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# Antioxidant and antiproliferative properties of some 2- (4h- [1,2,4] Triazol-3-Yl-sulfanyl) -acetamide derivatives

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## Abstract

In this study, the cytotoxic effects of some 2- (4H- [1,2,4] triazol-3-yl-sulfanyl)-acetamide derivatives compounds on the L1210 rodent leukemia cancer cell line were investigated. At the same time, the effect on MDA concentration showing the degree of lipid peroxidation in *Saccharomyces cerevisiae* yeast cells treated with these compounds and vitamin A, E and C values were investigated. In addition, the antioxidant properties were investigated by the DPPH radical scavenging method. It was determined that the compounds did not make a statistically significant difference in the A, E, C vitamin levels and MDA concentrations in *Saccharomyces cerevisiae* yeast cells. It was observed that the study groups did not show antioxidant activity in DPPH radical scavenging activity results. Based on the antitumor activity results, the compounds were generally found to have an effective cytotoxic activity on the L1210 cell line.

**Keywords**: Anticancer, antioxidant, DPPH, MDA, vitamin

# Bazı 2-(4h-[1,2,4] Triazol-3-İl-sulfanil)-asetamid türevlerinin antioksidan ve antiproliferatif özellikleri

## Öz

Bu çalışmada, bazı 2- (4H- [1,2,4] triazol-3-il-sulfanil)-asetamid türevleri bileşiklerinin L1210 kemirgen lösemi kanser hücre hattı üzerindeki sitotoksik etkileri araştırıldı. Aynı zamanda bu bileşiklerle muamele edilen *Saccharomyces cerevisiae* maya hücrelerinde lipid peroksidasyon derecesini gösteren MDA konsantrasyonu ve vitamin A, E ve C değerlerine etkisi araştırıldı. Ayrıca DPPH radikal süpürme yöntemi ile antioksidan özellikleri araştırıldı. Bileşiklerin *Saccharomyces cerevisiae* maya hücrelerinde A, E, C vitamin seviyeleri ve MDA konsantrasyonlarında istatistiksel olarak anlamlı bir fark yaratmadığı belirlendi. Çalışma gruplarının DPPH radikal süpürücü aktivite sonuçlarında antioksidan aktivite göstermediği görüldü. Antitümör aktivite sonuçlarına dayanarak, bileşiklerin genel olarak L1210 hücre hattı üzerinde etkili bir sitotoksik aktiviteye sahip olduğu bulundu.

**Anahtar Kelimeler:** Antikanser, antioksidan, DPPH, MDA, vitamin

## INTRODUCTION

Organic compounds containing 5-membered aromatic heterocyclic rings are compounds that can be found in many natural structures and have an important role in many biochemical events (Pekdemir and Coşkun, 2020). Thanks to these features, it has become a new field of study for researchers (Dalvie et al., 2002). Triazoles are becoming more preferred in biological studies because they have a slower and more gradual mechanism (Georgopapadakou, 1998). This situation has made the studies on the biological activities of triazole compounds detailed (Cansız et al., 2001; Parlak et al., 2016). These compounds, which contain three nitrogen atoms and are included in five-membered ring compounds, are known as triazole or triazocyclopent diene. The variation in the positions of the heteroatoms in the ring structures of the triazole creates three different isomers in the ring structure: 1,3,4-(symmetrical; sym-triazole), 1,2,4-(asymmetrical; asym-triazole), and 1,2,3-(vicinal triazole) (Timur et al., 2019).

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Studies have shown that some arylthiosemicarbazide derivatives and triazoles synthesized from them and their heterocyclic derivatives have antifungal (Holla et al., 1996), antibacterial (Pandeya S. N. et al., 2000), anticancer (Invidiata et al., 1991), antiviral (Todoulou et al., 1994) ve antimicrobial (Kidwai et al., 2001) properties. It has also been observed that thiosemicarbazides and triazole compounds synthesized from them have significant in vitro antibacterial activity and highly inhibit the growth of the tested organisms (Goswami et al., 1984). In another study, 1,3,4-thiadiazole and 1,2,4-triazole derivatives containing indole were applied on mice in specific tests and it was determined that these substances supported the development of blood-brain cells and reduced depression (Pandeya S. et al., 1999). In a recent study, Ragıp' s team investigated the catalytic activities of Pyridine substituted tyrazole compounds (Adiguzel et al., 2020). Still, different new triazole derivatives are being investigated and added to the literature.

