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In-vitro antiproliferative and antimigration activity against MDA-MB-231 cell line of new thiazole derivatives

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Summary

Extensive studies are performed in order to develop more safe and selective anticancer drugs in terms of decreasing treatment-associated toxicity. Special attention has been paid to molecules containing sulfur heterocycles as they consider an important structural unit of many marketed drugs. A series of 2-amino, 5-nitrothiazole derivatives were designed by our University. We aimed for *in vitro* testing of three compounds upon growth rates of MDA-MB-231 cell line and its ability for migration.

Materials and methods

Cytotoxicity of the mentioned compounds against the MDA-MB-231 cell line was assessed using MTT assay. Scratch assay was used to determine the possible effects of compounds on the migratory capacity of MDA-MB-231.

Results

Two compounds, i.e., 5-nitro-1,3-thiazol-2-amine and 4-{(E)-[(5-nitro-1,3-thiazol-2-yl)imino]methyl}benzaldehyde showed an inhibitory effect upon cancer cell migration while showing, no effect on the cytotoxicity of the MDA-MB-231 cancer cell line at increasing concentrations (1, 5, 10, 25, 50, and 100 μM/L) after 72 hours of incubation (with p.value=0.1076 and 0.8171 respectively).

In addition to cell migration inhibition, the derivate compound (5E)-5-(4-{(E)-[(5-nitro-1,3-thiazol-2-yl) imino]methyl}benzylidene)imidazolidine-2,4-dione showed a statistically significant cytotoxic effect upon MDA-MB-231 cell line following 72-h incubation at the drug concentration of 100 μM/L (p=0.0164).

Conclusion

The derivatives of 2-amino, 5-nitrothiazole are considered a promising starting point to synthesize further drug candidates to treat metastatic breast cancer.

Keywords

Thiazole derivatives, breast cancer, triple negative, cell line, MDA-MB-231, growth suppression, anti-migratory effect.

Introduction

Breast cancer is the most common cancer among women and a leading cause of cancer death worldwide. In 2020, for the first time, breast cancer has overtaken lung cancer as the most common malignancy, representing 11.7% of all cancer cases worldwide – according to the International Agency for Research on Cancer (IARC) [1]. Since metastatic diseases accounts for more than 90% of mortality in this cancer, the treatment is complemented with drugs that inhibiting the capacity of cancer cells to invade through the extracellular matrix (ECM) and establish secondary tumors [2]. Breast cancer is a heterogeneous disease with several biological subtypes. E.g., TNBC, triple-negative breast cancer, is the most aggressive subtype of breast cancer and known for its high recurrence rates. Thus, the mortality rate is higher in TNBC patients than among patients with other types of breast cancer [3].

Common therapeutic options are limited for TNBC, as neither hormone therapy nor HER2 targeting drugs do not work.

The response to available antitumor drugs is gradually decreasing among patients with metastatic breast cancer, possibly due to the tumor's resistance to a wide range of cancer drugs [3]. Additionally, most antitumor agents exhibit high toxicity [4]. In order to decrease toxicity levels of breast cancer treatment and increasing patients' survival rates, a search for researchers are working to develop more safe and selective anticancer drugs is underway [3, 5].

Thiazole derivatives have been reported to inhibit cancer cell growth and proliferation as well as neoangiogenesis through a variety of mechanisms and therapeutic targets [6]. E.g., incorporation of thiazole ring into different molecules have demonstrated a promising approach to design more potent and safer antitumor drugs [5]. Modifications on aminothiazole were found to cause antitumor activity against particular cell lines [7]. Adding an aromatic ring to 1,3-thiazole-2-amines provided a tubulin inhibitor with potent antiproliferative activity [8]. A series of substituted benzaldehydes exerted an inhibitory effect of MDA-MB-231 cell migration and proliferation [9]. Imidazolidine-2,4-dione moiety exhibited a potent anticancer activity [10].

