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RESEARCH ARTICLE

Synthesis and pro-apoptotic effects of new sulfonamide derivatives via activating p38/ERK phosphorylation in cancer cells

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Abstract

Herein, the compounds bearing sulfonamide fragment such as *N*-(2-amino-5-benzoylphenyl)-4-nitrobenzene sulfonamide hydrochloride (**1**), *N*-(quinolin-8-yl)-4-nitro-benzenesulfonamide hydrochloride (**2**), *N*-(pyridine-2-ylmethyl)-4-nitro-benzenesulfonamide hydrochloride (**3**) were synthesized by the reaction of 3,4-diaminobenzophenone, 8-aminoquinoline or 2-picoylamine and 4-nitrobenzenesulfonyl chloride, respectively. The structures of the newly synthesized compounds were elucidated on the basis of elemental and spectral analyses. All the prepared compounds were evaluated for their *in vitro* anti-cancer activity against various cancer cell lines and to explore the underlying molecular mechanisms involved in this process. *In vitro* cytotoxic activities of the compounds were screened against human hepatocellular (HepG2), breast (MCF-7) and colon (Colo-205) cancer cell lines by MTT assay, mRNA expression of genes with qPCR and phosphorylation of p38 and ERK1/2 with Western blot. Tested compounds could significantly reduce cell proliferation and induced mRNA expression of pro-apoptotic genes; caspase 3, caspase 8 and caspase 9. Activation of these apoptotic genes probably is mediated by activation of p38.

Introduction

Cancer mortality rate in the developed world have risen throughout in spite of advancement made in cancer diagnosis and therapy during the last several decades and it is the leading cause of worldwide deaths¹. Previous observations suggested that induction of apoptosis contributed to the high rate of cell loss in malignant tumors and, moreover, could promote tumor progression². Caspases are proteases, which have a central role in triggering and executing apoptosis. The two major pathways of triggering apoptosis are the intrinsic and extrinsic pathway³. The main intrinsic pathway is characterized by mitochondrial dysfunction, with the release of cytochrome c, activation of caspase-9, and subsequently of caspase-3. The extrinsic pathway is activated at the cell surface through death receptor mediated activation of caspase-8 or caspase-10, followed by caspase-3 activation⁴.

Mitogen-activated protein kinases (MAPKs) play an essential role in apoptotic signal transduction by modulating gene transcription in the nucleus in response to changes in the cellular environment^{5,6}. The most studied MAPKs are the extracellular signal-regulated protein kinases (ERK1 and ERK2), and p38 MAPKs (p38 α , p38 β , p38 γ , p38 δ). Recently, it was observed that chemotherapeutic agents and other novel compounds initiate cancer cell apoptosis through the activation of p38 MAP kinase⁷.

Keywords

Apoptosis, cancer, caspases, MAPK, sulfonamide derivatives

History

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ERK1/2 an inducible component of normal cellular signal transduction processes has been shown to be constitutively activated (phosphorylated) in several cancer cell lines^{8–10}. In contrast to such constitutive activity of ERK1/2, transient activation of the kinases may contribute to induction of apoptosis^{11,12}. ERK activity has also been involved in cell death induced by various antitumor compounds, such as resveratrol¹³, quercetin¹⁴, miltefosine¹⁵ and taxol¹⁶.

The compounds bearing sulfonamide piece are generally occurred from R-sulfonyl chloride with primary or secondary amines in basic media¹⁷. In recent times, there has been an increase in studies regarding the substances containing sulfonamide fragment because of their potential applications such as for coordination chemistry¹⁸, medicinal chemistry¹⁹, catalyst chemistry²⁰, chemical luminescence²¹ and analytical chemistry fields²². On the other hand, sulfonamide compounds are known to contain inherent pharmacological properties such as anti-microbial²³, anti-inflammatory²⁴, anti-viral²⁵, anti-proliferative²⁶, angiogenesis²⁷ and enzyme inhibitory (carbonic anhydrase) activities²⁸.

Therefore, based on these findings, sulfonamide compounds were synthesized by the reaction of sulfonamide fragments; *N*-(2-amino-5-benzoylphenyl)-4-nitrobenzenesulfonamide hydrochloride (**1**), *N*-(quinolin-8-yl)-4-nitro-benzenesulfonamide hydrochloride (**2**), *N*-(pyridine-2-ylmethyl)-4-nitro-benzenesulfonamide hydrochloride (**3**) with 3,4-diaminobenzophenone, 8-aminoquinoline or 2-picoylamine and 4-nitrobenzenesulfonyl chloride, respectively and we tested the effects compounds on cell viability, pro-apoptotic gene expression and of p38/ERK activation.

