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Study *in vitro* of the anticancer activity of [3-allyl-4-(4^1-methoxyphenyl)-3H-thiazole-2-ylidene]-(3^2-trifluoromethylphenyl) amine hydrobromide toward human tumor cells

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Aim. *In vitro* study and characterization of [the] anticancer activity of heterocyclic derivative — [3-allyl-4-(4^1-methoxyphenyl)-3H-thiazole-2-ylidene]-(3^2-trifluoromethylphenyl)amine hydrobromide. **Methods.** The cell culture; MTT assay. **Results.** We synthesized [3-allyl-4-(4^1-methoxyphenyl)-3H-thiazole-2-ylidene]-(3^2-trifluoromethylphenyl)amine hydrobromide, which possessed the cardioprotective, as well as the hypolipidemic, anti-inflammatory, analgesic, antihypertensive and antioxidant effects. Here, we investigated its growth inhibitory action towards tumor cell lines of various tissue origin[s]: leukemia (HL-60, Jurkat), liver (HepG2), breast (MCF-7), lung (A549), cervical (KB3-1) and glioma (U251, U373, T98G) cells. We found that the leukemia cells were the most sensitive to the action of [3-allyl-4-(4^1-methoxyphenyl)-3H-thiazole-2-ylidene]-(3^2-trifluoromethylphenyl)amine hydrobromide with a mean of IC_{50} values at 7.5-8.9 μg/mL. **Conclusions.** The anti-proliferative activity of [3-allyl-4-(4^1-methoxyphenyl)-3H-thiazole-2-ylidene]-(3^2-trifluoromethylphenyl)amine hydrobromide dropped in the order: leukemia > hepatocarcinoma ~ cervix > lung carcinoma > glioblastoma > breast carcinoma cells. Thus, we revealed in one molecule of ([3-allyl-4-(4^1-methoxyphenyl)-3H-thiazole-2-ylidene]-(3^2-trifluoromethylphenyl)amine hydrobromide) a combination of both the cardioprotective and anticancer activities that is of great significance for this agent as a potent anticancer medicine.

K e y w o r d s: [3-allyl-4-(4^1-methoxyphenyl)-3H-thiazole-2-ylidene]-(3^2-trifluoromethylphenyl)amine hydrobromide, cytotoxicity *in vitro*, anticancer activity.

Introduction

Cancer is one of the most challenging diseases in the world [1–3]. Significant progress has been achieved in the development of anticancer treatment. However, current chemotherapy lacks effective and safe drugs. The development of drug resistance and metastasis progression is another great challenge in anticancer therapy [3, 4]. Thus, the search for new compounds demonstrating high anticancer potency and fewer adverse effects is an urgent need in drug discovery.

The development of new heterocycles, namely thiazole derivatives, with certain biological and physicochemical properties as effective and safe drug-like molecules acting as a multi-target scaffold is an actual task of organic and medical chemistry [2, 3]. Thiazole derivatives demonstrated a wide spectrum of biological activities, e.g. antimicrobial [5], antifungal [6], anti-HIV [7], anti-inflammatory [8], anti-tubercular [9], and antitumor [9, 10]. [The] Authors showed high inhibitory effects of 3,3'-dimethoxy-N(4),N(4')-bis(4-(4-bromophenyl)thiazol-2-yl)-[1,1'-biphenyl]-4,4'-diamine on A549 and C6 cells with the IC_{50} values of 37.3 μg/mL and 11.3 μg/mL, and low toxicity against NIH-3T3 cells [11]. Wang *et al.* demonstrated a cytotoxic activity of β-pinene-based thiazole derivatives against the HeLa, CT-26, and SMMC-7721 cell lines [12]. Afifi *et al.* designed [the] purine-pyrazole hybrids combining thiazoles, thiazolidinones, and rhodanines that displayed anticancer activity *in vitro* for the lung (A549), liver (HepG-2), colon (Caco-2), prostate (PC3), and breast (MCF-7) tumor cells [13]. Noteworthy, the thiazole core is present in the structure of the currently used anticancer drug Dasatinib as well as in the structure of SNS-032, the drug under clinical trials [2, 14].