Due to the known antioxidant effect, we tested the effect of 5-nitro-1,3-thiazol-2-amine (compound 1), on the growth and the migration of MDA-MB-231 cell line. Moreover, we used it as initial compound for structural modifications. According to Rockwell et.al study, the nitro heterocyclic compound 2-amino-5-nitrothiazole (ANT) was evaluated as a hypoxic radiosensitizer. Experiments with bacteria showed that this agent was similar to misonidazole in radiosensitizing activity, but was less cytotoxic and less mutagenic than misonidazole [11].

Compound2, 4-{(E)-[(5-nitro-1,3-thiazol-2-yl)imino]methyl}benzaldehyde, was prepared by adding benzaldehyde group in compound 1 structure. Compound 3, (5E)-5-(4-{(E)-[(5-nitro-1,3-thiazol-2-yl)imino]methyl}benzylidene) imidazolidine-2,4-dione, was prepared by addition of Imidazolidine-2,4-dione moiety (Fig. 1).

The heterocycles constitute a common structural unit of most marketed drugs, thus drawing special attention to molecules containing sulfur heterocycles [5]. Thiazole, a 5-membered unique heterocyclic motif-containing sulfur and nitrogen, serves as an essential core scaffold in many medicinally important compounds [12].

Thiazole ring is a basic part of some clinically applied anticancer drugs, such as dasatinib, dabrafenib, bleomycin, thiazofurine, and epothilone [5, 12]. Its derivatives exhibit excellent pharmacological profiles, making this skeleton an ideal scaffold to develop more potent and safer drug candidates [5].

Purposes of the present study was to evaluate the effect of these compounds on the viability and migration of MDA-MB-231 cancer cells aiming for design of more safe and selective anticancer drugs.

