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ORIGINAL ARTICLE

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The assessment of the cytotoxic activity of 2-(1,1-dimethyl-1H-benzo[e]indolin-2-yl)-5,6,7-trichloro-1,3-tropolone against the human glioblastoma U87 MG cell line

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ABSTRACT

Purpose of the study. To study the cytotoxic effect of 2-(1,1-dimethyl-1H-benzo[e]indolin-2-yl)-5,6,7-trichloro-1,3-tropolone (JO-122 (2)) on the U87 MG cell line.

Materials and methods. The investigation of the cytotoxic effect of synthesized tropolone JO-122 (2) was performed using the standard MTT colorimetric assay on the human glioblastoma cell line U87 MG. Test substance samples were prepared by sequential twofold dilutions of the original stock solution with concentrations of 24 μM. Temozolomide was used as a reference drug, and its tested doses fell in the range of 250 to 0.4883 μM. Incubation time after the addition of the substances were 24, 48, and 72 hours. The statistical processing of the obtained data was carried out using Microsoft Excel 2013 and Statistica 10 software.

Results. The cytotoxic effect of 2-(1,1-dimethyl-1H-benzo[e]indolin-2-yl)-5,6,7-trichloro-1,3-tropolone on the U87 MG cell line was investigated in the study. The assessment of cytotoxicity showed that at all investigated doses of tropolone, there was a statistically significant inhibition of cell growth in the U87 MG cell line. After 24, 48, and 72 hours, the necessary minimum concentration of JO-122 (2) for suppressing tumor cell growth was 3 μM, 0.0469 μM, and 0.1875 μM, respectively.

The comparison drug showed less pronounced suppression of tumor cell growth compared to tropolone. For an incubation time of 24 hours, no significant decrease in cell viability was observed in any of the tested concentrations. The minimum concentration of Temozolomide required to inhibit U87 MG cell culture growth was obtained after 72 hours and was 3.9063 μM.

Conclusion. The conducted research demonstrated that both substances exhibited concentration-dependent toxicity towards the human glioblastoma cell line. However, tropolone JO-122 (2) showed a more pronounced ability to suppress the growth of the U87 MG cell line.

Keywords: glioblastoma, tropolone, U87 glioblastoma cell line, MTT assay, cytotoxicity assay

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Оценка цитотоксического действия 2-(1,1-диметил-1h-бензо[e]индолин-2-ил)-5,6,7-трихлор-1,3-трополона в отношении клеточной линии U87 MG глиобластомы человека

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РЕЗЮМЕ

Цель исследования. Изучить цитотоксический эффект 2-(1,1-диметил-1h-бензо[e]индолин-2-ил)-5,6,7-трихлор-1,3-трополона (JO-122 (2)) на клеточной линии глиобластомы человека U87 MG.

Материалы и методы. Исследование цитотоксического эффекта трополона JO-122 (2) было выполнено колориметрическим анализом с применением 3-[4,5-диметилтиазол-2- ил]-2,5-дифенилтетразолия бромида (МТТ-тест) на клеточной линии глиобластомы человека U87 MG. Образцы тестируемого вещества были подготовлены путем последовательных двукратных разведений исходного стокового раствора с концентраций 24 мкМ. В качестве препарата сравнения был использован Темозоломид, его исследуемые дозы находились в диапазоне 250–0,4883 мкМ. Время инкубации после добавления веществ: 24, 48 и 72 ч. Статистическая обработка полученных была проведена в программах Microsoft Excel 2013 и Statistica 10.

Результаты. В работе был исследован цитотоксический эффект трополона JO-122 (2) на клеточную линию U87 MG. Оценка цитотоксичности показала, что при исследуемых дозах трополона наблюдалось статистически значимое ингибирование роста клеток линии U87. Через 24, 48 и 72 часа необходимая минимальная концентрация JO-122 (2) для подавления роста опухолевых клеток составила 3 мкМ, 0,0469 мкМ и 0,1875 мкМ соответственно.

Препарат сравнения показал менее выраженное подавление роста опухолевой линии в сравнении с трополоном. Для времени инкубации 24 часа не наблюдалось достоверного снижения жизнеспособности клеток ни в одной из исследуемых концентраций. Минимальная концентрация Темозоломида, необходимая для ингибирования роста клеток культуры U87 MG, была получена через 72 часа и составила 3,9063 мкМ.