The fluoro-substituents are widely used in drug design [1, 15–18]. Moreover, the introduction of a trifluoromethyl group into drugs might improve their bioavailability, lipophilicity, metabolic stability, and promotes transport and absorption [15, 18, 19]. Koppireddi *et al.* reported that 3-(3-trifluoromethylphenyl)-6-phenylimidazo[2,1-b]thiazole possessed higher anti-proliferative properties towards HeLa cells among other 3,6-diphenylimidazo[2,1-b]thiazole derivatives [18].

The search for additional treatment activities in the existing medicines is a valuable trend in pharmacology, and sometimes it brings new inventions [20-23]. Recently, the com-

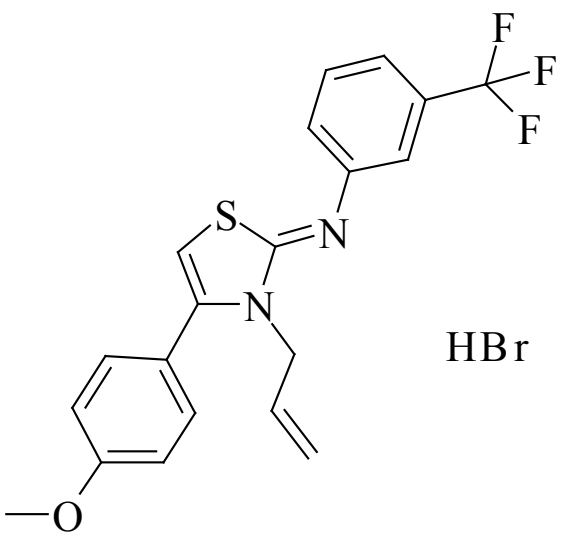

Fig. 1. [3-allyl-4-(4[1]-methoxyphenyl)-3H-thiazol-2-ylidene]-(3[2]-trifluoromethylphenyl)amine hydrobromide

pound [3-allyl-4-(4^1-methoxyphenyl)-3H-thiazole-2-ylidene]-(3^2-trifluoromethylphenyl) amine hydrobromide) was synthesized (Fig. 1) [24, 25] and, as described previously, it possesses a cardioprotective effect; besides, this compound exhibits the hypolipidemic, anti-inflammatory, analgesic, antihypertensive and antioxidant activities [24–30].

Here, we addressed the investigation of the anticancer potential of the [3-allyl-4-(4^1-methoxyphenyl)-3H-thiazole-2-ylidene]-(3^2-trifluoromethylphenyl)amine hydrobromide. A combination of the cardioprotective and anticancer activities in one molecule is of great significance, since a very potent anticancer drug, Doxorubicin, is extremely cardiotoxic that limits its applications as an anticancer remedy [31, 32].

Materials and methods

All reagents and solvents were purchased from commercial suppliers and were used directly without further purification. Melting points were measured in open capillary tubes on a BÜCHI B-545 melting point apparatus (BÜCHI Labortechnik AG, Flawil, Switzerland), and were uncorrected. The elemental analyses (C, H, N) were performed using the Perkin-Elmer 2400 CHN analyzer (Perkin-Elmer, Waltham, MA, USA) and the results were within ±0.4 % of the theoretical values. The 500 MHz 1H and 100 MHz ^{13}C NMR spectra were recorded on Varian Unity Plus 500 (500 MHz) spectrometer (Varian Inc., Paulo Alto, CA, USA). LC-MS spectra were obtained on a Finnigan MAT INCOS-50 (Thermo Finnigan LLC, San Jose, CA, USA).

[3-allyl-4-(4^1-methoxyphenyl)-3H-thiazole-2-ylidene]-(3^2-trifluoromethylphenyl)amine hydrobromide. The compound was synthesized, as described previously [24, 25]. Yield: 80 %, mp 220-222 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.32 (s, 3H, OCH_3), 4.61 (s, 2, CH_2), 4.82-5,17 (m, 1H, CH=), 5.29-5.73 (m, 2H, $=CH_2$), 6.95 (s, 1H, thiazole), 6.98–7.55 (m, 8H, arom.), 10.70 (s, 1H, NH^+). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 51.3 (CH_2), 55.3 (OCH_3), 115.2, 121.9 (d, J = 8.0 Hz), 122.0, 124.4, 125.0 (d, J = 200 Hz), 126.5, 127.8, 128.9, 131.2 (d, J = 49 Hz), 130.0, 131.4, 132.0, 149.1, 151.0, 152.6, 158.5. LCMS (ESI): m/z 391.0 (97.0 %, $[M+H]^+$). Anal. Calc. for $C_{20}H_{18}BrF_3N_2OS$: C 50.97 %; H 3.85 %; N 5.94 %. Found: C 63.55 %; H 4.20 %; N 12.30 %.