In this study, various compounds containing different triazole derivatives were applied to *Saccharomyces cerevisiae* yeast cells to determine their in vitro antioxidant effects, and at the same time, their antitumor activities in L1210 cell line cultures to which these compounds were applied.

## EXPERIMENTAL

### Acetamide-derived triazole compounds

All acetamide derivatives of triazole compounds, whose properties were investigated in this study, were synthesized in Fırat University, Faculty of Science, Department of Chemistry, Department of Organic Chemistry (Dinçer et al., 2006; Koparir et al., 2013).

### Cytotoxic effects of acetamide-derived triazole compounds on L1210 cell line

The L1210 murine leukemia cell line was purchased from the American Type Culture Collection (ATTC). Cytotoxicity studies were carried out in the Cell Culture laboratory of Fırat University, Faculty of Medicine, Department of Physiology. L1210 cell lines were cultured in 25 $cm^2$ flasks in an incubator containing 5% $CO_2$ and 37 °C condition. RPMI-1640 medium containing 10% fetal bovine serum (FCS), 100 µ/mL Penicillin, and 100 µg/mL streptomycin was used. The trypan blue test was performed for cytotoxicity analysis of the test compounds and 6 replicates of 1 x $10^5$ cells / mL L1210 cells per Eppendorf tube were seeded for this test. DMSO was used as the solvent of the test compounds. Live L1210 cells were seeded into flasks and incubated for 24 hours. After pre-incubation, the cell culture medium was replaced with fresh medium and test compounds prepared at concentrations of 7.5-15-30-60 µM were added to the medium. The viability of cells incubated at 37 °C, 5% CO2 after 24 and 48 hours was determined using the trypan blue exclusion method (Fenner et al., 1993; George et al., 1996). While vehicle-treated tubes served as control, it was observed that the DMSO concentration in the cell culture medium did not exceed 1%.

### Determination of MDA and Vitamin C

In this study, previously determined methods were used for MDA and vitamin C levels in *Saccharomyces cerevisiae* yeast cells treated with test compounds and their measurements were made with a high performance liquid chromatography (HPLC) device (Karatepe, 2004).

### Vitamin A, E

First, *Saccharomyces cerevisiae* yeast cells treated with test substances were rinsed by adding 250 µL of 15% trichloroacetic acid, 0.5 M 750 µL of $HClO_4$, and the cells were lysed. By adding 2 mL of ethyl alcohol containing 1% $H_2SO_4$ to the lysed cells, the proteins in its content were precipitated and the mixture was shaken with vortex for a while. Samples to which 0.3 mL n-hexane was added were homogenized in vortex and placed in the centrifuge. The hexane phase was carefully separated and taken into a glass tube. After repeating this process twice, the extracted hexane phase was separated in the presence of nitrogen. The residue was dissolved in 100 µL of methanol to make it suitable for analysis by HPLC. (Catignani and Bieri, 1983).

### DPPH antioxidant

DPPH radical scavening method was used to determine the radical scavenging power of the compounds to be studied. (Liyana-Pathirana and Shahidi, 2005). As a result, 4 mL of the DPPH solution prepared in methanol with a concentration of 25 mg/L was taken and the samples were added to the tubes at a final concentration of 100, 250, 500 and

