Yuzuncu Yil University
Journal of the Institute of Natural & Applied Sciences
https://dergipark.org.tr/en/pub/yyufbed

Research Article

Investigation of the Cytotoxic Effect of 2-Amino-4-phenylthiazole Derivative Against MCF-7 and AGS Cancer Cells

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Abstract: This study aimed to investigate the cytotoxic effects of 2-amino thiazole compound (**3**) on MCF-7 breast and AGS gastric cancer cells. We examined the cytotoxic effects of various concentrations (10-25-50-100 µg/mL) of 2-aminothiazol compound (**3**) on MCF-7 breast cancer and AGS gastric cells at 24, 48 and 72 hours using MTT assay. MTT assays demonstrate that the 2-amino thiazole (**3**) compound has a time- and dose-dependent inhibitory effect on the proliferation of MCF-7 and AGS cancer cells. Analysis of the data obtained from MTT assay showed that IC_{50} values for thiazole were 80.13, 71.03 and 59.24 µg/ml and 75.03, 38.12 and 28.01 µg/ml for 24, 48 and 72 hours on MCF-7 and AGS cells, respectively. The 100 µg/mL dose was demonstrated to be most effective on both cancer cells. Our results suggest that the 2-amino-4-phenylthiazole (**3**) compound has a dose-dependent effect on cytotoxicity in MCF7 breast and AGS gastric cancer cells.

Keywords: AGS cells, Cytotoxic, MCF-7 cell, MTT assay, Thizole

2-Amino-4-feniltiyazol Türevinin MCF-7 ve AGS Kanser Hücrelerine Karşı Sitotoksik Etkisinin Araştırılması

Öz: Bu çalışmada 2-amino-4-feniltiyazol bileşiğinin (**3**) MCF-7 meme ve AGS mide kanseri hücreleri üzerindeki sitotoksik etkilerinin incelenmesi amaçlanmıştır. 2-aminotiyazol bileşiğinin (**3**) çeşitli konsantrasyonlarının (10-25-50-100 µg/mL) MCF-7 meme kanseri ve AGS mide hücreleri üzerindeki sitotoksik etkilerini 24., 48. ve 72. saatlerde MTT testi kullanarak incelenmiştir. MTT deneyleri, 2-amino tiyazol (**3**) bileşiğinin MCF-7 ve AGS kanser hücrelerinin çoğalması üzerinde zamana ve doza bağlı bir inhibitör etkiye sahip olduğunu göstermektedir. MTT deneyinden elde edilen verilerin analizi, tiyazol için IC_{50} değerlerinin MCF-7 ve AGS hücreleri üzerinde 24, 48 ve 72 saat boyunca sırasıyla 80.13, 71.03 ve 59.24 µg/ml ve 75.03, 38.12 ve 28.01 µg/ml olduğunu göstermiştir.100 µg/mL dozunun her iki kanser hücresi üzerinde de en etkili olduğu gösterilmiştir. Sonuçlarımız 2-amino-4-feniltiyazol (**3**) bileşiğinin MCF-7 meme ve AGS mide kanseri hücrelerinde sitotoksisite üzerinde doza bağlı bir etkiye sahip olduğunu göstermektedir.

Anahtar Kelimeler: AGS hücreleri, MCF-7 hücresi, MTT deneyi, Sitotoksik, Tiyazol

Received: 23.10.2024
Accepted: 03.01.2025

How to cite: Biçer, A., & Çınar, İ. (2025). Investigation of the cytotoxic effect of 2-amino-4-phenylthiazole derivative against MCF-7 and AGS cancer cells. *Yuzuncu Yil University Journal of the Institute of Natural and Applied Sciences*, *30*(1), 61-68. https://doi.org/10.53433/yyufbed.1572502

