Antineoplastic activity of novel thiazole derivatives

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The development of novel efficient substances for anticancer chemotherapy is an important problem of medicinal chemistry. **Aim.** To evaluate the level of cytotoxic action of novel thiazole derivatives towards tumor cell lines of different origin. **Methods.** Four N acylated 2-amino-5-benzyl-1,3-thiazoles (**5a–d**) were synthesized by reaction of 2-amino-5-R-benzyl-1,3-thiazoles with acid chlorides in the presence of triethylamine in the dioxane medium. Anticancer screening of the synthesized thiazoles was performed by the MTT assay. **Results.** Thiazole derivatives were shown to exert antineoplastic activity towards different types of tumor cells. The anti-glioma and anti-melanoma selectivity of these derivatives action was demonstrated. The compound **5a** was found to be the most toxic for human glioblastoma U251 cells and human melanoma WM793 cells. At the same time, the created compounds possessed low toxicity towards pseudo-normal cells. **Conclusion.** The novel thiazole derivative **5a** was the most toxic against human glioblastoma and melanoma cells.

K e y w o r d s: thiazole derivatives, 2-amino-5-benzyl-1,3-thiazoles, anticancer activity, leukemia, glioblastoma, melanoma.

Introduction

The discovery and development of the conventional anticancer drugs have been mainly focused on the cytotoxic agents [1]. The perspective antineoplastic agents are expected to inhibit, delay or reverse the progression of cancer development through their cytotoxicity or apoptosis-inducing properties [2]. Cytotoxic drugs prevent the rapid growth and division (mitosis) of tumor cells [1]. However, many anticancer drugs do not possess enough selectivity towards their targets. Thus, their application for cancer treatment is associated with

numerous negative side effects in the organism [3, 4]. Drugs demonstrate cytotoxicity toward different normal cells and organs, including bone marrow cells, reproductive glands, mucous layer of the intestine and hair follicles. These effects limit significantly application of some drugs and lead to the development of novel drugs.

Thiazole derivatives have attracted the interest of medicinal chemists due to a variety of their biological activities including anti-bacterial, anti-fungal, anti-HIV, anti-hypertension, anti-inflammatory, anti-cancer, anti-con-

vulsive and anti-depressant [5–10]. The mechanisms of 1,3-thiazole derivatives antitumor activity may be associated with DNA intercalation [11, 12], PRL-3, SHP-2 and JSP-1 inhibition [13–16], tumor necrosis factor (TNFα) [17], anti-apoptotic bio-complex Bcl-XL-BH3 [18], integrin avb3 [19], others. Thiazole ring belongs to the privileged scaffolds in modern medicinal chemistry [11, 20, 21], particularly at discovering new anticancer agents.

Herein, we described novel N-acylated 2-amino-5-benzyl-1,3-thiazoles and discovered

1, 2, 3: R = H (**a**), 4-Et (**b**), 4-Br (**c**), 3,4-Cl$_2$ (**d**)
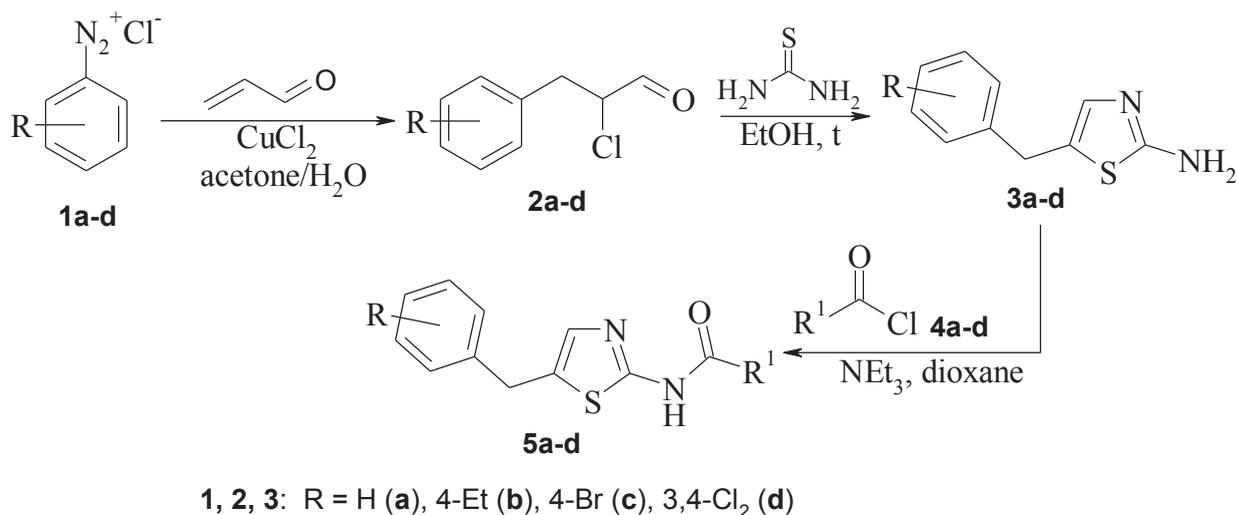
Entry	Compounds	Entry	Compounds
5a		5c	
5b		5d	