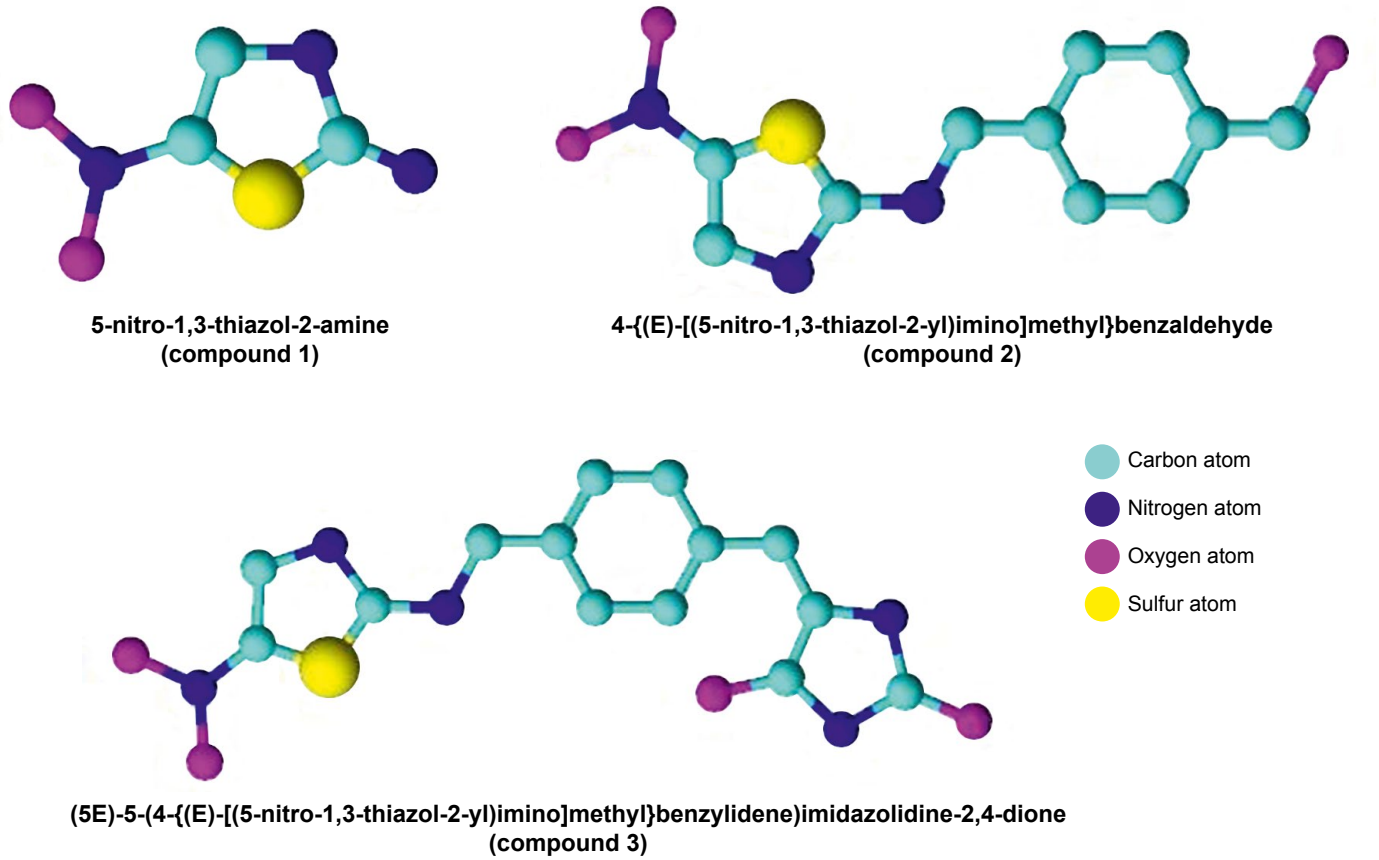


Figure 1. Chemical structures for compounds 1, 2, and 3

Materials and methods

Cell source and reagents

The breast cancer cell line MDA-MB-231 was obtained from The European Collection of Authenticated Cell Cultures (ECACC), Sigma-Aldrich (USA). Roswell Park Memorial Institute (RPMI)-1640 medium media (lot numbers: ECB9006L) and Fetal Bovine Serum (FBS) (lot number: ECS0180L) were acquired from EuroClone (Italy). The penicillin-streptomycin antibiotics (lot number: S11943L0022) were purchased from Biowest (USA). {3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide} (MTT) reagent and cell culture grade dimethyl sulfoxide (DMSO) were available from Sigma-Aldrich (USA).

Thiazole Derivatives

2-amino, 5-nitrothiazole derivatives were designed by the Faculty of Science-Department of Chemistry at the Damascus University by changing the substitution groups on the thiazole ring (Fig. 1). The Compound 1 was obtained from Sigma-Aldrich (USA) [13], and used as an initial chemical compound to prepare 4-{(E)-[(5-nitro-1,3-thiazol-2-yl)imino]methyl}benzaldehyde (Compound 2), and (5E)-5-(4-{(E)-[(5-nitro-1,3-thiazol-2-yl)imino]methyl}benzylidene) imidazolidine-2,4-dione (Compound 3). The drug samples were prepared as follows: the powder of each compound was dissolved in dimethyl sulfoxide (DMSO), and the final dilutions of 1 μM/L, 5 μM/L, 10 μM/L, 25 μM/L, 50 μM/L, 100 μM/L were prepared.

Cell-line characteristics and culture

For this research, we used the MDA-MB-231 cell line, since the triple negative breast cancer (TNBC) can be perfectly modeled using this cell line. The cells of this line are distinguished by invasive phenotype and high proliferation rate.

The MDA-MB-231 cell line was cultured in RPMI1640 media supplemented with 10% heat-inactivated FBS and 1% penicillin-streptomycin antibiotics. Cells were cultured in 25 cm^3 flasks and kept in a 5% CO_2 incubator at 37°C.

MTT assay

Tetrazolium salt is the first and most commonly used indicator dye for cell cultures, i.e., MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) introduced by Mosmann to evaluate proliferation and cytotoxicity of malignant cells.

Due to its lipophilic side groups and positive charge, MTT may pass the cell membranes and is reduced in viable cells by mitochondrial or cell plasma enzymes like dehydrogenases to the water-insoluble formazan [14].