Results and discussion

Synthesis

The aromatic sulfonamide compounds (**1–3**) were successfully synthesized by the reaction of aryl sulfonyl chloride with 3,4-diaminobenzophenone, 8-aminoquinoline or 2-picoylamine. In the $^1\text{H-NMR}$ spectra for the synthesized compounds (**1–3**), for **1**, the $-H_1$, $-H_2$, $-H_3$ protons were located 7.08, 7.44 and 6.99 as doublet, respectively. the $-H_a$ and $-H_b$ could be were assigned 8.24 and 8.30 as doublet, respectively. For **2**, the $-H_a$ and $-H_b$ protons were observed 8.11 and 8.30 as doublet, respectively. For **3**, the $-H_1$, $-H_2$, $-H_3$ and $-H_4$ protons could be assigned 7.98 as doublet, 8.47 as triplet, 7.88 as triplet and 8.78 as doublet. The representative NMR spectrums are attached in Figure S1 as supplementary materials.

In the IR spectra for **1–3**, $N-H$ stretching frequency peaks belonging to the sulfonamide groups appeared at 3210, 3342 and 3239 cm^{-1} and NH_2 stretching frequency peaks were observed at 3463–3380 for **1**. In addition, the SO_2 stretch peaks appeared at 1314–1155 for **1**, 1350–1167 for **2**, 1334–1160 for **3**. All the measurements and interpretations are compatible with the proposed structure of compounds.

Biological activity

The sulfonamides constitute an important class of therapeutic agents in current medicinal science. Although they have a common chemical motif of an aromatic/heterocyclic sulfonamide, there are a variety of mechanisms for their anti-tumor action, such as disruption of microtubule assembly, cell cycle arrest in the G1 phase, angiogenesis inhibition and carbonic anhydrase inhibition. Furthermore, some of these compounds selected via elaborate preclinical screenings are currently being evaluated in clinical trials¹⁹.

To test the effect of our compound, we used MTT assay which measure levels of cellular metabolism with decreased levels indicating cell death. Treatment with compounds during 24h decreased cell viability in MCF-7 (Figure 1), HEPG2 (Figure 2) and Colo-205 (Figure 3) cell lines. Decrease in cell viability in response to 12 and 24 h treatment with compounds correlated with a significant increase in pro-apoptotic gene expressions. Caspase 3 mRNA expression (Figure 4) increased following by 12h treatment with our tested compounds in three different types of cancer cell lines. Especially in MCF-7 cells increasing in caspase

3 mRNA levels were measured after 24 h treatment with all tested compounds. Compound **1** and compound **2** treatments during 12 h might induce apoptosis via activating caspase 9 mRNA expressions in MCF-7 and HEPG2 cell lines (Figure 5). In addition to these, Caspase 9 mRNA expression increased in MCF-7 cell line following 24 h treatments with compound **1** and compound **2**. In both 12 and 24 h treatment periods, compound **2** caused to an increasing in caspase 8 mRNA expression in MCF-7 cell line (Figure 6).

Based on the finding of apoptosis signaling activation in cancer cells, we were interested in which signaling pathway was involved in the activation of pro-apoptotic gene expression. Thus we further detected the activation of MAPK pathway. Therefore, activated ERK is usually translocated from the cytosol to the nucleus, where it can affect cellular functions, such as gene transcription, cell proliferation, differentiation, and apoptosis²⁰. Phosphorylation of ERK was markedly demonstrated in colo-205 cell line after 12 h treatment with all tested compounds (Figure 7). Activation of caspase 3 mediated apoptosis in colo-205 cell line after 12 h treatments with all tested compounds might regulated with the activation of ERK phosphorylation. Activation of p38

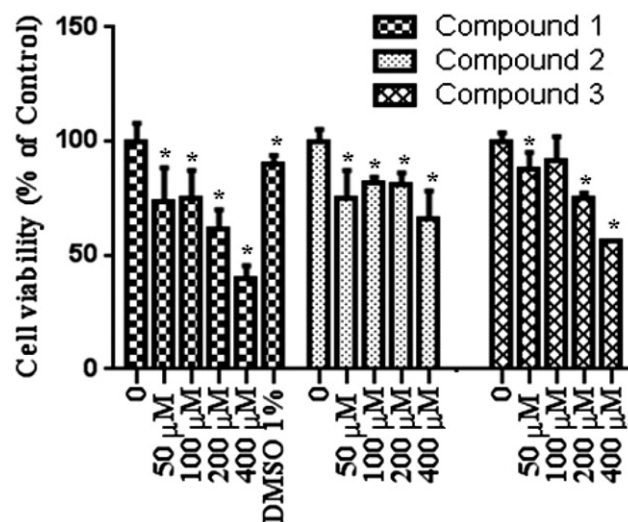


Figure 2. Proliferation inhibiting effects of compounds in HEPG2 cell line. $n = 4$, $*p < 0.05$ versus control.