Fig. 1. General scheme of synthesis of thiazole derivatives

anticancer activity of the obtained amides. The synthesis of the target acylated 5-R-benzyl-1,3-thiazol-2-amines 5 is presented in Fig. 1. At the first step, the acrolein reacts with arene-diazonium salts (1a–d) in the presence of copper(II) chloride under the Meerwein arylation conditions. 3-Aryl-2-chloropropanals (2a–d) react with the thiourea in ethanol at refluxing and form 2-amino-5-R-benzyl-1,3-thiazoles (3a–d) with good yield [22, 23]. Previously, we have discussed the synthetic possibilities of 5-benzyl-2-aminothiazoles during the synthesis of 2-[(5-benzyl-1,3-thiazol-2-yl)imino]-1,3-thiazolidin-4-ones as potential biologically active compounds [24, 25]. In this paper, we described N-acylated 2-amino-5-benzyl-1,3-thiazoles (5a–d) obtained by the reaction of 2-amino-5-R-benzyl-1,3-thiazoles 3a–d with acid chlorides 4a–d in the presence of trietylamine in the dioxane medium.

The present study was addressed on the synthesis of thiazole derivatives containing some heterocyclic cores and the evaluation of their anticancer activity towards tumor cell lines of different tissue origin.

Materials and Methods

Thiazole derivatives

A 10 mM stock solution of thiazole derivatives was prepared in the dimethyl sulfoxide (DMSO, Sigma-Aldrich, USA), and additionally dissolved in a culture medium prior to addition to the cell culture.

General Procedure for the Synthesis of 3-aryl-2-chloropropanales 2a–d [23]

A three-necked flask equipped with a dropping funnel, a stirrer, and a gas-outlet tube attached to a bubble counter was charged with acrolein (0.2 mol or 13.5 cm³), $CuCl_2 \cdot 2H_2O$ (10 g), and acetone (50 cm³). Then, cold aqueous solution of arenediazonium chloride 1a–d prepared by diazotization of aniline (0.2 mol) was added drop-wise to the flask under vigorous stirring. The temperature of the mixture was kept within 10–30 °C. The organic phase was separated when the reaction was completed, and the aqueous phase was extracted with chloroform. The extract was combined with the previous organic phase, dried over magnesium sulfate, evaporated, and the residue was distilled under reduced pressure.

General Procedure for the Synthesis of 2-amino-5-arylmethylthiazoles 3a–d

A mixture of 8 g of thiourea and 0.1 mol of 3-aryl-2-chloropropanal 2a–d in 50 cm³ of ethanol was heated for 2 h under reflux. Then, it was cooled, diluted with 300 cm³ of water, and alkaline pH (~ 9) was achieved by adding aqueous ammonia. The precipitate was filtered off and recrystallized from carbon tetrachloride. 5-Benzyl-1,3-thiazol-2-amine 3a has been described earlier [22, 23].

5-(4-Ethylbenzyl)-1,3-thiazol-2-amine 3b. Yield 86 %. M.p. 105–106 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: 7.11 (d, J = 7.8 Hz, 2H), 7.08 (d, J = 7.8 Hz, 2H), 6.64 (s, 1H), 6.60 (s, 2H), 3.81 (s, 2H), 2.58 (q, J = 7.7 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H). Calculated, %: C 66.02, H 6.46, N 12.83. $C_{12}H_{14}N_2S$. Found: C 65.85, H 6.33, N 12.58.