The stock solution of the compound in 50 mg/mL concentration was prepared in dimethyl sulfoxide (DMSO, Sigma-Aldrich, USA). Before adding to cells, further dilutions were prepared using a culture medium. Doxorubicin (Dox, Actavis, Romania) was used as a positive control drug.

Cells culture. The human myeloid leukemia HL-60 cells, human T cell leukemia Jurkat cells, human hepatocarcinoma HepG2 cells, human glioblastoma cells of U251, U373, and T98G lines were from a collection at the Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine (Kyiv, Ukraine). The human breast adenocarcinoma MCF-7 cells and human lung carcinoma A549 cells, human epidermoid cervix carcinoma KB3-1 cells were from Cell Collection of R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology (Kyiv, Ukraine).

The cells were grown in RPMI-1640 (BioWest, France) or Dulbecco's modified

Eagle's (BioWest, France) culture medium supplemented with 10 % fetal bovine serum (BioWest, France). The cells were cultivated at 37 ºC in the atmosphere of 5 % CO_2 and 95 % air.

MTT assay for evaluation of cell proliferation. The antineoplastic activity of the synthesized compound and Doxorubicin towards the cell lines of different tissue origin was examined using the MTT test (EZ4U, Biomedica, Austria). Briefly, the cells were seeded overnight into 96-well plates in 100 μL at concentrations of 5,000 cells/well (substrate-dependent cells) or 10,000 cells/well (suspension cells). The aliquots of 100 μL of experimental compounds (0-100 μg/mL) were added to the culture medium and [the] cells were incubated for the next 72 h. The 72 h term of the compound exposure was used in order to analyze the possible cytotoxic activity of studied compounds without any time-related limitations. The MTT reagent (3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide) was added to the cells following the manufacturer's recommendations (EZ4U, Biomedica, Austria). The results of the reaction were determined by an Absorbance Reader BioTek ELx800 (BioTek Instruments Inc., USA) at 490 nm and 630 nm. The relative amount of untreated (control) cells was taken as 1. The IC_{50} of tested compounds was calculated as the drug concentration that reduced cell viability by 50 % [33].

Data analysis. The results were analyzed and illustrated using GraphPad Prism 6 software (GraphPad Software, USA). All data are presented as the mean (M) ± standard deviation (SD) of at least three independent experiments. A two-way ANOVA test (by Dunnett's test) and the column statistics of GraphPad Prism 6 software were used for the statistical analysis of data. Statistical significance was identified at $P \leq 0.05$.

Results and Discussion

The growth inhibitory activities of [3-allyl-4-(4^1-methoxyphenyl)-3H-thiazole-2-ylidene]-(3^2-trifluoromethylphenyl)amine hydrobromide (tested compound) and Doxorubicin (positive control) towards leukemia (HL-60, Jurkat), liver (HepG2), breast (MCF-7), lung (A549) and glioma (U251, U373, T98G) tumor cells *in vitro* were evaluated by the MTT assay. The studied derivative displayed diverse anti-proliferative activities towards studied tumor cells. It was effective in inhibiting the growth of human leukemia cells with the IC_{50} value of 7.5 μg/mL for HL-60 cells and 8.9 μg/mL — for Jurkat cells (Fig. 2, table 1).

Next, we studied the anti-proliferative activity of [3-allyl-4-(4^1-methoxyphenyl)-3H-thiazole-2-ylidene]-(3^2-trifluoromethylphenyl) amine hydrobromide towards human tumor cells of the epithelial origin (HepG2, MCF-7, A549). The [3-allyl-4-(4^1-methoxyphenyl)-3H-thiazole-2-ylidene]-(3^2-trifluoromethylphenyl) amine hydrobromide demonstrated a potent anti-proliferative activity in the human hepatocarcinoma cells (IC_{50} = 53.0 μg/mL, Fig. 3, table 1). This compound exhibited a weaker cytotoxic activity towards the MCF-7 and A549 cells. The IC_{50} was 95.5 μg/mL for MCF-7 cells and 77.1 μg/mL –for A549 cells (Fig. 3, table 1). The [3-allyl-4-(4^1-methoxyphenyl)-3H-thiazole-2-ylidene]-(3^2-trifluoromethylphenyl)amine hydrobromide demonstrated a lower toxicity for carcinoma cells than the Doxorubicin (table 1). The tox-