1. Introduction

The existence of 1,3-thiazole rings in the structures of many drug molecules and bioactive molecules has led to the increased studies on this ring system (Ghorab & Al-Said, 2012; Mirza et al., 2017). Numerous clinically used drugs containing 1,3-thiazole nuclei such as abafungin, dasatinib, dabrafenib, epothilone, fentiazac, ixabepilone, itazoxanide, meloxicam, nitazoxanide, nizatidine, niridazole, patellamide A, ritonavir, sulfathiazole and thiazofurine are used to treat cancer, inflammation, parasitic diseases, etc. (Figure 1) (Mirza et al., 2017; Ammar et al., 2018; Sharma et al., 2020; Moghaddam-manesh et al., 2021; Tavallaei et al., 2021; Othman et al., 2022). Bioactivity studies of thiazole derivative molecules demonstrate that they have a broad spectrum of bioactivity (Mirza et al., 2017). Some thiazole ring containing molecules have been developed as polymerase and microtubular inhibitors. These compounds have been reported to exhibit potent anti-cancer activity and less toxicity (Sharma et al., 2020). Thiazole compounds have a large number of studies on anti-cancer activity (Mirza et al., 2017). Ammar et al. (2018) investigated the cytotoxic activity of novel thiazole-oxoindole compounds against cancer cell lines (MCF-7(breast), HepG-2 (liver), HCT-116 (colon)). It was found that the synthesized compounds showed good cytotoxic activity against HepG-2, HCT-116 cell lines. Mohamed et al. (2017) investigated the cytotoxic effect of benzothiazole derivatives against MCF-7 cell lines. It was revealed that many of the derivatives they synthesized showed good cytotoxic effect compared to cis-platinum reference (Mohamed et al., 2017). Mirza et al. (2017) synthesized substituted aryl-thiazole and investigated their cytotoxicity against various cancer cell lines (MCF-7, HCT116, MDA-MB-231, and HeLa). Patil et al. (2010) investigated the anti-cancer properties of 5-benzylidene-2,4-thiazolidinediones derivatives on 7 different cell lines. They obtained the best results against MCF-7, K562 (leukemia) and GURAV (nasopharyngeal cancer) cell lines (Patil et al., 2010; Fayed et al., 2020).

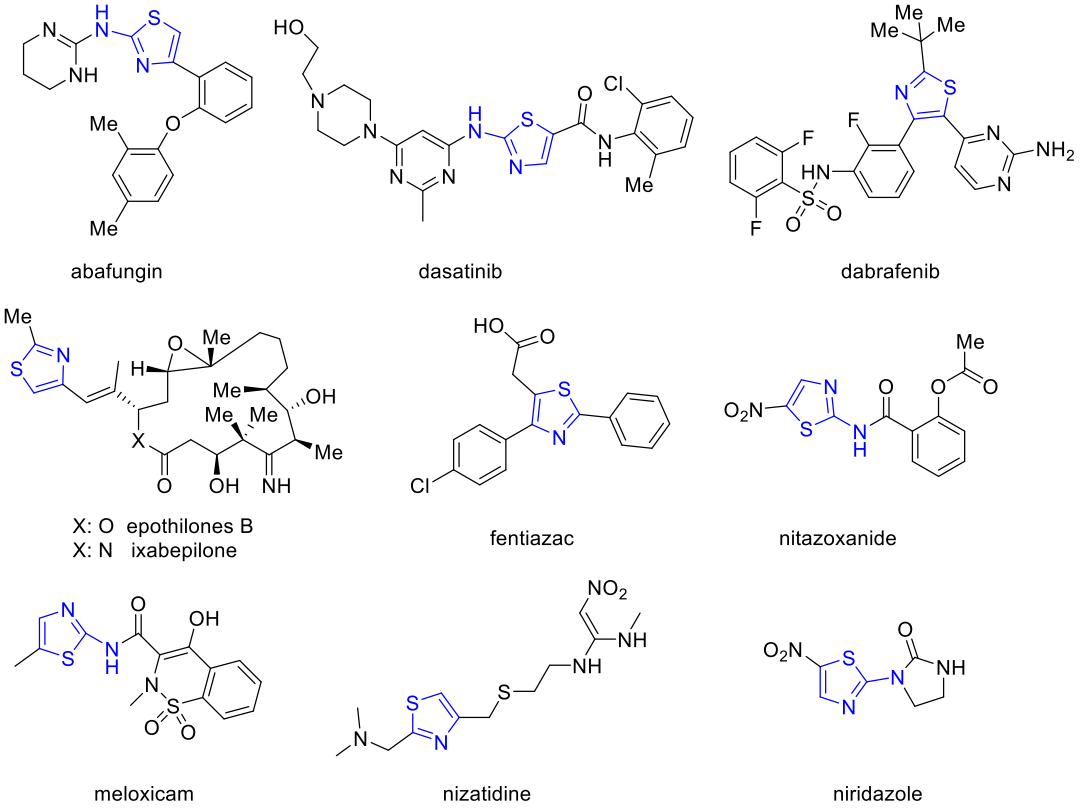

Figure 1. Some drug molecules containing thiazole groups.