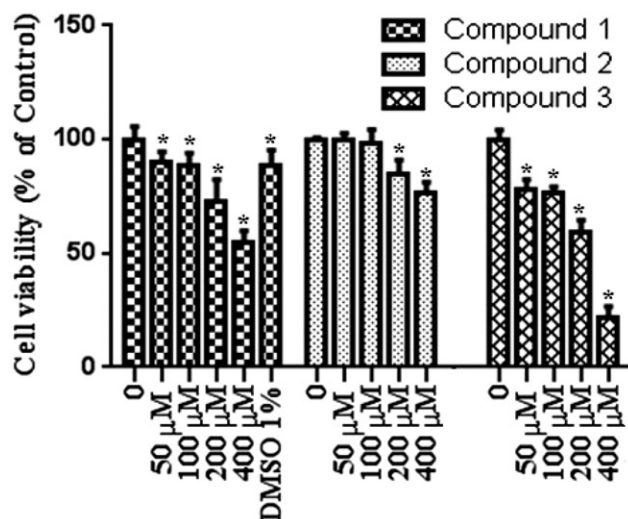


Figure 1. Proliferation inhibiting effects of compounds in MCF-7 cell line. $n = 4$, $*p < 0.05$ versus control.

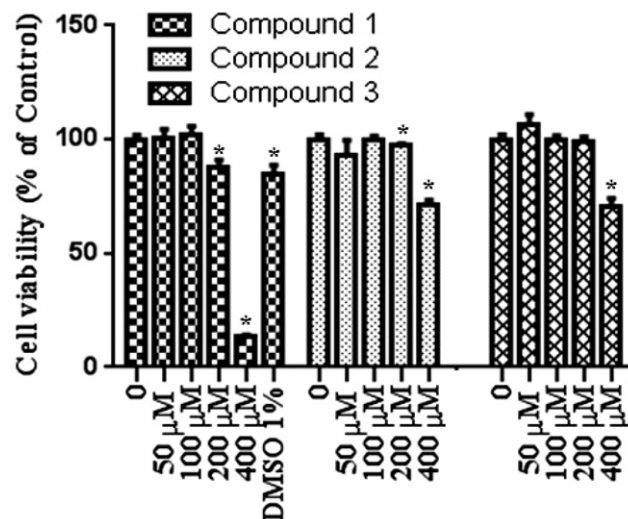


Figure 3. Proliferation inhibiting effects of compounds in Colo-205 cell line. $n = 4$, $*p < 0.05$ versus control.

Figure 4. (A) Caspase 3 mRNA levels following 12 h treatment with compounds, (B) Caspase 3 mRNA levels following 24 h treatment with compounds. Concentration of tested compounds were 400 $\mu\text{mol/L}$, $n = 3$, $*p < 0.05$ versus control.

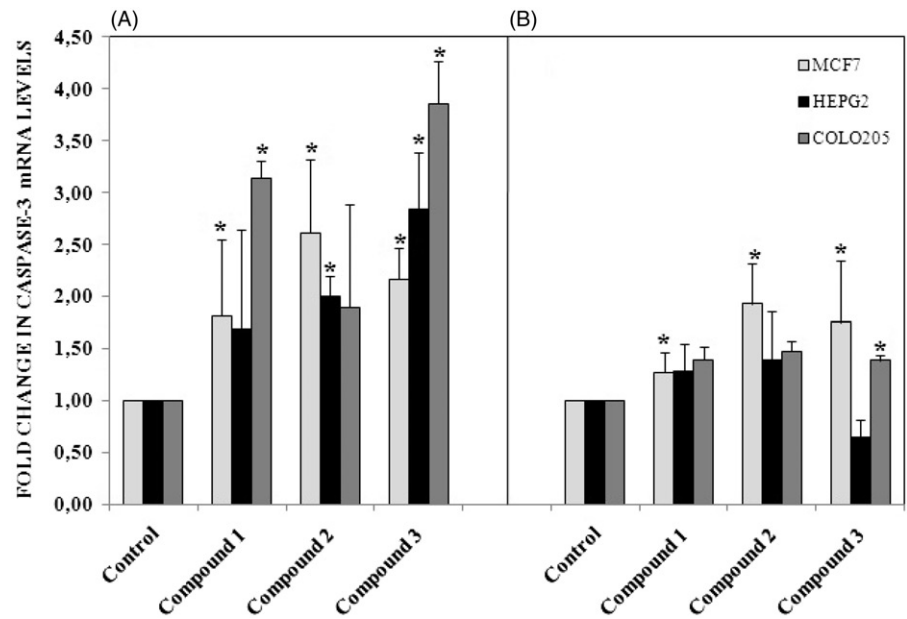


Figure 5. (A) Caspase 9 mRNA levels following 12 h treatment with compounds in different cancer cells, (B) 24 h treatment with compounds. $n = 3$, $*p < 0.05$ versus control.