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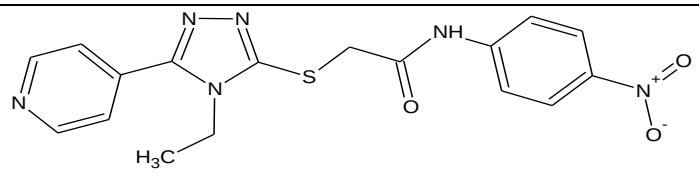
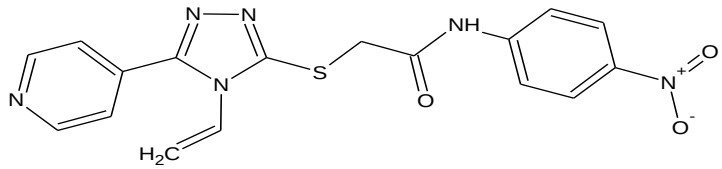
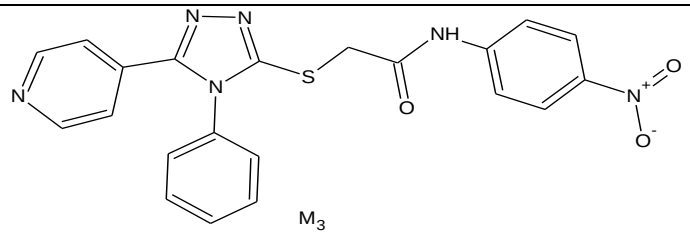
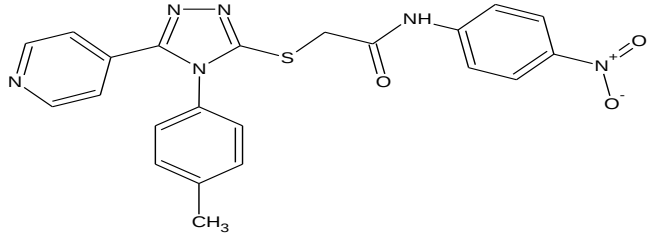
1000 M, respectively. The samples were kept in a dark place and at room temperature for about 30 minutes. At the end of the time, absorbance measurements were made with a UV spectrophotometer at a wavelength of 517 nm. Low absorbance values in the study groups indicate high radical scavening power. The DPPH radical scavenging percentage was calculated using equation 1 given below.

$$DPPH\ radical\ scavening\ activity\ \% = \frac{Control\ absorbance - Sample\ absorbance}{Control\ absorbance} x100 \quad (1)$$

**Table 1.** *Chemical structures and IUPAC names of the compounds whose properties were investigated*

| No | Compounds | Compounds Structure | IUPAC name and formules |
|---|---|---|---|
| 1 | M1 |  $M_1$ | 2-{[4-etil-5-(piridin-4-il)-4H-1,2,4-triazol-3-il]sulfanil}-N-(4-nitrofenil)asetamit |
| 2 | M2 |  $M_2$ | N-(4-nitrofenil)-2-{[4-(prop-2-en-1-il)-5-(piridin-4-il)-4H-1,2,4-triazol-3-il] sulfanil}-asetamit |
| 3 | M3 |  $M_3$ | N-(4-nitrofenil)-2-{[4-fenil-5-(piridin-4-il)-4H-1,2,4-triazol-3-il]sulfanil}asetamit |
| 4 | M4 |  $M_4$ | 2-{[4-(4-metilfenil)-5-(piridin-4-il)-4H-1,2,4-triazol-3-il]sulfanil}-N-(4-nitrofenil) asetamit |

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| Groups (N=6) | 24 h 7.5 µM | 24 h 15 µM | 24 h 30µM | 24 h 60µM | 48 h 7.5 µM | 48 h 15 µM | 48 h 30 µM | 48h 60 µM |
|---|---|---|---|---|---|---|---|---|
| Control | 72.75±0.95 | 67.75±0.63 | 69.00±0.41 | 62.75±0.85 | 65.75±0.48 | 61.50±0.65 | 60.00±1.63 | 54.75±1.65 |
| M1 | 56.50±0.87$^{c}$ | 47.25±0.63$^{c}$ | 36.50±0.65$^{c}$ | 27.50±1.19$^{c}$ | 45.00±1.08$^{c}$ | 33.75±1.25$^{c}$ | 21.50±1.19$^{c}$ | 11.75±1.03$^{c}$ |
| M2 | 52.50±1.05$^{c}$ | 41.50±1.04$^{c}$ | 35.25±2.39$^{c}$ | 27.50±1.55$^{c}$ | 42.75±0.85$^{c}$ | 27.75±1.44$^{c}$ | 18.25±1.80$^{c}$ | 12.75±1.31$^{c}$ |
| M3 | 54.50±1.32$^{c}$ | 44.75±1.49$^{c}$ | 29.25±1.93$^{c}$ | 19.25±0.75$^{c}$ | 42.25±0.85$^{c}$ | 27.00±1.08$^{c}$ | 19.00±0.91$^{c}$ | 9.00±0.41$^{c}$ |
| M4 | 58.25±0.48$^{c}$ | 48.25±1.31$^{c}$ | 29.00±0.91$^{c}$ | 17.25±0.85$^{c}$ | 46.00±0.82$^{c}$ | 32.75±1.49$^{c}$ | 17.75±1.38$^{c}$ | 9.50±0.65$^{c}$ |