5-(4-Bromobenzyl)-1,3-thiazol-2-amine 3c. Yield 84 %. M.p. 123–125 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: 7.42 (d, 2H, J = 8.1 Hz), 7.15 (d, 2H, J= 8.1 Hz), 6.61 (s, 2H), 6.64 (s, 1H), 3.86 (s, 2H). Calculated, %:

44.62, H 3.37, N 10.41. $C_{10}H_9BrN_2S$. Found: C 44.34, H 3.32, N 10.25.

5-(3,4-Dichlorobenzyl)-1,3-thiazol-2-amine 3d. Yield 83%. M.p. 92–94°C. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: 7.47 (d, 1H, J=8.4 Hz), 7.40 (d, 1H, J=1.8 Hz), 7.17 (dd, 1H, ^{4}J=1.8 Hz, ^{3}J=8.4 Hz), 6.67 (br. s, 3H), 3.90 (s, 2H). Calculated, %: C 46.35, H 3.11, N 10.81. $C_{10}H_8Cl_2N_2S$. Found: C 46.22, H 3.08, N 10.69.

General Procedure for the Synthesis of compounds 5a–d

5 mmol of 2-amino-5-arylmethylthiazole 3a–d was dissolved in the mixture of 5 ml dioxane and 5 mmol triethylamine. Solution of 5 mmol acid chloride 4a–d in 3 ml dioxane was added drop-wise to the reaction mixture under vigorous stirring. Mixture was stirred for 2 h, and diluted with 50 cm^3 of water. The precipitate was filtered off and recrystallized from mixture EtOH/DMF.

N-(5-Benzyl-1,3-thiazol-2-yl)-3,5-dimethyl-1-benzofuran-2-carboxamide 5a. Yield 75 %. M.p. 198 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: 12.42 (s, 1H), 7.54 (s, 1H), 7.49 (d, 1H, J = 8.5 Hz,), 7.35–7.26 (m, 6H), 7.25–7.21 (m, 1H), 4.10 (s, 2H), 2.54 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d$_6$), δ: 152.10, 142.44, 140.64, 133.87, 133.04, 131.92, 131.80, 129.66, 129.55, 129.07, 129.01, 128.89, 126.98, 124.10, 121.23, 111.93, 32.54, 21.36, 9.39. Calculated, %: C, 69.59; H, 5.01; N, 7.73. $C_{21}H_{18}N_2O_2S$. Found: C, 69.29; H, 4.94; N, 7.63.

N-[5-(4-Ethylbenzyl)-1,3-thiazol-2-yl]-1-oxo-1H-isothiochromene-3-carboxamide 5b. Yield 83 %. M.p. 190 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: 13.09 (s, 1H), 8.36 (s, 1H), 8.18 (d, 1H, J = 7.9 Hz), 7.99–7.88 (m, 2H), 7.77 (t, 1H, J = 7.1 Hz), 7.33 (s, 1H), 7.19 (d, 2H, J = 7.7 Hz), 7.16 (d, 2H, J = 8.1 Hz), 4.02 (s, 2H), 2.56 (q, 2H J = 7.7 Hz), 1.15 (t, 3H, J = 7.5 Hz). ^{13}C NMR (101 MHz, DMSO-d$_6$),δ: = 187.30, 156.46, 155.32, 146.97, 142.55, 137.57, 136.91, 135.26, 132.92, 131.54, 129.01, 128.86, 128.77, 128.55, 128.48, 128.46, 125.67, 32.43, 28.26, 16.11. Calculated, %: C, 65.00; H, 4.46; N, 6.89. $C_{22}H_{18}N_2O_2S_2$. Found: C, 64.57; H, 4.39; N, 6.75.

N-[5-(4-Bromobenzyl)-1,3-thiazol-2-yl]-2-(2,4-dimethylphenoxy)acetamide 5c. Yield 80 %. M.p. 150°C. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: 12.15 (s, 1H), 7.49 (d, 2H, J = 8.2 Hz), 7.26 (s, 1H), 7.21 (d, 2H, J = 8.2 Hz), 6.95 (s, 1H), 6.89 (d, 1H, J = 8.2 Hz), 6.66 (d, 1H, J = 8.2 Hz), 4.77 (s, 2H), 4.06 (s, 2H), 2.17 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d$_6$), δ:162.19, 162.12, 154.31, 140.20, 135.40, 131.90, 131.82, 131.47, 131.09, 130.06, 127.46, 126.33, 120.03, 111.72, 66.91, 31.65, 20.52, 16.48. Calculated, %: C, 55.69; H, 4.44; N, 6.49. $C_{20}H_{19}BrN_2O_2S$. Found: C, 55.32; H, 4.39; N, 6.33.