Viable cells with active metabolism convert MTT into a purple-colored formazan product with maximal light absorbance of ca. 570 nm after solving the formazan crystals with DMSO. Meanwhile, dead cells lose the capacity to convert MTT to formazan, thus allowing the color development to be a useful marker of viable cell population only [15].

Hence, the cytotoxicity of the tested compounds on the MDA-MB-231 cancer cell line was evaluated in 96-well flasks by using the MTT colorimetric assay. The growing cells were harvested, counted with a haemocytometer, and plated in a 96-well plate at a cell density of 12,000 cells *per* 100 μL *per* well. After overnight incubation, the medium was removed and 100 uL of fresh medium was added at different concentrations of the compounds (1, 5, 10, 25, 50, and 100 μM/L). The cells have been treated with compounds for different time periods (24, 48, and 72h). Following the incubation period, 10 uL MTT (5 mg/mL) was added to each well and incubated for a further 4-hrs period. Media was removed from each well and 100 μL of DMSO was added to each well to solubilize formazan crystals. Viable cells were estimated by measuring the absorbance at 540 nm using a microplate ELISA reader (HumaReader HS, Human, Germany) [16].

Scratch assay

Cell migration is a fundamental process that controls morphogenesis and inflammation. Its deregulation is central to tumor cell dissemination and metastasis [17].

To determine the possible effects of the synthesized thiazole derivatives on cancer cell migration, we performed a scratch assay using an invasive MDA-MB-231 breast cancer cell line [6].

The scratch assay is a simple, reproducible assay commonly used to measure basic cell migration parameters, e.g., its speed, persistence, and polarity. The cells are grown to confluence and a thin "scratch" is introduced by incision with a scratcher. Cells at the scratch edge become polarized and migrate into the scratch space [17].

Briefly, the MDA-MB-231 cells (3×10^6 cells/well) were plated onto 6-well plates for 24 h at a confluence of about 80% and then wounded with a scratcher. Thereafter, the debris was removed by rinsing the cells once with 1 mL of PBS.

The cells were then incubated with RPMI medium containing 10% FBS and treated with 10 μM/L of each compound. The control sample contained the cells and a standard medium without any active agents. The video images were taken at specific intervals, retrieved and embedded by ScopeImage software (version 9.00, Bioimager Inc. Company, Canada). The area of the initial scratch was measured, followed by gap area measurements after 24-h and 48-h incubation. The inhibition rate was presented as the gap area value over the initial scratch area [3].

Statistical Analysis

The results were analyzed using GraphPad Prism (version 7.00). All results are expressed as means ± SD and were obtained from separate experiments. A p.value was calculated using a one-way ANOVA test and a p-value less than 0.05 was considered statistically significant in all analytic series. Dunn's multiple comparisons test was used to compare the difference in the sum of ranks between two columns, comparing the effects at different drug concentrations with control sample.

Results

MTT assay

All tested compounds did not show any effect on the cytotoxicity of the MDA-MB-231 cancer cell line after incubation periods of 24 and 48 h when using concentrations ranging

from 1 to 100 µM/L (data not shown). Figure 2 shows the effect of Compounds 1, 2, and 3 after the 72-h incubation period.