Заключение. В результате проведенного исследования было показано, что оба вещества продемонстрировали зависящую от концентрации токсичность в отношении клеточной линии глиобластомы человека. Однако трополон JO-122 (2) показал более выраженную способность подавлять рост культуры U87 MG.

Ключевые слова: глиобластома, трополон, опухолевая культура клеток U87, МТТ-тест, оценка цитотоксичности

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Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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INTRODUCTION

Malignant primary brain tumors originate from the tissues that make up the central nervous system and its membranes and are dangerous types of neoplasms. This is due to both, the deterioration of cognitive functions and the quality of life of patients in general, and to an extremely unfavorable prognosis [1]. The causes of primary brain malignancies may be genetic abnormalities, changes in metabolism or hormonal background, environmental influences, ionizing radiation, viral infections or injuries, however, to date, the pathogenesis of brain tumors has not been fully elucidated [2].

Among malignant primary brain tumors, glioblastoma (GBM) is the most common, characterized by rapid progression over several months, as well as, like most gliomas, diffuse growth with invasion into surrounding normal brain tissues [1]. GBM treatment includes neurosurgery, fractional radiation and chemotherapy. One of the standard antitumor drugs widely used in GBM treatment is temozolomide (TMZ), which has a cytostatic effect, as well as targeted drugs such as bevacizumab (vascular endothelial growth factor inhibitor), dabrafenib and vemurafenib (BRAF kinase inhibitors with activating mutations in the V600E codon) [3], however, the effectiveness of treatment is very low. The median overall survival of patients with GBM does not exceed 15 months [4]. Therefore, at the present, the urgent task is to develop new drugs for the treatment of GBM.

In recent years, tropolone alkaloids (tropolones), which can have antioxidant, antibacterial, anti-inflammatory, and antitumor effects, have been of great interest in this aspect. Among the proposed mechanisms of antitumor activity of tropolones and their derivatives are activation of caspases-3 and -9, inhibition of tubulin polymerization, inhibition of matrix metalloproteinases and histone deacetylases, induction of apoptosis, and other actions [5]. The most studied tropolones are β-thujaplicin (hinokitiol), colchicine, and colhamine. The studies of foreign scientists have shown their cytotoxic effect on some tumor lines [6–8].

It was previously found that 2-(1,1-dimethyl-1h-benzo[e]indoline-2-yl)-5,6,7-trichloro-1,3-tropolone (JO-122(2)) has cytotoxic activity against skin cancer cell culture A431 and lung cancer H1299 [9]. In this regard, it was suggested that this tropolone may have a cytotoxic effect on other tumor cell lines.

Purpose of the study: to study the cytotoxic effect of 2-(1,1-dimethyl-1h-benzo[e]indoline-2-yl)-5,6,7-trichloro-1,3-tropolone (JO-122(2)) on the human glioblastoma cell line U87 MG.

MATERIALS AND METHODS

2-(1,1-dimethyl-1h-benzo[e]indoline-2-yl)-5,6,7-trichloro-1,3-tropolone with the non-commercial name JO-122 (2) was synthesized at the Research Institute of Physical and Organic Chemistry, Southern Federal University. The substance under study belongs to the compounds of the 2-hetaryl-1,3-tropolones family. It is a yellow powder formed because of several stages of the expansion reaction of the o-quinone cycle [9].

The cytotoxic effect of tropolone JO-122 (2) was studied on a culture of human glioblastoma U87 MG cells, which is widely used in biological research related to the study of brain cancer. Tumor cells were cultured in DMEM medium (Gibco, USA) with the addition of 10 % fetal bovine serum (BioloT, Russia), 2 mM L-glutamine (PanEco, Russia) and an antibiotic (100 u/ml penicillin, 100 mg/ml streptomycin, BioloT, Russia) at a temperature of 37 °C and an atmosphere of 5 % CO_2. The U87 MG culture was replanted 2–3 times a week to achieve 80 % monolayer confluence.

The viability of tumor cells was analyzed with use of the MTT colorimetric test. For this purpose, the U87 MG cell culture was seeded into 96-well plates at a concentration of 5×10^3 cells per well. A day later, after attaching tumor cells to the tablet, a solution of tropolone JO-122 (2) was added to the wells in concentrations of 24, 12, 6, 3, 1.5, 0.75, 0.375, 0.1875, 0.0938, 0.0469 μm with further incubation under standard conditions in three time intervals – 24, 48 and 72 hours. Then, the medium with the test substance was replaced with a medium without serum and 20 μl of a working solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (Maclin Inc., China) was added. After 2 hours of incubation, the medium was removed, 100 μl of DMSO was added to each well (BioloT, Russia),

pipetted, and then incubated in a thermostat for 5 minutes. The optical density was then measured using a Stat Fax 2100 microplate reader (Awareness Technology, USA) at a wavelength of 540 nm. DMSO at a concentration of 1 % was used as a control. Temozolomide was used as a comparison drug in concentrations of 250, 125, 62.5, 31.25, 15.625, 7.8125, 3.9063, 1.9531, 0.9766, 0.4883 μm. In total, there were 8 repetitions for each experience option. The experiment was performed three times.