Fayed et al. (2020) investigated the synthesis of thiazole-indenoquinoxaline derivative compounds and reported that they showed anti-proliferative activity against cancer cell (HCT-116, HepG-2, MCF-7). Ansari et al. (2020) investigated the anti-cancer activity of 4-(3,4,5-

trimethoxyphenyl) moiety thiazole-2(3H)-thiones anologues against cancer cell lines (A549(lung), MCF-7 and SKOV3(ovarian)). The best inhibitory effect was obtained against the MCF-7 cell lines (Ansari et al., 2020). Salehi et al. (2013) investigated the antiproliferative activity of 2-alkylthio-4-(2,3,4-trimethoxyphenyl)-5-aryl-thiazole analogues against human cancer cell lines (HT-29(colon), MCF-7, AGS(stomach)). These compounds were reported to show good activity against the MCF-7 and AGS cell lines (Salehi et al., 2013). Zou et al. (2021) synthesized ligands containing pyridine thiazole groups and their Cd and Zn complexes and tested the antimicrobial and antitumor activities of the ligands and metal complexes on four human cancer cell lines (SK-NSH, HCT-116, AGS and MCF-7). In their study, they reported that metal complexes showed better activity than ligands (Zou et al., 2021). Habibzadeh et al. (2020) synthesized (3-Chloropropyl) trimethoxysilane (CPTMOS)-coated Fe_3O_4 nanoparticles and attached to its surface the compound 1-((3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-(4-phenylthiazol-2-yl) hydrazine containing thiazole ring. They examined the anti-cancer properties of the nanoparticle they obtained against gastric AGS cancer cells (Habibzadeh et al., 2020). Amooie et al. (2023) synthesized $ZnFe_2O_4$-Ag nanocomposite using Chlorella vulgaris and investigated its cytotoxic activity against some cell lines.

In this study, we investigated the cytotoxic effect of 2-amino-4-phenylthiazole derivatives (**3**) containing *N*,*N*-dimethylformamide and aldehyde functional groups against AGS and MCF-7 human cancer cell lines. The cytotoxicity of thiazole compounds containing these two groups against AGS and MCF-7 human cancer cell lines has not been previously evaluated.

2. Material and Methods

2.1. Chemistry

All chemicals were purchased from commercial suppliers and were used without further purification. FTIR spectra were recorded on Perkin Elmer FTIR spectrometer using the KBr disk in the range of 4000–400 cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Inova 500 MHz spectrometer using $CDCl_3$ as a solvent and tetramethylsilane (TMS) as an internal standard. Splitting patterns are designated as follows; s, singlet; d, doublet; m, multiplet. Chemical shift (d) values are given in ppm.

2.1.1. Synthesis of Thiazole compounds

2-Amino-4-phenylthiazole derivative were synthesized by following the reaction pathway shown in Figure 2. Preparation of the thiazole compound (**2**) was synthesized by Hantzsch reaction starting from acetophenone (**1**). The amino group of compound (**2**) was protected with benzoyl chloride. Then compound (**3**) was synthesized from compound (**2**) by Vilsmayer-Haack reaction (Biçer & Altundaş, 2023).

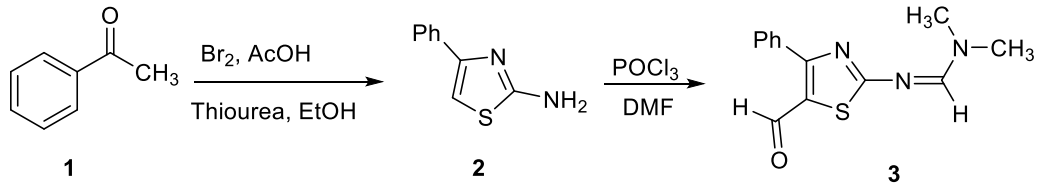

Figure 2. Synthesis scheme of thiazole derivative (**3**).