N-[5-(3,4-Dichlorobenzyl)-1,3-thiazol-2-yl]-2H-chromene-2-carboxamide 5d. Yield 85%. M.p. 216°C. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: 12.32 (s, 1H), 7.69 (s, 1H), 7.57 (d, 2H, J = 8.3 Hz), 7.33 (s, 1H), 7.31–7.22 (m, 3H), 6.99–6.95 (m, 1H), 6.86 (d, 1H, J = 8.0 Hz), 4.98 (s, 2H), 4.12 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d$_6$), δ: = 154.88, 142.01, 132.33, 132.22, 131.50, 131.47, 131.19, 131.14, 130.84, 130.76, 129.58, 129.50, 129.46, 129.33, 129.27, 122.44, 121.38, 116.28, 64.44, 31.21. Calculated, %: C, 57.56; H, 3.38; N, 6.71. $C_{20}H_{14}Cl_2N_2O_2S$. Found: C, 57.30; H, 3.31; N, 6.62.

Cell culture

Human breast adenocarcinoma cells of MCF-7 line, lung adenocarcinoma cells of A549 line, glioblastoma cells of U251 line, myeloid leukemia cells of K562 line, acute T-cell leukemia cells of Jurkat line, and embryonic kidney cells of HEK293 line were obtained from Cell Collection of R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiology (Kyiv, Ukraine). Human melanoma cells of WM793 line were provided by Dr. O. Stasyk (Institute of Cell Biology, National Academy of Sciences of Ukraine, Lviv, Ukraine). Cells were grown in the RPMI (APP, Austria) or DMEM (Sigma-Aldrich, USA) culture medium supplemented with 10 % fetal bovine serum (FBS, APP, Austria). Cells were cultivated in the CO_2-thermostat at 37ºC in atmosphere of 95 % air and 5 % CO_2.

Cell proliferation assay

Antineoplastic activity of the synthesized compounds towards cancer cell lines was measured by the MTT (3-(4,5-Dimethylthiazole-2-yl)-2,5-diphenyl-tetrazolium bromide) test (Sigma-Aldrich, USA) [26]. The antitumor drug doxorubicin (Pharmachemie B.V., the Netherlands) was used as a reference drug control. Tumor cells were seeded for 24 h in 96-well plates in 100 µl at the concentration of 5,000 cells/well (substrate-dependent cells) or 10,000 cells/well (suspension cells). After that, cells were incubated for next 72 h with various additions of the synthesized compounds or doxorubicin (0–100 µM). MTT was added to the cells according to the manufacturer's protocol (Sigma-Aldrich, USA). The results of the reaction were determined by an Absorbance Reader BioTek ELx800 (BioTek Instruments, Inc., USA). The IC_{50} of tested compounds was calculated as a lethal concentration of drug killing 50 % of the cells in comparison with an untreated culture.

Statistical analysis

All data are presented as the mean ± standard deviation. The results were analyzed and illustrated with GraphPad Prism (version 6; GraphPad Software, USA). Statistical analysis was performed using two-way ANOVA tests. P-value of <0.05 was considered as statistically significant.

Results

The synthesis of different derivatives of 2-amino-5-arylmethylthiazoles is described in the Materials and Methods section. The compounds under study were added to the cultured human tumor and pseudo-normal cells in different final concentrations (0; 1; 10; 50 µM) for 72 h. Doxorubicin was used as a reference positive control. The obtained results were expressed as IC_{50} and presented in Figures 2–4. The synthesized thiazoles were shown to possess diverse anti-proliferative action towards tumor cells of different tissue origin.