**Table 2.** *% inhibition ± standard deviation values of organic compounds in L-1210 cancer cell line*
$^{a}$ $p < 0.05$; $^{b}$ $p < 0,01$; $^{c}$ $p < 0.001$

**Statistical Evaluation**

All statistical analyzes in the study were performed using the SPSS/PC package program. Analysis of variation was applied to the results to reveal statistical differences between activities. The data obtained at the end of the experimental studies were evaluated by Oneway Anova analysis for antitumor properties, Tukey test and LSD test for MDA, vitamin A and E analysis.

## RESULT

**In vitro antitumor activities on L1210 cell lines**

Determination of cell viability activity of test compounds was carried out by tryphan blue test. Cultures grown on each L1210 cell line in the study were exposed to different doses of test compounds for 24 and 48 hours. At the end of the study, it was determined that there was a decrease in the proliferation of the examined cell lines depending on the dose. The effects of compounds numbered M1, M2, M3 and M4 on the L1210 cell line depending on the dose and time are shown in Figure 1. Cells treated with compounds were found to differ statistically from control groups. (Table 2).

**In vivo antioxidant activities**

**Levels of vitamins A, E, C and MDA**

The effects of triazole derivative compounds treated on *Saccharomyces cerevisia* yeast cells on vitamin A, E, C and MDA levels were examined (Table 3). It was observed that the two-dose groups caused a slight decrease in vitamin levels, but did not show any significant variability. It was also determined that the groups that received two doses increased their MDA levels (Table 4).

**DPPH radical scavenging activity**

The DPPH radical scavenging model is more preferred because it takes a shorter time to evaluate antioxidant activities compared to other methods. The activity evaluation in this method is determined by the fact that the antioxidant molecules cause a decrease in the absorbance of the DPPH radical, either directly or due to the reactions between radical propagation. It was determined that the DPPH radical scavenging activities of all triazole derivatives used in the study were considerably lower than the standard antioxidant tocopherol (Table 5).

**Table 3.** *The mean values of the levels of vitamin E (mg / 1.10$^{6}$ cells) of Saccharomyces cerevisiae yeast cells treated with the compound*

| **Groups N=4** | **Vitamin E** | | **Vitamin A** | | **Vitamin C** | |
|---|---|---|---|---|---|---|
| | **26µM** | **52µM** | **26µM** | **52µM** | **26µM** | **52µM** |
| **Control** | 0.65 ± 0.01 | 0.65 ± 0.01 | 0.55 ± 0.02 | 0.55 ± 0.02 | 11.89 ± 0.41 | 11.89 ± 0.41 |
| **M1** | 0.55 ± 0.09 | 0.65 ± 0.89 | 0.44 ± 0.08 | 0.46 ± 0.04 | 13.58 ± 0.32$^{b}$ | 12.98 ± 0.44$^{a}$ |

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| | | | | | | |
|---|---|---|---|---|---|---|
| **M2** | 0.44 ± 0.19 | 0.41 ± 0.002 | 0.44 ± 0.001 | 0.36 ± 0.006[b] | 12.60 ± 0.33 | 12.96 ± 0.34[a] |
| **M3** | 0.50 ± 0.12 | 0.29 ± 0.003[a] | 0.47 ± 0.04 | 0.44± 0.05 | 11.84 ± 0.22 | 11.99 ± 0.11 |
| **M4** | 0.42 ± 0.11 | 0.33 ± 0.045[a] | 0.42 ± 0.02[a] | 0.52 ± 0.01 | 12.04 ± 0.25 | 11.76 ± 0.35 |