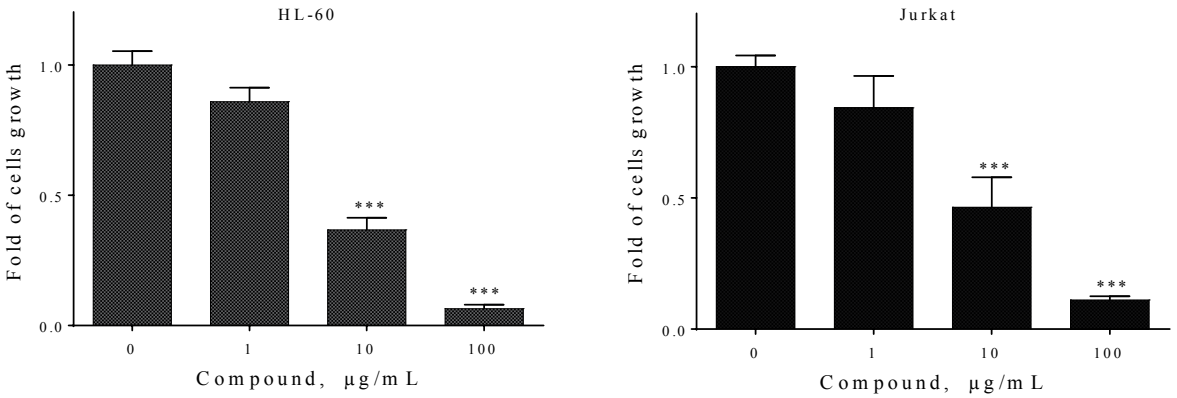

Fig. 2. The anti-proliferative activity of [3-allyl-4-(4[1]-methoxyphenyl)-3H-thiazole-2-ylidene]-(3[2]-trifluoromethylphenyl)amine hydrobromide towards human leukemia cell lines (HL-60 and Jurkat). Cell viability was examined using the MTT assay after 72 h of the exposure to studied derivative. *** - $P \leq 0.001$.

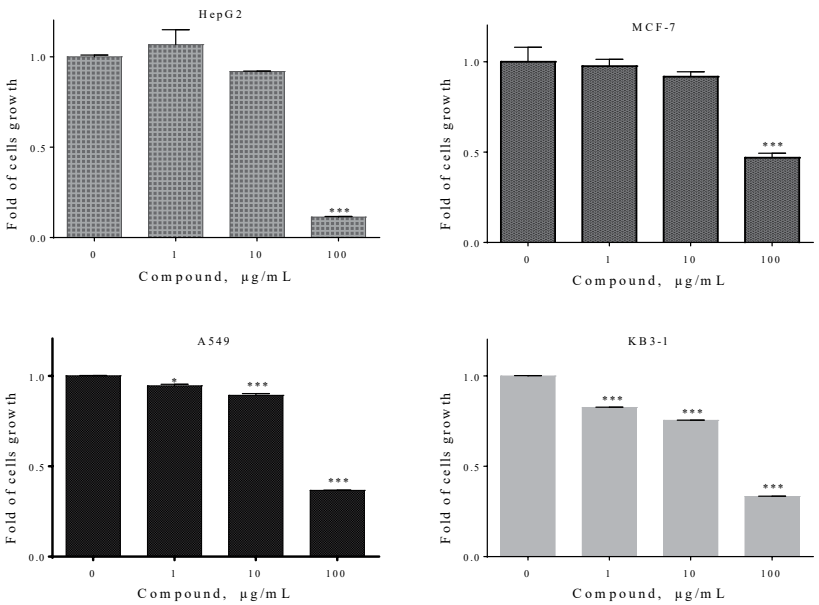

Fig. 3. The anti-proliferative activity of [3-allyl-4-(4[1]-methoxyphenyl)-3H-thiazole-2-ylidene]-(3[2]-trifluoromethylphenyl)amine hydrobromide towards human hepatocellular (HepG2), breast (MCF-7), lung (A549) and cervix (KB3-1) carcinoma cell lines. Cell viability was examined using the MTT assay after 72 h of the exposure to studied derivative. * — $P \leq 0.05$, *** — $P \leq 0.001$.

icity of [3-allyl-4-(4[1]-methoxyphenyl)-3H-thiazole-2-ylidene]-(3[2]-trifluoromethylphenyl) amine hydrobromide was also examined towards human epidermoid cervix carcinoma KB3-1 cells. In 63.1 µg/mL dose, it induced 50 % death of KB3-1 cells (Fig. 3, table 1).