In the first set of experiments, the anticancer effect of compounds was studied towards adenocarcinoma cells, namely human breast adenocarcinoma cells of MCF-7 line and human lung adenocarcinoma cells of A549 line. Doxorubicin demonstrated a much stronger cytotoxicity for MCF-7 cells comparing to the A549 cells (Fig. 2). However, both cell lines were relatively not sensitive to the action of studied thiazoles used in doses up to 50 µM.
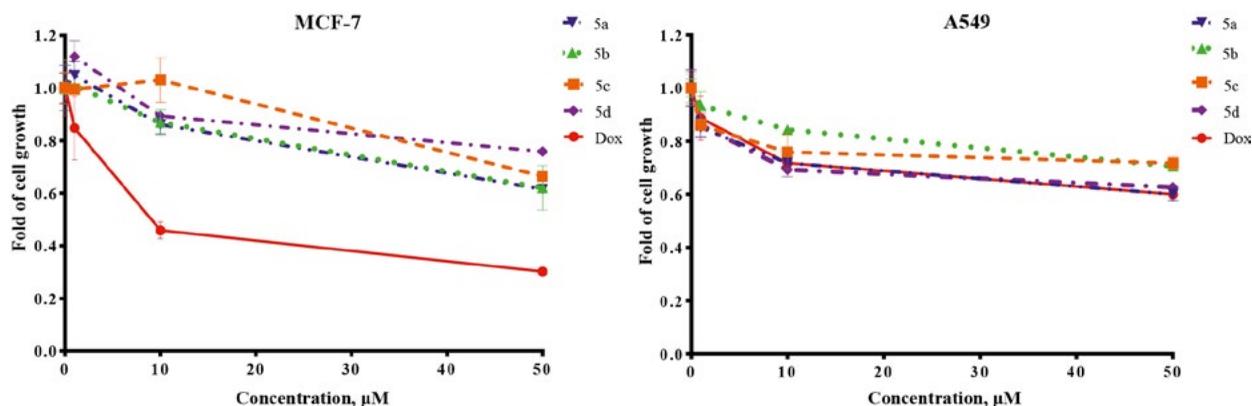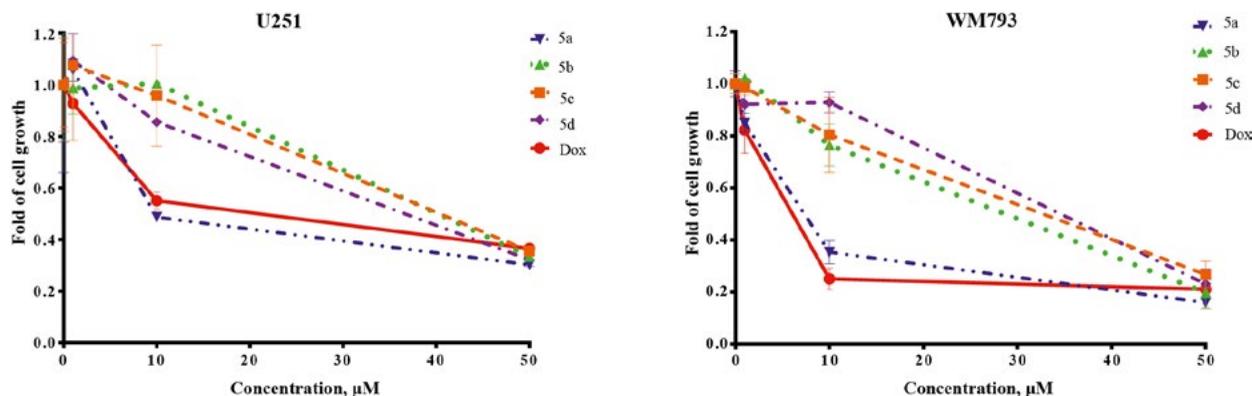
Fig. 2. Characteristics of cytotoxicity of thiazole derivatives (5a–d) and doxorubicin (Dox) towards human breast adenocarcinoma MCF-7 cells and human lung adenocarcinoma A549 cells.

The antineoplastic effect of the thiazole derivatives was also studied using human glioblastoma cells of U251 line and human melanoma cells of WM793 line. The concentration-dependent cytotoxicity effect of the thiazoles was found when the glioblastoma cells were treated. The synthesized 5c, 5d and 5b displayed a weak activity towards glioblastoma U251 cells (IC_{50} for 5c was 40.0±2.46 μM; IC_{50} for 5d was 36.5±1.96 μM and IC_{50} for 5b was 40.0±2.82 μM), and demonstrated cytotoxicity only when used in high dose (50 μM).

At the same time, the 5a compound was highly toxic for the glioblastoma cells (IC_{50} = 9.8±0.82 μM), and even more toxic than the doxorubicin (IC_{50} = 21.0±1.64 μM) that is considered to be a "golden standard" in the anticancer chemotherapy (Fig. 3).