Synthesis of thiazole compound (**2**): Acetophenone (**1**) (1 equivalent, 10 g) was dissolved in 40 mL ethanol. Bromine (1,2 equivalent, 4 mL) dissolved in 10 mL AcOH was added. The mixture was placed in an oil bath at 60 ^{o}C and refluxed for 3 hours. Thiourea (1 equivalent, 6.50 g) was then added. As a result of TLC analyses, the reaction was terminated after 24 hours. As the reaction proceeds, when acetophenone reacts with bromine to form the intermediate product, the colour of bromine disappears and white solid product is obtained after thiourea. After the reaction solvent was evaporated, the crude product was washed with plenty of water and dried. Compound (**2**) was obtained in 87% yield. For Compound (**2**): M.P. 114-115 ^{o}C (Lit. 114-118 ^{o}C (Kidwai et al., 2011)), IR (cm^{-1}): 3380-3266 (NH_2

strech.), 3125 (Ar-CH strech.), 1597-1625 (C=C and C=N strech.), 722 (C-S-C strech.). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J*=4.0 Hz, 2H), 7.37 (t, *J*=6.0 Hz, 2H), 7.28 (t, *J*= 6.0 Hz, 1H), 5.02 (s, 2H).

2.1.2. Synthesis of formylation products (3)

The synthesis of compound (**3**) was carried out as in the literature (Biçer & Altundaş, 2023). In the literature, when these reactions carried out in nitrogen atmosphere are carried out without using nitrogen atmosphere, the same products are formed, but the yield decreases since the starting compounds are not finished.

2.2. Cytotoxicity evaluation

The cytotoxicity of 2-Amino-4-phenylthiazole derivatives (**3**) against two human cancer cell lines MCF-7, AGS was determined using MTT (3-(4,5-dimethylthiazole-2-yl]-2,5-diphenyl-tet razolium bromide) colorimetric assay.

2.2.1. Cell culture and cell cytotoxicity evaluation

Dulbecco's modified eagle medium (DMEM) and cell culture medium and reagents such as fetal bovine serum, penicillin/streptomycin, and trypsin-EDTA were purchased from GIBCO (Invitrogen Inc., NY, USA). MCF-7 and AGS cell lines were obtained from the American cell bank (ATCC, USA). The cell lines in the liquid nitrogen tank were removed from the tank and kept in a water bath at 37° C for a short time to thaw. The lysed cells were seeded in T75 cm^2 flasks. After 48 hours, MCF-7 and AGS cells were seeded at $5x10^3$ cells/well in DMEM containing 10% FBS, planted in 96-well plates and incubated at 37°C in an oven containing 5% CO_2. After 24 h, cells were exposed to Thiazole at different concentrations (100–10 µg/ml (dissolved with 1% DMSO) (Dang et al., 2021) that have been previously studied in the literature. Afterwards, at 24, 48 and 72 hours, MTT 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) (Cat no: 11465007001, Roche, Germany) method was applied to the cells and absorbance values were measured at 570 nm with a microplate reader spectrophotometer (Epoch, BioTek, USA). was done repeatedly.

Viability rates were analyzed by comparison with control wells (source). All cell culture applications were carried out in accordance with the previously mentioned standards and literature (Cinar et al., 2020). (All medium and other solutions used in cell culture were obtained from Thermo Fisher).

2.2.2. Statistical analysis

For statistical analysis, all data were calculated using Graphpad 8.0.1 software program and the results are presented as mean±standard deviation. Data analysis was performed by one-way analysis of variance (ANOVA), followed by Duncan's test. $P<0.05$ was considered statistically significant**.**

3. Results

3.1. In vitro cell toxicity

Different doses of thiazole (**3**) were tested for cytotoxicity on MCF-7 and AGS cell lines three time-dependent assays using MTT assay for 24 hours, 48 hours and 72 hours. After the examination, the data obtained from the MTT assay were calculated as a percentage to test the growth of the cells. Cell viability was calculated as a percentage using absorbance values at 570 nm for 4 different concentrations (100-10 µg/ml) of media. Based on the data shown in Scheme 2-3, cell viability in the normal control (NC) group was taken as reference and the percentage was determined as 100%.