The anti-proliferative effects of [3-allyl-4-(4[1]-methoxyphenyl)-3H-thiazole-2-ylidene]-

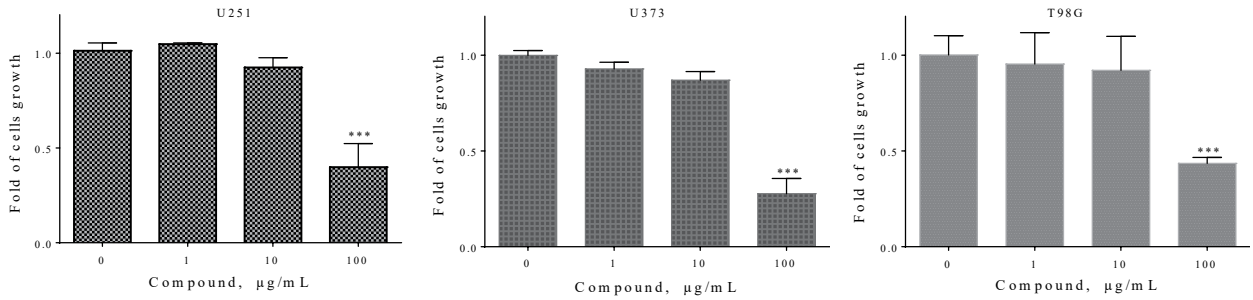

Fig. 4. The results of measuring the anti-proliferative activity of hydrobromide [3-allyl-4-(4[1]-methoxyphenyl)-3H-thiazole-2-ylidene]-(3[2]-trifluoromethylphenyl) amine towards human glioblastoma (U251, U373, T98G) cells. Cell viability was examined using the MTT assay after 72 h of the exposure to studied derivative. *** - $P \leq 0.001$.

(3[2]-trifluoromethylphenyl)amine hydrobromide towards [the] glioblastoma (U251, U373, T98G) cells were found to be similar to its effect towards the carcinoma cells. The IC_{50} of the studied compound was 66.1 μg/mL for U373 cells, 81.6 μg/mL — for U251 cells, and 88.0 μg/mL — for T98G cells (Fig. 4, table 1) that is higher than the Doxorubicin action (table 1).

Based on the results of the cytotoxicity study, the leukemia cells were the most sensitive to the action of [3-allyl-4-(4[1]-methoxyphenyl)-3H-thiazole-2-ylidene]-(3[2]-trifluoromethylphenyl)amine hydrobromide. [The] Anti-proliferative action of this compound dropped in the order: leukemia > hepatocarcinoma ~ cervix > lung carcinoma > glioblastoma > breast carcinoma cells. Further studies of the mechanism of antitumor action of the 3-allyl-4-(4[1]-methoxyphenyl)-3H-thiazole-2-ylidene]-(3[2]-trifluoromethylphenyl)amine hydrobromide are necessary as the diverse

Table 1. **Cytotoxicity indicator (IC_{50}) of hydrobromide [3-allyl-4-(4[1]-methoxyphenyl)-3H-thiazole-2-ylidene]-(3[2]-trifluoromethylphenyl) amine hydrobromide and Doxorubicin targeting cells of different tissue origin (72 h, MTT assay)**

Human tumor cell line	IC_{50} for derivative, μg/mL	IC_{50} for Doxorubicin, μg/mL
Human myeloid leukemia HL-60 cells	7.50 ± 0.61	0.07 ± 0.01
Human T cell leukemia Jurkat cells	8.90 ± 0.66	0.80 ± 0.05
Human hepatocarcinoma HepG2 cells	53.00 ± 4.71	0.55 ± 0.03
Human breast adenocarcinoma MCF-7 cells	95.50 ± 9.51	0.70 ± 0.04
Human lung carcinoma A549 cells	77.10 ± 5.42	0.90 ± 0.07
Human epidermoid cervix carcinoma KB3-1 cells	63.10 ± 5.19	0.83 ± 0.05
Human glioblastoma U251 cells	81.60 ± 7.86	0.43 ± 0.03
Human glioblastoma U373 cells	66.10 ± 4.79	0.58 ± 0.05
Human glioblastoma T98G cells	88.00 ± 7.08	0.40 ± 0.03