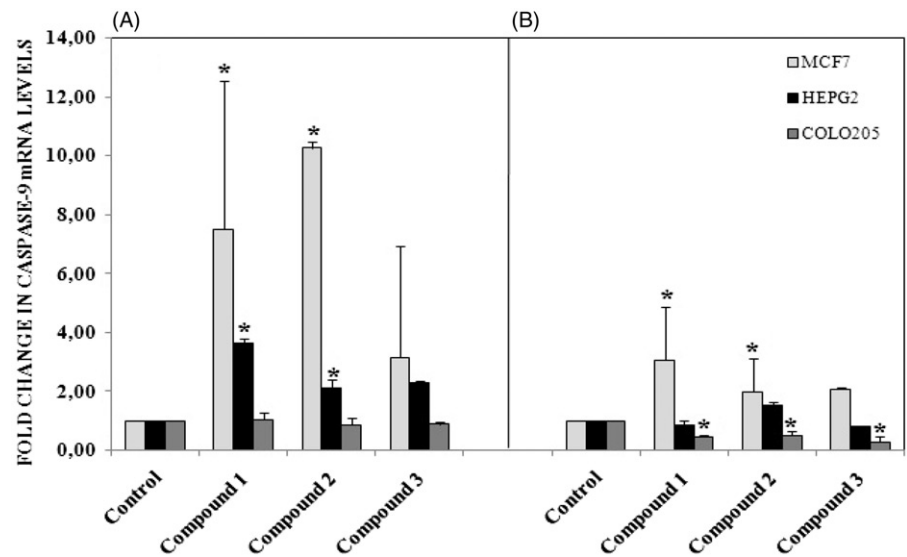


Figure 6. (A) Caspase 8 mRNA levels following 12 h treatment with compounds in different cancer cells, (B) 24 h treatment with compounds. $n = 3$, $*p < 0.05$ versus control.

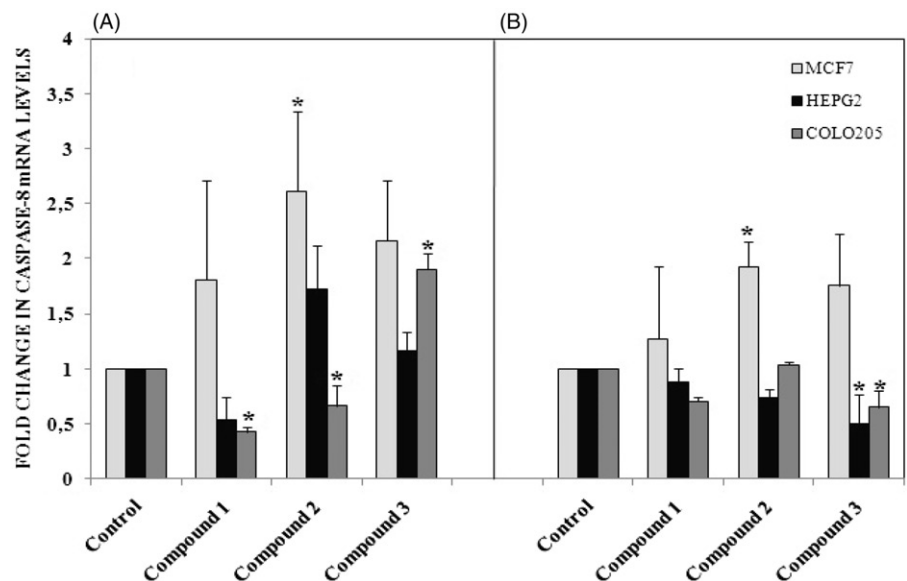


Figure 7. (A) Activation of ERK phosphorylation following 12 h treatment with compounds in different cancer cells, (B) 24 h treatment with compounds. $n = 3$, $*p < 0.05$ versus control.

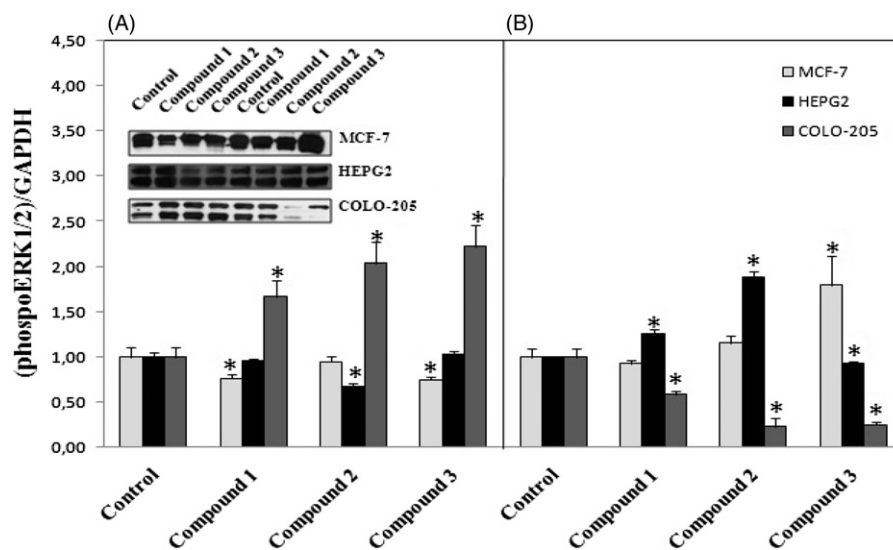
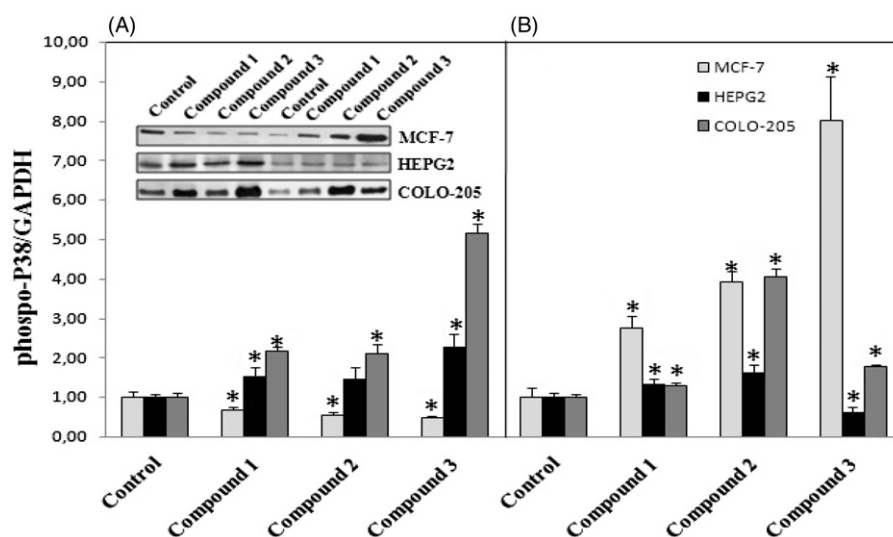