The results demonstrated that in vitro growth of MCF-7 and AGS cells was suppressed by thiazole in a time- and dose-dependent manner (Fig.3-4). Cell viability increased at all doses after the addition of thiazole (**3**) at concentrations of 100-10 µg/ml for 24, 48 and 72 hours. Looking at the experimental groups, it was found that the proportion of viable cells decreased significantly as the

concentration of thiazole used increased. Moreover, by analyzing the data provided by the MTT assay, it was determined that the IC_{50} values for thiazole on MCF-7 and AGS cells for 24, 48 and 72 hours were 80.13, 71.03 and 59.24 µg/ml and 75.03, 38.12 and 28.01 µg/ml, respectively.

At the 24th hour, no statistically significant difference was detected in viability between MCF-7 and AGS cells applied at doses of 100 µg/ml and 10 µg/ml and the control group ($p>0.05$). No statistically significant difference was detected in terms of viability between MCF-7 and AGS cells applied at 10 µg/ml doses at the 48th hour and the control group ($p>0.05$). However, at the 72nd hour, a statistically significant difference was detected in viability between MCF-7 and AGS cells of all administered doses and the control group ($p>0.05$). A significant decrease in viability was observed with increasing doses. The lowest viability was detected in the cell group to which the highest dose was applied. Best doses of 100 µg/ml and 50 µg/ml of thiazole (**3**) inhibited growth and proliferation in MCF-7 and AGS cells. It has been observed that thiazole (**3**) concentrations have a cytotoxic effect on MCF-7 and AGS cancer cells. Based on these findings, it has been determined that MCF-7 and AGS cancer cells provide a positive response to reduce their viability.

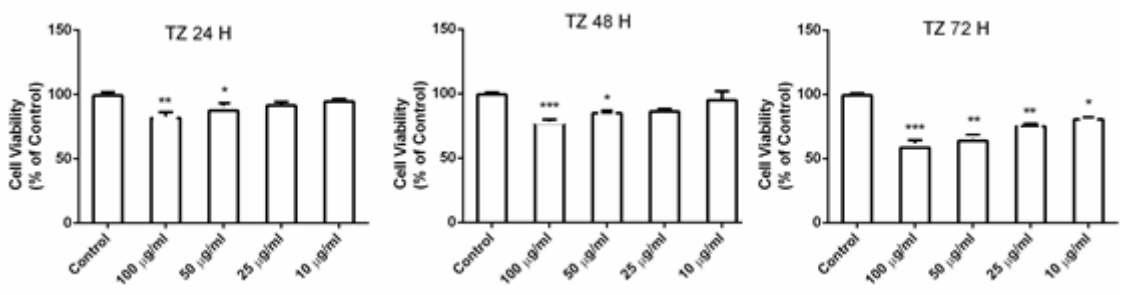

Figure 3. MTT of MCF-7 cells applied with various amounts of thiazole (**3**) results.

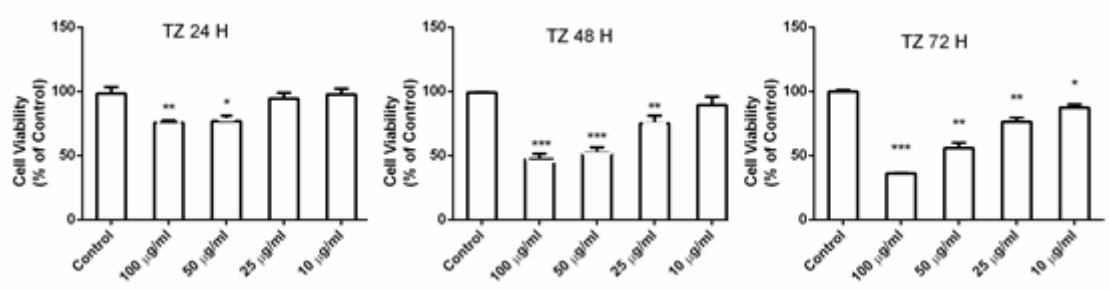

Figure 4. MTT of AGS cells applied with various amounts of thiazole (**3**) results.