The general pattern of the cytotoxic activity of 5a–d thiazoles and doxorubicin towards human melanoma cells of WM793 line was similar to that described above for human glioblastoma U251 cells. IC_{50} for 5c was 32.3±2.15 μM, IC_{50} for 5d was 34.6±2.24 μM,

Fig. 3. Characteristics of cytotoxicity of thiazole derivatives (5a–d) and doxorubicin (Dox) towards human glioblastoma U251 cells and human melanoma WM793 cells.
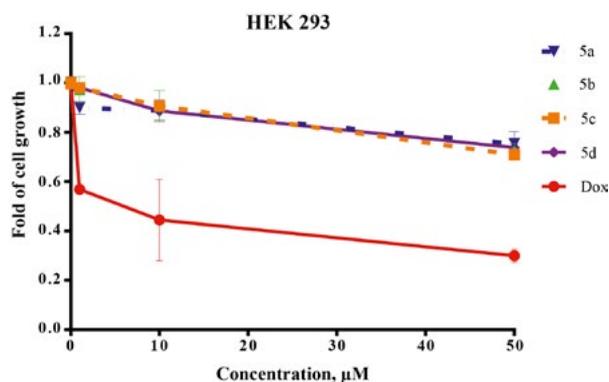
140
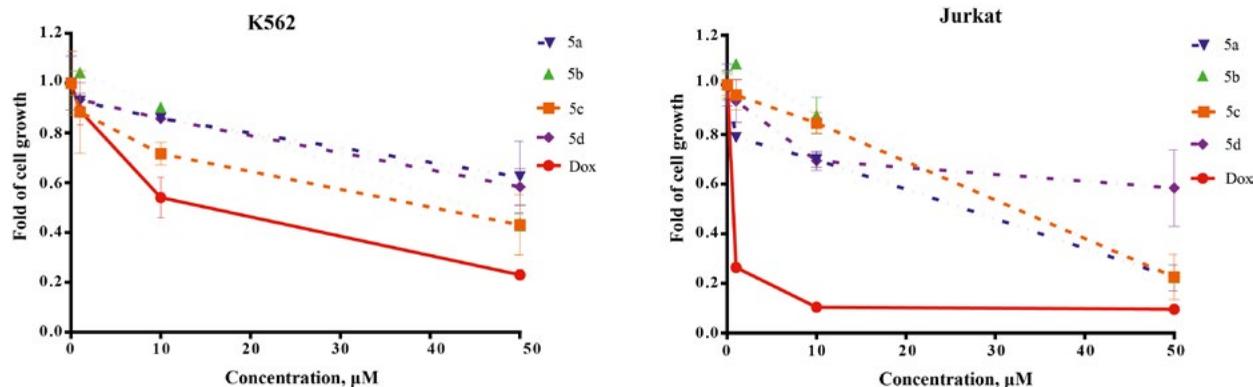
Fig. 4. Characteristics of cytotoxicity of thiazole derivatives (5a–d) and doxorubicin (Dox) towards human myeloid leukemia cells of K562 line and human acute T-cell leukemia cells of Jurkat line.

and IC_{50} for 5b was 28.5±2.06 μM, whereas the 5a compound was highly toxic for the melanoma cells (IC_{50} = 7.2±0.48 μM), and the toxicity of doxorubicin was similar to such effect of the 5a compound (IC_{50} = 6.1±0.38 μM) (Fig. 3).

As four human tumor cell lines used above belong to the substrate-dependent type of cells, it was reasonable to study the effect of 5a–d thiazoles and doxorubicin on the inhibition of growth of the leukemia cells in suspension. Thus, human myeloid leukemia cells of K562 line and human acute T-cell leukemia cells of Jurkat line were treated *in vitro* with the doxorubicin and experimental anticancer agents. We have found that 5c and 5b compounds possessed a moderate toxicity for leukemia K-562 cells (IC_{50} for 5c was 40.0±2.65 μM and IC_{50} for 5b was 44.7±3.15μM). 5d and 5a compounds were relatively non-toxic for the leukemia K-562 cells in the concentration up to 50 μM (Fig. 4), whereas the toxicity of doxorubicin was much higher comparing to the effect of thiazoles and IC_{50} for doxorubicin was 15.2±1.14 μM.