Figure 8. (A) Activation of P38 phosphorylation following 12 h treatment with compounds in different cancer cells, (B) 24 h treatment with compounds. $n = 3$, $*p < 0.05$ versus control.



MAPK was measured in HEPG2 and colo-205 cell lines following 12 h treatment with all tested compounds (Figure 8). Interestingly, P38 phosphorylation decreased in 12 h treatment groups in MCF-7 cells but increased following 24 h treatments with all tested compounds.

In conclusion, all tested compounds had anti-proliferative effects in different cancer cell lines. Decrease in cell viability in response to 12 and 24 h treatment with compounds correlated with a significant increase in pro-apoptotic gene expressions. The underlying molecular mechanisms involved in apoptotic cancer cell death after treatment with our newly synthesized compounds might be the activation of MAPK pathways.

Experimental

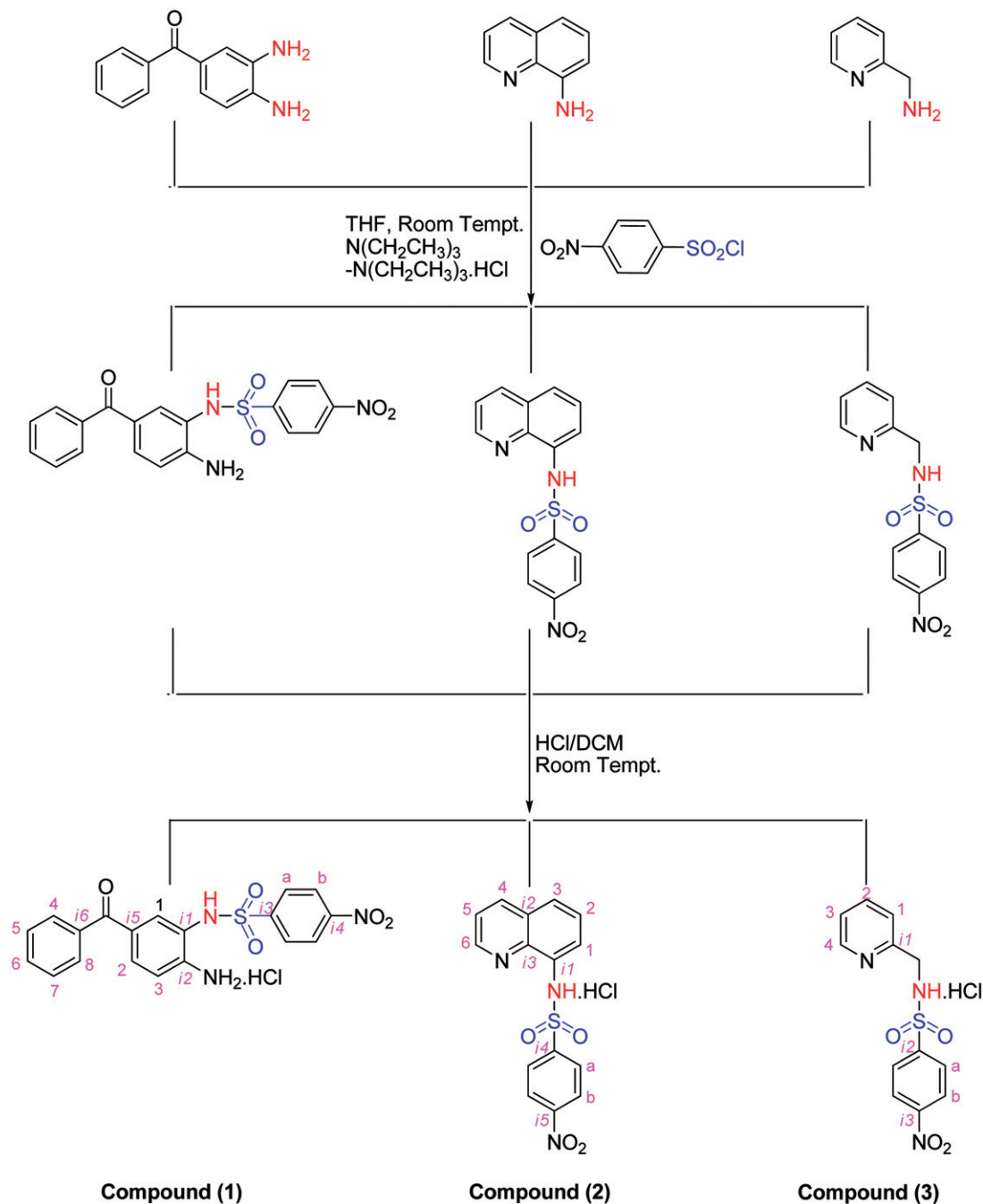
All chemicals used in the synthesis process (reagents and solvents) were purchased from chemical companies (Sigma-Aldrich, Merck and Alfa Aesar) and used as received unless otherwise stated. The 400 MHz $^1\text{H-NMR}$ and 100.56 MHz $^{13}\text{C-NMR}$ spectra were recorded at ambient temperature on a Bruker 400 NMR spectrometer in CDCl_3 as solvent. NMR signals are given in parts per million (ppm) as δ downfield from tetramethylsilane (TMS) (δ 0.00) as an internal standard. Coupling constants are given in Hertz. The multiplicity of NMR peaks is abbreviated as follows: br = broad, d = doublet,