The IC_{50} values obtained against MCF-7 and AGS cells were compared with some literature data (Table 1). Habibzadeh et al. (2020) found the IC_{50} value of 1-((3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-(4-phenylthiazol-2-yl) hydrazine derivatives containing pyrazole and thiazole rights as 95.65 µg/ml against AGS cells. This value is higher than the IC_{50} value of our thiazole (**3**) compound. When Salehi et al. (2013) investigated the cytotoxic activity of 2-alkylthio-4-(2,3,4-trimethoxyphenyl)-5-aryl-thiazoles molecules, IC_{50} values against AGS cell lines were found to be 18.1-100<µM, some derivatives did not show activity against MCF-7 cell lines and IC_{50} values of the compounds showing activity were found in the range of 11-27.3 µM. Here, it is seen that our results show better cytotoxic activity than some of the synthesized thiazole derivatives (Salehi et al. 2013).

Mohamed et al. (2017) found the cytotoxicity of benzothazole derivatives against MCF-7 cells and IC_{50} values between 5.15- 553.1 µM. Tavangar et al. (2020) investigated the cytotoxic activity of *N*-heteroaryl enamino amides and dihydropyrimidinethione compounds against both cell cultures AGS; IC_{50} 453.14 µM and MCF-7; IC_{50} 761.90 µM (RPS-15-154). The cytotoxic activity of thiazole (**3**) compound against MCF-7 and AGS cell lines seems to be better than these results (Tavangar et al., 2020).

Mahmoudi et al. (2009) investigated the cytotoxic activity of extracts of Artemisia khorasanica collected from different regions using methanol, EtOAc, dichloromethane and hexane solvents.

Methanol extracts showed IC_{50} values in the range of 89-152 µg/ml against AGS cells, EtOAc extracts 96-338 µg/ml against AGS cells, dicholoromethane extracts 67-197 µg/ml against AGS cells, hexane extracts 263- 1575 µg/ml against AGS cells. When we compare these results with the cytotoxic activity of the thiazole compound, it is seen that it gives better cytotoxic activity than the results obtained from the hexane extract (Mahmoudi et al., 2009).

Table 1. Cytotoxic activities of some thiazole compounds against AGS and MCF-7 cell lines

AGS (IC_{50})	MCF-7 (IC_{50})	Literature
95.65 µg/ml	-	Habibzadeh et al., 2020
18.1- 100 < µM	11-27.3 µM	Salehi et al., 2013
-	5.15- 553.1 µM	Mohamed et al., 2017
453.14 µM	761.90 µM	Tavangar et al., 2020
89-152 µg/ml (Methanol extracts)	-	Mahmoudi et al., 2009
96-338 µg/ml (EtOAc extracts)	-	
67-197 µg/ml (DCM extracts)	-	
263-1575 µg/ml ((Hekzane extracts)	-	

4. Conclusion

A significant decrease in viability was found with increasing application dose. The best doses of 100 µg/ml and 50 µg/ml of Thiazole (**3**) inhibited the growth and replication of MCF-7 and AGS cells. MCF-7 and AGS cancer cells were found to respond affirmatively to reduce their viability. 4-phenyl 2-Amino-4-phenylthiazole derivative (**3**) showed cytotoxic activity against MCF-7 and AGS cells. The thiazole compound (**3**) containing *N*,*N*-dimethylformamide and aldehyde functional groups was compared with the literature data in Table 1 and it was revealed that it showed better cytotoxic activity than these molecules in the literature. We think that our findings from this study will shed a guiding light for scientists who plan to conduct new studies on thiazole derivaitves containing *N*,*N*-dimethylformamide and aldehyde functional groups.

Acknowledgements

This work has been supported by Bilecik Şeyh Edebali University Scientific Research Projects Coordination Unit under grant number 2023-01.BŞEÜ.35-04.

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