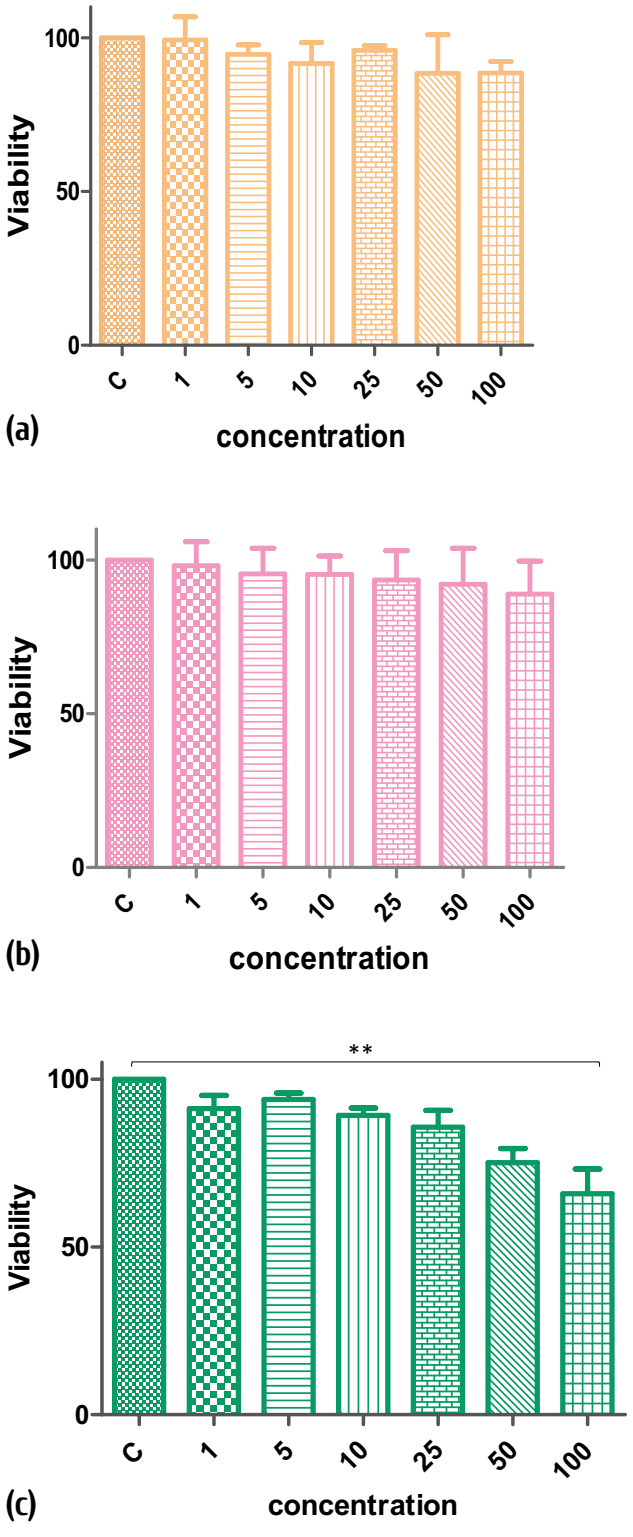


Figure 2. Viability effects of three thiazole compounds using different concentrations after 72 h incubation period on the breast cancer cell line MDA-MB-231 using MTT assay

*The results were presented as a mean and standard deviation of three independent experiments (**significant difference vs. control, P ≤ 0.01).*

(a): Compound 1, (b): Compound 2, (c): Compound 3.

Compounds 1 and 2 showed no effect on the cytotoxicity of the MDA-MB-231 cancer cell line using different concentrations of the compounds (1, 5, 10, 25, 50, and 100 µM/L) after incubation for 72 hours (with p. value=0.1076 and 0.8171 respectively). Compound 3 showed a significant effect on the cytotoxicity of the MDA-MB- 231 cell line at the concentration of 100 µM/L after incubation for 72 hours (p. value=0.0079). Meanwhile, no significant effect was observed using concentrations (1, 5, 10, 25, and 50 µM/L) after the 72-h incubation period.

Scratch assay

The results of the scratch assay are presented in Figure 3. In the control group, cell migration was very extensive with no evidence of the scratch after 24 h. For all of the studied compounds, an inhibitory effect was shown upon MDA-MB-231 cell migration *in vitro*. Using a 10 µM dose, compound 1 inhibited the motility of the MDA-MB-231 cells line. The inhibition rate was 64.52% after 24 hours and 28.19% after 48 h later.

Compound 2 showed the minimal migration inhibitory effect among the three studied compounds with an inhibition rate of 36.87% after 24 h and 18.93% after 48 h of treatment.

Meanwhile the inhibition rate with compound 3 was 41.30% after 24 h and 16.19% after 48 h.

Discussion

Research for new anticancer therapies is prompted by cancers' high mortality rate.

