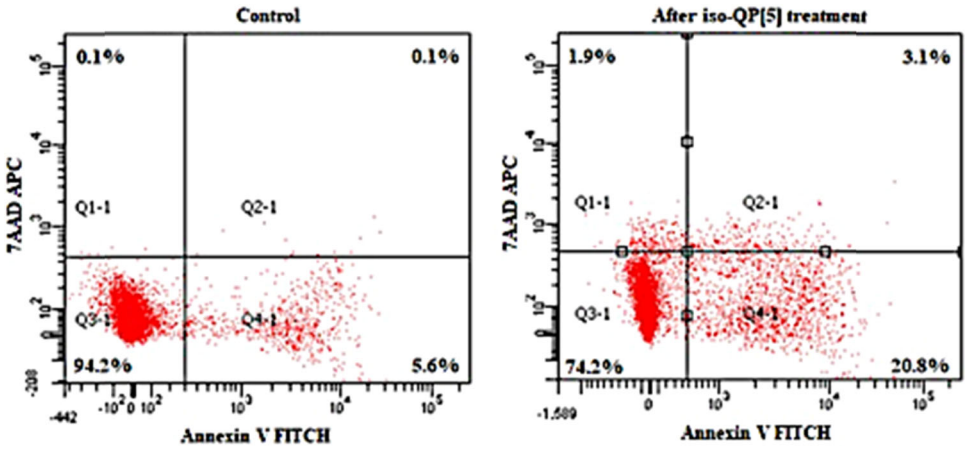

Fig. 4 Flow cytometric apoptosis image

area shows early apoptosis, only 7AAD positive area shows necrosis, annexin V and 7AAD show positive area late apoptosis. In the light of this information, early apoptosis rate was 5.6%, late apoptosis rate was 0.1%, and necrosis rate was 0.1% in the control group. After 25 μM iso-QP [5] treatment, early apoptosis, late apoptosis, and necrosis rates were 20.8, 3.1, and 1.9%, respectively. The flow cytometry image of the control and iso-QP [5] is shown in Fig. 4.

Phosphatidylserine (PS) is located on inner surface of cell membrane in normal cells. However, PS translocated to outer surface from inner of cell membrane in process of apoptosis. Annexin V is an important protein, which binds to PS in the presence of Ca^{2+} ions (Wuest et al. 2019). Su et al. reported that new synthesized quinoline derivatives exhibited antiproliferative activity with low IC_{50} value against seven human tumor cell lines. Moreover, N-(3-methoxyphenyl)-7-(3-phenylpropoxy)quinoline-4-amine was found to be the most potent antiproliferative agent. Furthermore, it was showed that this compound induced apoptosis in HCT116 human colon cancer cells using the annexin V-FITCH/PI assay (Su et al. 2019). In the present study, annexin V assay indicated that iso-QP[5] treatment caused early and late apoptosis in MCF7 cells.

Conclusion

In this study, pillar[5]arene derivative having quinoline units was designed, synthesized, and anticancer effects of new target molecule were investigated in MCF7 human breast cancer cells. This newly synthesized molecule exhibited antiproliferative effect in MCF7 cells via genes that are important in apoptosis. It is thought that new target molecule may be potent anticarcinogenic agent. However, more detailed studies should be performed to revealed anticarcinogenic activity of novel molecule iso-QP[5].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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