It was found that 5c, 5a and 5b did not demonstrate significant toxicity for human acute T-cell leukemia cells of Jurkat line (IC_{50} for 5a was 27.0±2.13 μM, IC_{50} for 5c was 32.3±2.73 μM, and IC_{50} for 5b was 33.0± 2.85 μM). The 5d was poorly active towards the Jurkat leukemia cells in dose to 50 μM, whereas the doxorubicin was extremely toxic for these cells (IC_{50} = 0.7±0.05 μM) (Fig. 4).

Fig. 5. Characteristics of cytotoxicity of thiazole derivatives (5a–d) and doxorubicin (Dox) towards human embryonic kidney cells of HEK 293 line.

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Thus, the tested thiazole derivatives showed a broad spectrum of the growth inhibition activity against human tumor cells of different tissue origin and the melanoma and glioma cells appeared to be more sensitive to the action of these derivatives comparing to human leukemia cells.

Finally, we have studied the cytotoxic effect of the novel thiazoles towards non-tumor pseudo-normal cells – human embryonic kidney cells of HEK293 line (Fig. 5). Notably, these cells demonstrated the resistance to the cytotoxic action of the thiazoles in dose up to 50 μM, whereas doxorubicin showed significant cytotoxicity with the IC50 = ~20 μM.

Discussion

The tumor targeting technologies are focused on creating novel agents that effectively inhibit, reverse or delay carcinogenesis [27] through selective affecting tumor cells mostly by impairing their antioxidant potential [28] or inducing apoptosis [29, 30]. Additionally, the potential drugs should combat tumor cells of the advanced stages of malignancy (metastasis) that is a major cause of patients' mortality [1].

We have screened the anti-proliferative activity of the novel synthesized thiazoles 5a–d towards human tumor cells of various tissue origin. The MTT assay-based evaluation of the survival of treated human breast adenocarcinoma cells of MCF-7 line and human lung adenocarcinoma cells of A549 line showed that these cells were sensitive to the cytotoxic action of the thiazoles used only in high doses (up to 50 μM). At the same time, these compounds possessed a distinct antineoplastic activity towards the human glioblastoma cells of

U251 line and human melanoma cells of WM793 line, whereas the human myeloid leukemia cells of K562 line and human acute T-cell leukemia cells of Jurkat line were less sensitive to the cytotoxic action of the experimental anticancer agents. The ranking of the toxic action of thiazoles and doxorubicin towards the glioblastoma U251 cells was as following: 5a > doxorubicin > 5d > 5c ≈ 5b. IC_{50} of 5a for the glioblastoma cells equaled 9.8±0.82 μM, whereas doxorubicin was less toxic for these cells (IC_{50} = 21.0±1.64 μM). Obviously, the amides endowed with the benzofuran moiety (5a) possess a higher anticancer activity [31, 32]. Glass *et al.* (2000) showed an inhibition of growth in human glioblastoma cell lines by the farnesyltransferase inhibitor SCH66336. However, the concentration of that inhibitor, which is required to achieve 50 % inhibition (IC_{50}) ranged from 30 μM (single 24 h treatment) to 10 μM (5 day treatment). This is a higher dose compared to the dose required for distinct effect of 5a used in our study.

Malignant melanoma is a disease with a high mortality rate caused by rapid metastasis. Ciołczyk-Wierzbicka *et al.* [35] showed the inhibition of proliferation of human melanoma cells by using specific siRNA for silencing the N-cadherin gene. Its silencing arrests the cell growth at the G1-phase of cell cycle and inhibits the cell entry into the S-phase. Noteworthy, there are no effective chemotherapies for the melanoma treatment [33]. The immunomodulating approaches used in clinics are still very costly and possess high general toxicity [34].

During studying the anti-proliferative activity of the synthesized thiazoles towards the

human melanoma WM793 cells, we have found that 5a was also the most cytotoxic agent (IC_{50} = 7.2±0.48 μM) the action of which was comparable with the action of doxorubicin (IC_{50} = 6.1±0.38 μM). The toxicity rank of thiazoles and doxorubicin for the melanoma WM793 cells was: doxorubicin ≈ 5a > 5b > 5c > 5d.