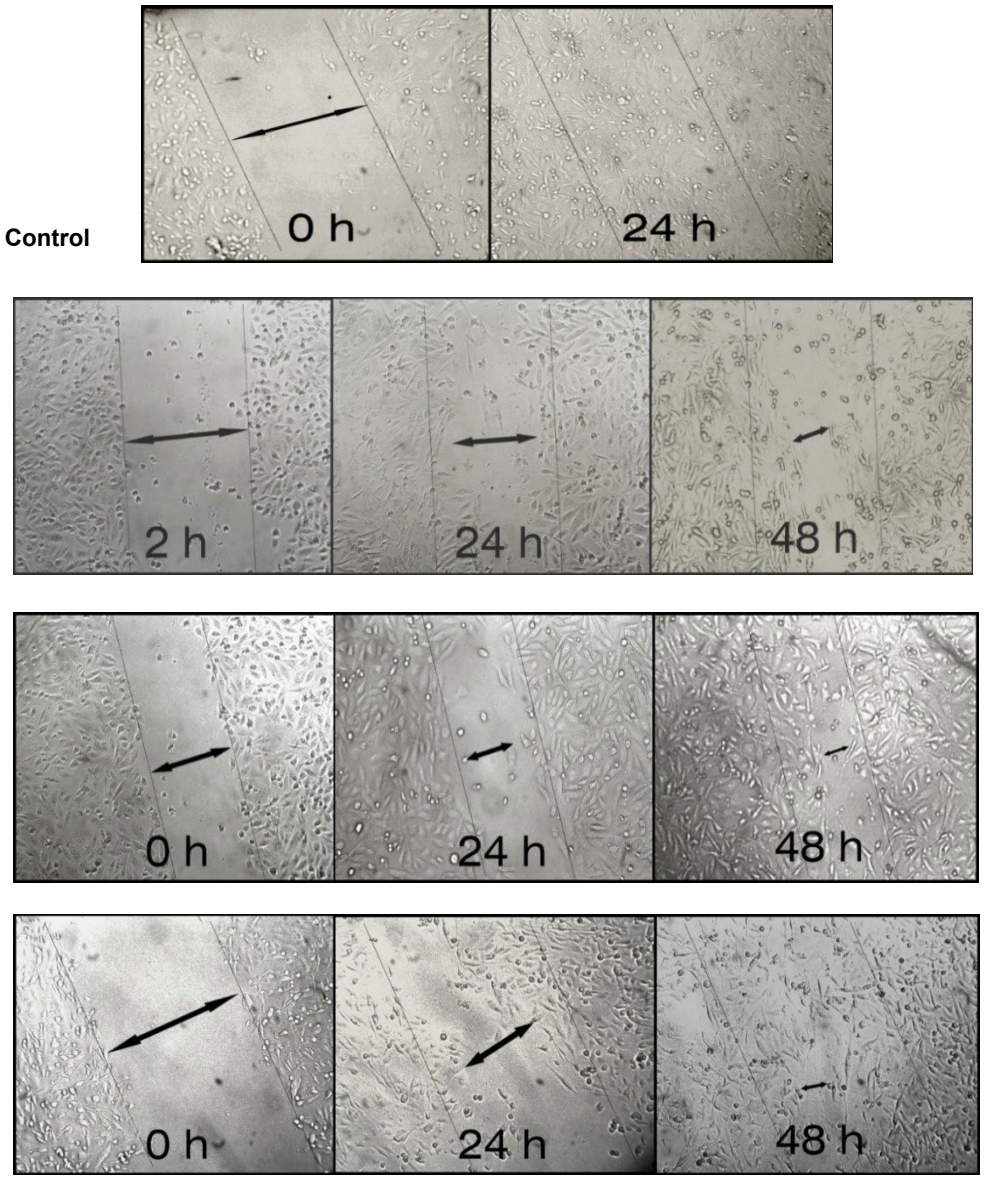
Our study was performed with MDA-MB-231 being one of the most studied breast cancer cell lines in medical research laboratories [18]. It is a highly aggressive and invasive TNBC cell line due to the lack of expression of estrogen receptor (ER) and progesterone receptor (PR), as well as the absence of HER2 (human epidermal growth factor receptor 2) overexpression [19].