[a] $p < 0.05$; [b] $p < 0,01$; [c] $p < 0.001$

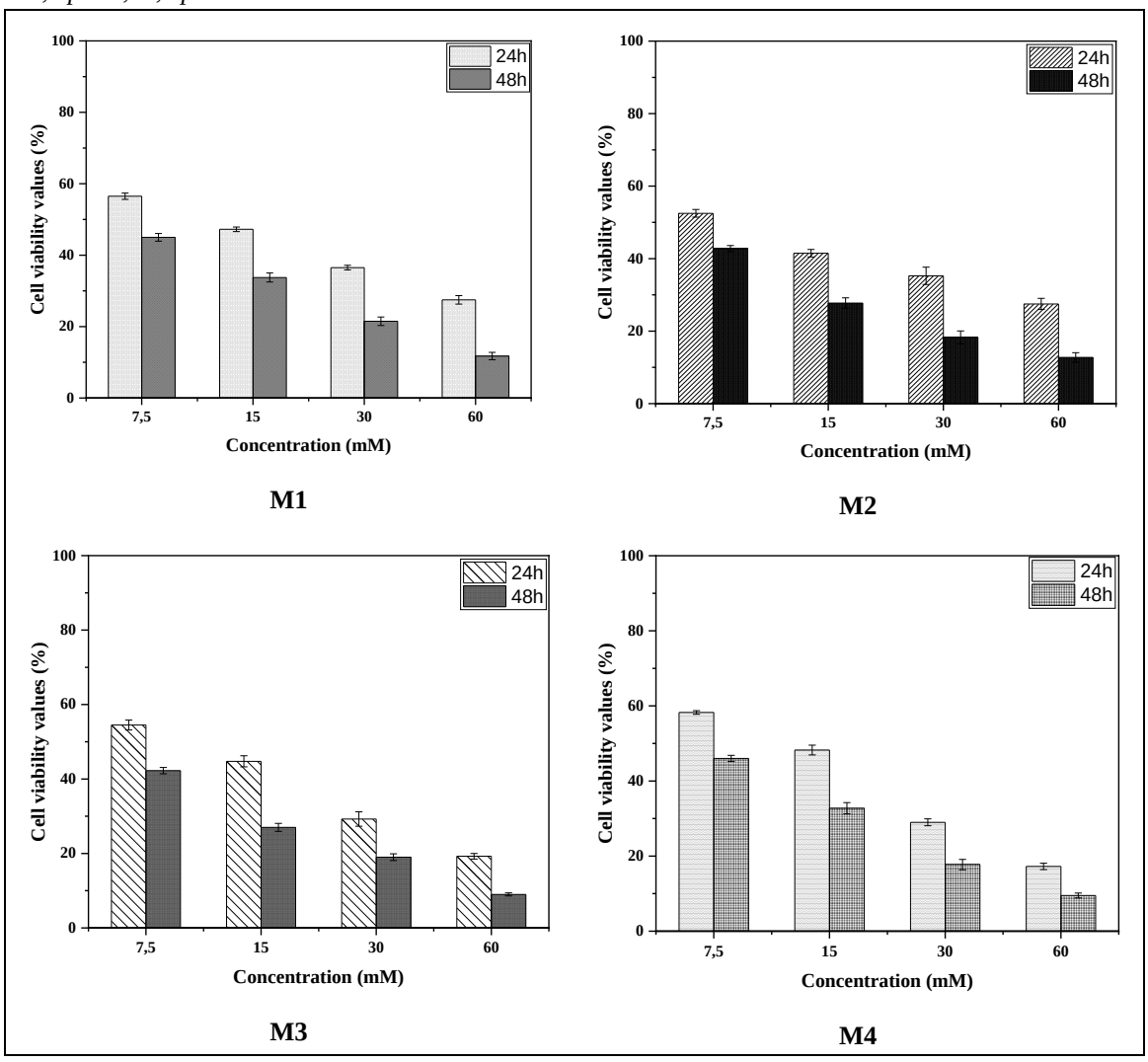


**Figure 1.** *Graphs of cell viability values of compounds no. M1, M2, M3 and M4 in L-1210 cell lines depending on the dose for 24 and 48 hours*

| MDA | 26 µM | 52 µM |
|---|---|---|
| **Control** | 0.29 ± 0.029 | 0.29 ± 0.029 |
| **M1** | 0.30 ± 0.01 | 0.34 ± 0.02[a] |
| **M2** | 0.44 ± 0.03[c] | 0.43 ± 0.04[c] |
| **M3** | 0.34 ± 0.02[b] | 0.40 ± 0.01[c] |
| **M4** | 0.44 ± 0.04[c] | 0.43 ± 0.03[c] |