m = multiplet, s = singlet, t = triplet. The elemental analyses were carried out using a Truspec MICRO (LECO) instrument. A Perkin-Elmer Spectrum 400 FTIR system with universal ATR sampling accessory was used to obtain the FT-IR spectra. For melting point determination, an Electrothermal 9100 instrument was used with open capillary tubes in Department of Chemistry, Faculty of Science, Erciyes University, Kayseri, Turkey.

General procedure for the synthesis of aromatic sulfonamide compounds 1–3

Stage-1

A solution of $\text{N}(\text{CH}_2\text{CH}_3)_3$ (15 mmol) in THF (tetrahydrofuran) (5 ml) was slowly added to a solution of R-sulfonyl chlorides (10 mmol) in THF (10 ml), immediately followed by 3,4-diaminobenzophenone, 8-aminoquinoline or 2-picoylamine, (10 mmol) in THF (5 ml). After the desired time, the reaction mixture was filtered and the volatiles were removed *in vacuo*. The residue was dissolved in DCM (dichloromethane) (20 ml) and washed with H_2O (3×10 ml), dried over anhydrous MgSO_4 , filtered and concentrated to half of its volume under reduced pressure. The solution was purified by precipitation with diethyl ether from a CH_2Cl_2 solution to give a microcrystalline product. All the desired products were checked by FT-IR and NMR.



Scheme 1. Synthesis of the compounds together with NMR numbering scheme.

Stage-2

The HCl solution (5 mmol) was slowly added to DCM solutions of the each desired products (5 mmol) with a dropping funnel and stirred at ambient temperature in a Schlenk tube for 1 h. After the desired time, the mixture was filtered. The crude product can be used without further purification. An analytically pure sample can be characterized with NMR, FT-IR and EA (Scheme 1).

Data for the compounds 1–3

For *N*-(2-amino-5-benzoylphenyl)-4-nitrobenzenesulfonamide hydrochloride (**1**)

Color: Light yellow. Yield: 76%. M.P.: 202 °C. ¹H-NMR (CDCl₃, δ ppm): 6.89 (d, 1H, *J* = 8 Hz, -H₃), 7.08 (s, 1H, -H₁), 7.44 (d, 1H, *J* = 8 Hz, -H₂), 7.54–7.89 (m, 5H, -H_{4,5,6,7,8}), 8.24 (d, 2H, *J* = 8 Hz, -H_a), 8.41 (d, 2H, *J* = 8 Hz, -H_b). ¹³C-NMR (CDCl₃,

ppm): 113.5 (-C₁), 117.0 (-C₃), 124.4 (-C_b), 128.3 (-C_a), 129.2 (-C_{5,7}), 130.4 (-C_{4,8}), 131.8 (-C₁₁), 132.1 (-C₁₅), 133.2 (-C₆), 135.8 (-C₁₆), 143.9 (-C₁₂), 150.3, (-C₁₃), 151.1 (-C₁₄), 193.5 (-C=O). IR (cm⁻¹): 3463 (NH₂), 3380 (NH₂), 3210 (-NH), 3061, 2986, 2770, 2532, 1662 (-C=O), 1625, 1597, 1577, 1533, 1507, 1484, 1405, 1374, 1354, 1314 (ν_{as}-SO₂), 1303, 1285, 1238, 1181, 1155 (ν_s-SO₂), 1126, 1109, 1081, 1047, 999, 975, 941, 909, 892, 872, 854, 841, 826, 795, 737, 722, 698, 680, 626, 608, 589, 568, 540, 453. Anal. Calcd. for: [C₁₉H₁₆ClN₃O₅S], C: 52.60, H: 3.72, N: 9.68, S: 7.39. Found: C: 52.82, H: 3.91, N: 9.49, S: 7.74.