The drugs containing thiazole rings are considered new effective medicines have taken their place in the research field. Hence, several studies have been conducted aiming to synthesize thiazole derivatives with different biological activities.

In 2013, Zheng *et al.* results demonstrated that the synthetic thiazole derivatives are effective migration inhibitors [6]. Later on, in 2014, the study of Grozav *et al.* have shown arylidene-hydrazinyl-thiazole derivatives significant anti-proliferative activity on the MDA-MB-231 cancer cell line[20]. Furthermore, Sbenati *et al.* (2011-2020) studied a series of new imidazo[2,1-b]thiazole-based aryl hydrazones. These compounds were designed and synthesized to evaluate their anti-tumor activity on some human cancer cell lines. The agents exhibited high cytotoxicity of these derivatives against the MDA-MB-231 cell line [21].

The structure-activity relationship (SAR) study revealed that the antitumor and antimigration activity was significantly affected by the substituents on the thiazole ring [22]. This indicated the importance of understanding the structure-

(a)



(b)

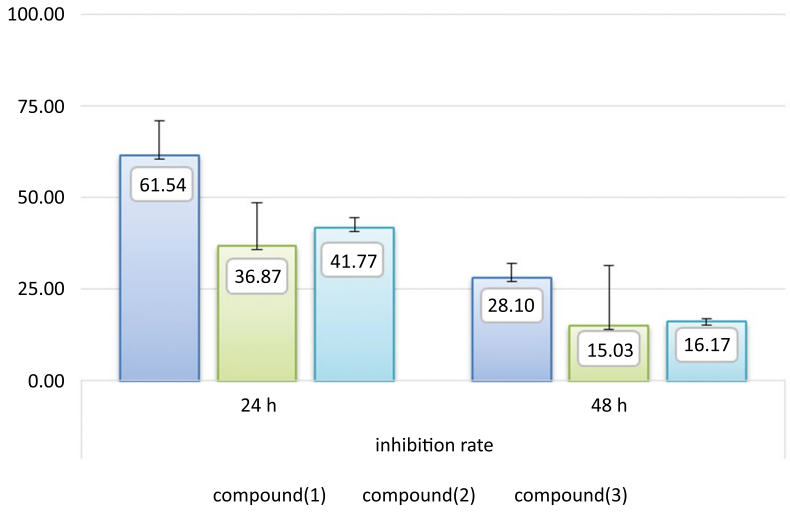


Figure 3. Effects of compounds on the migratory capacity of MDA-MB-231 (a), Statistical analysis of migration inhibition rate of MDA-MB-231 after incubation with compounds 1, 2, and 3 (b). Comparison between these three compounds shows that compound 1 has a greater influence on cell migration inhibition in MDA-MB-231 than compounds 2 and 3 treatment with a dose of 10 µM.

activity relationships for further optimization of a pharmacological index for the thiazole derivatives [7].

To our knowledge, this study presents the first results of testing the 2-amino, 5-nitrothiazole derivatives in the field of cancer. We compared the cytotoxic properties of the three compounds (by MTT assay) against MDA-MB-231 cells using different concentrations of the test drugs and different incubation periods. All tested compounds showed no effect on the cytotoxicity of the MDA-MB-231 cancer cell line after incubation periods of 24 and 48 h using a range of concentrations from 1 to 100 μM/L. This effect was cell line-dependent as our compounds showed an inhibition effect on the growth of myelogenous leukemia cell line K562 which was used as a positive control (data not shown). A significant effect on the cytotoxicity of the MDA-MB-231 cell line was observed specifically with compound 3 at a concentration of 100 μM/L after incubation for 72 hours.

The concentration of 10 μM/L was chosen for the cellular migration test since it did not show any effect upon cell growth and, therefore, doesn't affect the results. All the studied compounds showed an inhibitory effect of cellular migration of MDA-MB-231 *in vitro*.

Our results show that the thiazole derivatives produced by modification on (2-amino, 5-nitro thiazole) exert inhibition of MDA-MB-231 cancer cell growth and/or migration. These effects depend on replacement of functional groups at site-2 within the thiazole ring.