**Table 4.** *Mean values of MDA (mg / 1.10$^6$ cells) levels of the Saccharomyces cerevisiae yeast cells treated with the compound according to the doses*
[a] $p < 0.05$; [b] $p < 0,01$; [c] $p < 0.001$

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**Table 5**. *Measurement results by DPPH radical reduction method*

| Gruplar (1000 µg/mL) | DPPH˙ Yok Etme Aktivitesi (%) |
|---|---|
| **Kontrol** | 0 |
| **M1** | 17.68 |
| **M2** | 17.29 |
| **M3** | 18.25 |
| **M4** | 21.04 |
| **Tokoferol** | 87.44 |

## DISCUSSION

The cytotoxic action mechanisms of xenobiotics, which are not produced in an organism and are defined as foreign substances to the biochemical metabolism of the organism; it is thought to be caused by damage to the cellular regulation system, the formation mechanism of intracellular synthesis products, or cellular transduction signaling. For this reason, it is known that there are many methods and experiments determined for cytotoxicity studies (Turan et al., 2011). In the investigation of the cytotoxic effects of the test components in our study, a method was used to determine the amount of cell viability.

Acetamide derivatives of triazole compounds investigated in the study were observed to inhibit proliferation on L1210 murine leukemia carcinoma cell lines when compared with control groups ($P < 0.05$). Although it was seen in Figure 1 that acetamide derivatives of M2 and M3 coded triazole compounds had antiproliferative effects on L1210 cell lines in proportion to the dose and time increase, it was determined that the most effective concentrations were 60 µM for 48 hours ($P < 0.05$).

In antioxidant studies, MDA levels of 2-(4H-[1,2,4]triazol-3-yl-sulfanyl) acetamide derivatives applied to *Saccharomyces cerevisiae* yeast cells were examined and statistical differences were determined in comparison with the control group. This difference is due to the increased MDA levels for all compounds compared to the control, and it is possible to say that the investigated test substances increase lipid peroxidation and cause cell damage.

A non-significant decrease in vitamin A and E levels of *Saccharomyces cerevisiae* cells treated with test substances was observed in control and dose-dependently. While there was an increase in vitamin C levels in the samples except the M3 compound compared to the control, a decrease was observed in the vitamin C levels of M1 and M4 compounds depending on the dose increase. One of the results obtained from antioxidant studies is that not all compounds whose properties were investigated by DPPH free radical scavenging method did not show radical scavenging properties. As a result, it can be said that antioxidant studies show parallelism and some 2-(4H-[1,2,4]triazol-3-yl-sulfanyl)-acetamide derivatives that have been synthesized do not have antioxidant activity.

Our findings show that especially high MDA levels and low vitamin levels in the compounds tested on yeast cells may create a mechanism that can cause oxidative damage by causing lipid peroxidation. In summary, it is possible to say that the compounds investigated in our study cause oxidative stress. Differences in the organic conformation of test compounds are also known to cause differences in biological functions (Guler et al., 2021).

## CONCLUSION

In this study, it was determined that some 2-(4H-[1,2,4]triazol-3-yl-sulfanyl)-acetamide derivatives had different effects on the duration and dose-dependent antitumor activities and some antioxidant parameter levels on the L1210 leukemia cancer cell line. The compounds were found to have a cytotoxic effect on the L1210 cancer cell line. At the same time, it was determined that the organic compounds caused a partial increase in the amount of MDA in the yeast cells of *Saccharomyces cerevisiae*, and a partial decrease in the levels of antioxidant vitamins A and E. In addition to the results obtained, it was determined that the organic compounds used in the DPPH radical scavenging experiments did not show antioxidant activity. It can be said that the organic compounds used in the study show antitumor activity by creating oxidative damage in

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cells. The positive findings of the antiproliferative effects in this study pave the way for studies on the existence of different mechanisms of action of the test compounds.

## CONFLICT OF INTEREST

The Author report no conflict of interest relevant to this article

## RESEARCH AND PUBLICATION ETHICS STATEMENT

The author declares that this study complies with research and publication ethics.

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