For *N*-(quinolin-8-yl)-4-nitro-benzenesulfonamide hydrochloride (**2**)

Color: Light yellow. Yield: 69%. M.P.: 216 °C. ¹H-NMR (CDCl₃, δ ppm): 6.07 (-NH), 7.57–7.87, (m, 4H, -H_{1,2,3,5}), 8.11 (d, 2H, *J* = 8 Hz, -H_a), 8.30 (d, 2H, *J* = 8 Hz, -H_b), 8.57 (d, 1H, *J* = 8 Hz,

$-H_4$), 8.92 (d, 1H, $J = 8$ Hz, $-H_6$). $^{13}\text{C-NMR}$ (CDCl_3 , ppm): 122.1 ($-C_3$), 122.9 ($-C_5$), 124.8 ($-C_b$), 125.6 ($-C_1$), 127.1 ($-C_2$), 129.0 ($-C_a$), 129.1 ($-C_{12}$), 132.4 ($-C_4$), 135.7 ($-C_{13}$), 139.2 ($-C_{11}$), 145.4 ($-C_{14}$), 149.4 ($-C_6$), 150.3 ($-C_{15}$). IR (cm^{-1}): 3342 (NH), 3096, 2958, 2806, 2741, 1634, 1606, 1593, 1557, 1532, 1469, 1423, 1403, 1368, 1350 ($\nu_{\text{as-SO}_2}$), 1301, 1257, 1215, 1167 ($\nu_{\text{s-SO}_2}$), 1088, 1038, 1014, 947, 916, 878, 854, 838, 809, 797, 776, 761, 738, 682, 637, 611, 601, 560, 528, 483, 465. Anal. Calcd. for: $[\text{C}_{15}\text{H}_{12}\text{ClN}_3\text{O}_4\text{S}]$, C: 49.25, H: 3.31, N: 11.49, S: 8.77. Found: C: 49.51, H: 3.19, N: 11.61, S: 8.93.

For N-(pyridine-2-ylmethyl)-4-nitro-benzenesulfonamide hydrochloride (3)

Color: Light yellow. Yield: 73%. M.P.: 224 °C. $^1\text{H-NMR}$ (CDCl_3 , δ ppm): 4.53 (d, 2H, $J = 4$ Hz, $-\text{CH}_2\text{-NH-}$) 7.88 (t, 1H, $J = 8$ Hz, $-H_3$), 7.98 (d, 1H, $J = 8$ Hz, $-H_1$), 8.12 (d, 2H, $J = 8$ Hz, $-H_a$), 8.38 (d, 2H, $J = 8$ Hz, $-H_b$), 8.47 (t, 1H, $J = 8$ Hz, $-H_2$), 8.78 (d, 1H, $J = 8$ Hz, $-H_4$), 10.61 ($-\text{NH}$). $^{13}\text{C-NMR}$ (CDCl_3 , ppm): 49.0 ($-\text{CH}_2\text{-NH-}$) 113.3 ($-C_1$), 116.16 ($-C_3$), 125.1 ($-C_b$), 128.9 ($-C_a$), 142.3 ($-C_2$), 145.6 ($-C_{12}$), 145.8 ($-C_4$), 150.2 ($-C_{13}$), 153.6 ($-C_{11}$). IR (cm^{-1}): 3239 (NH), 3102, 3068, 2853, 2390, 2051, 1987, 1939, 1616, 1536, 1473, 1431, 1399, 1362, 1334 ($\nu_{\text{as-SO}_2}$), 1311, 1290, 1233, 1180, 1160 ($\nu_{\text{s-SO}_2}$), 1093, 1036, 1007, 964, 852, 823, 771, 749, 737, 679, 648, 626, 604, 557, 532, 515, 462. Anal. Calcd. for: $[\text{C}_{12}\text{H}_{12}\text{ClN}_3\text{O}_4\text{S}]$, C: 43.71, H: 3.67, N: 12.74, S: 9.72. Found: C: 43.82, H: 3.53, N: 12.55, S: 9.81.

Cell culture

The cell lines (Human colon carcinoma cell line Colo-205, Human hepatocellular carcinoma cell line HepG2 and Human breast adenocarcinoma cell line MCF7, Human Lung adenocarcinoma alveolar basal epithelial cell line A549) used in the study were purchased from American Type Culture Collection (ATCC). Colo-205 were maintained in RPMI 1640 Medium and HepG2 and MCF7 cells were maintained in Dulbecco's Modified Eagle's Medium (DMEM). Cell cultures were supplemented with 10% fetal bovine serum (FBS), 2 mM L-Glutamine, 10 000 units/ml penicillin, and 10 mg/mL streptomycin and maintained under an atmosphere of 5% CO_2 with 90% relative humidity at 37 °C, according to standard protocols.