mechanisms of the antineoplastic action of thiazole-derived compounds were reported. The clinically available thiazole-containing anticancer drug Tiazofurin inhibits the inosine-5′-monophosphate (IMP) dehydrogenase, Dasatinib (Sprycel) targets Abl, Arg, KIT, PDGFR, Src in chronic myelogenous leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia, Ixabepilone stabilizes microtubules, Dabrafenib inhibits B-RAF activity [34], and Voreloxin binds to DNA, interacts with topoisomerase II that resulting in DNA double-strand cracks and G2 cell cycle arrest [35]. Turan-Zitouni *et al.* (2016) reported that 3,3′-dimethoxy-N4,N4′-bis(4-(4-bromophenyl)thiazol-2-yl)-[1,1′-biphenyl]-4,4′-diamine inhibits DNA synthesis in A549 cells [11]. Thiazole derivatives inhibited the growth of tumor cells through ROS-mediated mitochondrial dysfunction signaling pathways [12, 36], and arrest cells in G0/G1 phase [12, 18] or G2 phase [37]. Additionally, the thiazole-containing derivatives possessed antioxidant potential [13]. Othman *et al.* (2022) synthesized the derivatives bearing pyrazoline-3-one ring conjugated with the fused thieno[3,2-d]thiazole scaffold via an NH linker that were reported as multi-targeting kinase inhibitors against EGFR, VEGFR-2, and $BRAFV^{600E}$ [37].

Concluding, our findings demonstrate that in addition to earlier detected cardioprotective effect, 3-allyl-4-(4^1-methoxyphenyl)-3H-thiazole-2-ylidene]-(3^2-trifluoromethylphenyl) amine hydrobromide also possesses distinct anticancer action towards human tumor cells of various tissue origin. That makes this novel compound a promising candidate for deeper investigation of its anticancer action as a chemotherapy agent of dual (cardioprotective and anticancer) activity.

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Вивчення протипухлинної активності 3-аліл-4-(4^1-метоксифеніл)-3H-тіазол-2-іліден-(3^2-трифторметилфеніл)амін гідробро міду *in vitro* **щодо пухлинних клітин людини**

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Мета. *in vitro* дослідження та характеристика протипухлинної активності гетероциклічної сполуки 3-аліл-4-(4^1-метоксифеніл)-3H-тіазол-2-іліден-(3^2-трифлуорометилфеніл)амін гідроброміду. **Методи.** Культури клітин, МТТ тест. **Результати.** Ми синтезували сполуку 3-аліл-4-(4^1-метоксифеніл)-3H-тіазол-2-іліден-(3^2-трифлуорометилфеніл)амін гідроброміду, яка проявляє кардіопротекторну, а також гіполіпідемічну, протизапальну, знеболюючу, гіпотензивну та антиоксидантну дію. У даній роботі досліджували антинеопластичну дію даної речовини щодо ліній

пухлинних клітин різного тканинного походження: лейкозу (HL-60, Jurkat), гепатокарциноми (HepG2), карциноми молочної залози (MCF-7), легені (A549), шийки матки (KB3-1) та гліоми (U251, U373, T98G) *in vitro*. Досліджувана сполука виявила широкий спектр протипухлинної активності. Клітини лейкемії були найбільш чутливими до дії досліджуваної сполуки із середніми значеннями IC_{50} 7,5-8,9 мкг/мл. **Висновки.** Чутливість пухлинних клітин до дії 3-аліл-4-(4^1-метоксифеніл)-3Н-тіазол-2-іліден-(3^2-трифлуорометилфеніл)амін гідроброміду знижувалася у наступному порядку: лейкемія ~ карцинома шийки матки > карцинома легені > гліобластома > карцинома молочної залози. Таким чином, поєднання в одній молекулі (3-аліл-4-(4^1-метоксифеніл)-3Н-тіазол-2-іліден-(3^2-трифлуорометилфеніл)амін гідроброміду) як кардіопротекторної так і протипухлинної активностей робить дану речовину перспективним протипухлинним засобом.

Ключові слова: 3-аліл-4-(4^1-метоксифеніл)-3Н-тіазол-2-іліден-(3^2-трифлуорометилфеніл)амін гідробромід, цитотоксичність *in vitro*, протипухлинна активність.

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