The addition of the benzaldehyde (Compound 2) to the thiazole ring does not affect the cytotoxic effect, whereas it decreases the anti-migration effect of the compound towards the MDA-MB-231 cancer cell line. The addition of the imidazole ring (compound 3) provided with the thiazole ring causes cytotoxic effect towards the MDA-MB-231 cell line as it keeps the anti-migration effect associated with addition of this ring. Our results are in line with the study by Petrou *et al.* (2021), who observed that hybrid derivatives of thiazole with different heterocyclic rings such as piperazine, pyridine, thiophen, imidazole, triazine, coumarin etc. as well as hydrazonyl thiazole derivatives are responsible for the anticancer activity [4].

Our results were consistent with Zheng *et al.* study that showed that synthetic thiazole derivatives are effective inhibitors of MDA-MB-231 cell migration at a concentration of 10 μmol/L [6].

Furthermore, these compounds exhibited low to negligible cytotoxicity, whereas they inhibited the *in vitro* ability of cancer cells to migrate. Thus, our study provides a novel type of small molecule therapeutic agents that aim to block cancer cell migration without exerting cell toxicity [6].

Conclusion

The derivatives of 2-amino, 5-nitrothiazole are considered as an excellent starting point to synthesize future drug candidates to treat breast cancer. Compound 3 is the most active molecule among our compounds against MDA-MB-231 cell growth. Using the compound 1 results in deeper inhibition of MDA-MB-231 cell migration when compared to other compounds.

These findings are helpful for the development of new potent anticancer agents using thiazole scaffold.

Therefore, additional *in vitro* and *in vivo* investigation into the mechanism of action, potential drug interactions, and adverse effects of these compounds allow us to evaluate the possibility of using these agents in breast cancer treatment in the future.

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Competing interest

The authors declare no conflict of interest.

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Подавление *in vitro* пролиферации и миграции клеток линии MDA-MB-231 новыми производными тиазола

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Резюме

Проведены обширные исследования по разработке более безопасных и избирательных противораковых препаратов для снижения токсичности, связанной с терапией. Особое внимание уделяется молекулам, содержащих серусодержащие гетероциклы, так как они рассматриваются как важная структурная единица многих коммерческих препаратов. В нашем университете был разработан ряд производных 2-амино, 5-нитротиазола. Нашей целью было тестирование *in vitro* трех подобных соединений на темпы роста клеточной линии MDA-MB-231 и на ее способность к миграции.

Материалы и методы

С помощью МТТ-теста определяли цитотоксичность указанных соединений. Скрэтч (scratch)-тест применяли для оценки возможных эффектов этих соединений на миграционную активность клеток линии MDA-MB-231.

Результаты

Два соединения, а именно: 5-нитро-1,3-тиазол-2-амин и 4-{(E)-[(5-нитро-1,3-тиазол-2-ил)имино]метил}бензальдегид, проявили ингибирующий эффект на миграцию раковых клеток, не оказывая при этом влияния на цитотоксичность в отношении линии MDA-MB-231 при использовании их в возрастающих концентрациях (1, 5, 10, 25, 50 и 100 мкМ/л) после 72 часов инкубации (p=0,11 и 0,83, соответственно).

Наряду с подавлением клеточной миграции, добавление к клеткам соединения (5E)-5-(4-{(E)-[(5-ниторо-1,3-тиазол-2-ил)имино]метил}бензилиден) имидазолидин-2,4-дион вызывало статистически достоверный цитотоксический эффект на клетках MDA-MB-231 после 72 часов инкубации при концентрации препарата 100 мкМ/л (p=0,016).

Выводы

Производные 2-амино, 5-нитротиазола можно рассматриваться в качестве перспективного исходного вещества для синтеза последующих кандидатных препаратов для лечения метастатического рака молочной железы.

Ключевые слова

Производные тиазола, рак молочной железы, трижды негативный, линия клеток, MDA-MB-231, подавление роста, подавление миграции.