The synthesized thiazoles were also found to be toxic for leukemia cells – the human myeloid leukemia cells of K562 line and the human acute T-cell leukemia cells of Jurkat line, however, demonstrated their cytotoxicity only at high doses. The ranking of the toxic action of thiazoles and doxorubicin on the leukemia K562 cells was the following: doxorubicin (15.2±1.14 μM) > 5c (40.0±2.65 μM) > 5b > 5d > 5a. Thus, the rank of toxicity of the 5a for these leukemia cells growing only in suspension is opposite to the rank found for the glioblastoma and melanoma cells growing in the monolayer culture. Thus, the role of silencing N-cadherin (participates in cell attachment) for the inhibition of melanoma cells should be reminded here [35]. Doxorubicin was the most effective inhibitor of growth of the human acute T-cell leukemia cells of Jurkat line, and the rank of inhibitory effects dropped in the following manner: doxorubicin (IC_{50} = 0.7±0.05 μM) > 5a (IC_{50} = 27.0±2.13 μM) > 5c > 5b >5d. Obviously, amides 5 endowed with benzofuran moiety (5a) have a higher anticancer activity [31, 32].

It was also shown that thiazoles were not toxic for human embryonic kidney HEK293 cells, while doxorubicin had high cytotoxity towards these cells (IC_{50} was 5.7±0.42 μM).

The tested thiazole derivatives showed a broad spectrum of the anti-proliferative activity against human tumor cells of different tissue origin and the melanoma and glioma cells appeared to be more sensitive to the action of these derivatives comparing to human leukemia cells.

Conclusion

Four novel thiazole derivatives were synthesized and screened for their anticancer activity *in vitro*. These derivatives selectively inhibited the growth of human tumor cells, and 5a was the most potent agent demonstrating a selective action towards the glioma and melanoma cells, comparing to the leukemia cells. Thus, the thiazole derivatives are a perspective source of the innovative anticancer agents.

Acknowledgments

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Антинеопластична активність нових похідних тіазолів

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Створення нових ефективних субстанцій для використання у протипухлинній хіміотерапії є актуальним напрямком медичної хімії. **Мета.** Дослідити цитотоксичну дію нових похідних тіазолу щодо пухлинних клітин різного тканинного походження. **Методи.** Чотири нові N-ацильованих 2-аміно-5-бензил-1,3-тіазолів (субстанції 5a-d) були синтезовані взаємодією 2-аміно-5-R-бензил-1,3-тіазолів з ацилхлоридами у середовищі діоксану за наявності триетиламіну. Для дослідження протипухлинної активності похідних тіазолу використовували МТТ-тест. **Результати.** Встановлено, що

деякі похідні тіазолу мають антинеопластичну активність щодо пухлинних клітин різного тканинного походження. Показано селективну антигліомну та антимеланомну дію досліджуваних сполук. Речовина 5а має найбільш виражену цитотоксичну дію щодо клітин лінії U251 гліобластоми людини і лінії WM793 меланоми людини. Синтезовані сполуки мають низьку токсичність щодо псевдонормальних ембріональних клітин нирки. **Висновок.** Нове похідне тіазолу (речовина **5а**) є перспективним цитотоксичним чинником для дії на клітини гліобластоми і меланоми.

Ключові слова: похідні тіазолу, 2-аміно-5-бензил-1,3-тіазоли, протипухлинна активність, лейкоз, гліобластома, меланома.

Антинеопластическая активность новых производных тиазола

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Разработка и синтез новых производных тиазола являются перспективным направлением медицинской химии и противоопухолевой терапии. **Цель.** Изучение цитотоксического действия новых производных тиазола в отношении злокачественных клеток различного тканевого происхождения. **Методы.** Четыре новых N-ацилированных 2-амино-5-бензил-1,3-тиазола (5a–d) были синтезированы взаимодействием 2-амино-5-R-бензил-1,3-тиазолов с ацилхлоридами в присутствии триэтиламина в среде диоксана. Исследование противоопухолевой активности тиазолов проводили с использованием МТТ-анализа. **Результаты.** Установлено, что производные тиазола оказывают противоопухолевое действие на некоторые типы опухолей. Было подтверждено селективное антиглиомное и антимеланомное действие соединений. Соединение 5а проявляет наиболее выраженное цитотоксическое действие на опухолевые клетки U251 глиобластомы человека и WM793 меланомы человека. Исследованные соединения обладают низкой токсичностью по отношению к псевдо-нормальным эмбриональным клеткам почек. **Вывод.** Соединение 5а является перспективным токсическим агентом для клеток глиобластомы и меланомы.

Ключевые слова: производные тиазола, 2-амино-5-бензил-1,3-тиазолы, противоопухолевая активность, лейкоз, глиобластома, меланома.