MTT reduction assay

Anti-proliferative effect of the compounds (**1–3**) was evaluated by MTT reduction assay. Cells were treated with 0–400 μM of compounds (compound **1** and **2** dissolved in DMSO 5% and 2.5 %, respectively). Compound **3** dissolved in water. Final concentration of DMSO 1% for compound **1** treatment and 0.5% for compound **2** treatment in wells) in without phenol red 10% FBS supplemented mediums for 24 h and then rinsed 3 times with ice cold PBS. MTT was added to the final concentration of 0.5 mg/mL. After from MTT incubation (4 h), solubilization buffer (10% sodium dodecyl sulfate in 0.01 mol/L HCl) was added and the colored formazan crystals were gently re-suspended. The absorbance data at 570 nm were recorded with a microplate reader (Bio-Tek ELX800, BioTek Instruments Inc., Winooski, VT).

Quantitative real-time PCR

Total RNA isolation from cells was performed via phenol-guanidine thiocyanate extraction using TriPure isolation reagent (Roche Diagnostics GmbH, Mannheim, Germany), according to the manufacturer's instructions. Total RNA (1 μg) was reverse-transcribed to cDNA using a Transcriptor High Fidelity cDNA Synthesis Kit (Roche Diagnostics GmbH, Mannheim, Germany) in a 20 μL reaction mixture. Real-time PCR was carried out using a Light Cycler Nano System (Roche Diagnostics GmbH,

Mannheim, Germany). To quantify cDNA, qPCR was performed using Fast Start Essential DNA probe master mix (Roche Diagnostics GmbH, Mannheim, Germany). The reaction mixture (15 μL) was prepared in Ligh Cycler 8-tube strips (Roche Diagnostics GmbH, Mannheim, Germany) and included 10 μL of 2 \times Master Reaction Mix (Roche Diagnostics GmbH, Mannheim, Germany), 4 μL PCR grade water, 1 μL catalogue assay kit (Caspase9, Caspase 8, Caspase 3, β -actin) and 5 μL of cDNA. Real-time PCR was performed according to following conditions: activation of Taq DNA polymerase and DNA denaturation at 95 °C for 10 min, followed by 45 amplification cycles for 10 s at 95 °C and for 30 s at 60 °C. For each sample the level of target gene transcripts was normalized to β -actin.

Western blot analysis

Cells were incubated with 400 μM concentrations of compounds for 12 h and 24 h. Cellular protein extract (20–25 μg) isolated with RIPA buffer (Sigma-Aldrich, St. Louis, MO) supplemented with protease and phosphatase inhibitory cocktail (Santa Cruz Biotechnology, Santa Cruz, CA), was subjected to discontinuous 5% to 12% SDS-PAGE. The primary antibodies were used rabbit-anti-phospho-p38 (1:1000 Cell signaling, Danvers, MA). After serial washes, primary antibodies were detected by secondary antibodies conjugated with horseradish peroxidase. Specific signals were visualized with enhanced chemiluminescence detection kits (Pierce WestPico, Rockford, IL).

Statistical analysis

Data are expressed as mean \pm standard deviation (SD). Significance of the difference between the control and treated group(s) was assessed by Student's *t*-test. Values of $p < 0.05$ were taken to be significant. Expression of the target genes' mRNA corresponding to that of the housekeeping gene mRNA was analyzed by a relative expression software tool (REST 2009, v.2.0.13). The statistical significance was established via the pairwise fixed reallocation randomization test. *p* Values < 0.05 were reflected on statistically significant.

Conclusion

Herein, we synthesized the new compounds (**1–3**) bearing sulfonamide moiety and tested cytotoxic effects of compounds (more than 3 compounds (data unpublished)) but, only three compound (Compound **1–3**) were active (decreased cancer viable cell number) according to the results of MTT assay. Lead compounds **1**, **2**, and **3** merit further studies (qPCR and western blot analysis) as novel promising anti-cancer agents against different cell lines.

Furthermore, all the experiments show that to us, (**1**) compound was generally found to be the most active compound compared to others for cells viability. So, the 3,4-diaminobenzophenonesulfonamide derivative is superior from others and this compound may be derivatized for anti-cancer activity in the future. In addition, it is clear that the *N*-(2-amino-5-benzoylphenyl)-4-nitrobenzenesulfonamide hydrochloride (**1**), *N*-(quinolin-8-yl)-4-nitro-benzenesulfonamide hydrochloride (**2**) and *N*-(pyridine-2-ylmethyl)-4-nitro-benzenesulfonamide hydrochloride (**3**) compounds could significantly reduce cell proliferation and induced mRNA expression of pro-apoptotic genes; caspase 3, caspase 8 and caspase 9. The fabricated compounds bearing sulfonamide moiety can be used herein show moderate efficiency as anti-cancer agents for treatment of various malignancies³⁰.

Declaration of interest

The authors declare that they have no conflict of interest.

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Supplementary material available online.

Supplementary Figure S1.