The effect of tropolone on the distribution of the cell population by phases of the cell cycle was evaluated using an ADAMII LS analyzer (Nano Entek, Korea). Previously, JO-122 (2) was introduced into the U87 MG cell culture at concentrations of 2, 1, and 0.5 μm and incubated for 24 hours. At the end of incubation, the cells were washed with a solution of phosphate-salt buffer. Propidium iodide was added in equal volume to an aliquot containing 106 washed pipetted cells, and the sample was placed on an ADAMII slide. The analysis was performed by ADAMII LS software. For control of each concentration, the experiment was repeated three times.

Statistical analysis

Statistical data processing was performed using Microsoft Excel 2013 and Statistica 10 software. The IC50 concentration of tropolone, which caused 50 % death of tumor cells, was determined for a time interval of 72 hours by constructing dose-effect curves. A comparative analysis of the values was performed using the Student's t-test at a confidence level ($p < 0.05$). When making multiple comparisons, the Bonferroni correction was used.

STUDY RESULTS AND DISCUSSION

Despite the progress in the treatment of cancer, glioblastoma is one of the most aggressive and resistant to existing types of tumor therapy. Therefore, the search and testing of new substances with antitumor potential is an urgent task.

To assess the cytotoxic effect of tropolone JO-122 (2) on glioblastoma, a DNA analysis was performed on the human glioblastoma cell line U87 (Fig. 1).

The minimum concentration of JO-122 (2) at which there was a statistically significant inhibition of tumor cell growth compared with the control at incubation times of 24, 48 and 72 hours was 3 μm, 0.0469 μm and 0.1875 μm, respectively. With an increase in the concentration of the test substance, the proportion of living cells in the culture decreased naturally, which indicates the dose-dependent nature of the action of the test compound.

Temozolomide is known to be used for the treatment of glioblastoma after surgical resection [2, 3]. Therefore, this drug was chosen as a reference drug during the MTT test (Fig. 2).

Inhibition of cell growth in U87 culture at an incubation time of 48 hours after the addition of Temozolomide occurred at a concentration of 62.5 microns, and at 72 hours – 3.9063 μm and increased as the dose of the drug increased. 24 hours after exposure to the reference drug, there was no significant decrease in cell viability in any of the studied concentrations.

During this work the IC50 of substances was also compared at an incubation time of 72 hours (Fig. 3).

At an exposure time of 72 hours, both substances demonstrated dose-dependent toxicity to U87 MG cells. The IC50 value for JO-122(2) was 1.9559 microns, and for Temozolomide it was 191.824 microns, which is significantly higher than that of tropolone. This indicates a more pronounced ability of JO-122 (2) to inhibit the growth of U87 MG culture cells.

Cell cycle assessment using a cell analyzer showed that incubation for 24 hours with JO-122 (2) at concentrations of 2 μm, 1 μm and 0.5 μm for U87 MG culture showed a decrease in the percentage of cells in the G1 phase and an increase in cells in the G2/M phases of the cell cycle, suggesting induction of apoptosis (Table 1).

The obtained data is comparable with the results of other scientists. For example, in the work of Ma QG et al. [10], the antiproliferative activity of 9 new tropolones and 14 known tropolone derivatives was investigated. Of all the candidates, 5 demonstrated moderate antiproliferative activity *in vitro* against the following human tumor cell lines: HGC-27, MDA-MB-231, A-549, HCT-116, and A2780, with IC50 values ranging from 0.5 ± 0.2 to

15.5 ± 2.7 μm. Balsa LM et al. [11] demonstrated a stronger cytotoxic effect of tropolone copper (II) than when exposed to cisplatin against human breast cancer cells cultured in 2D and 3D. The IC50 for MCF7 culture was 5.2 ± 1.8 μm, for MDA-MB-231–4.0 ± 0.2 μm. In a study by Haney SL et al. [12], the antitumor effect of α-substituted tropolone was evaluated on five human osteosarcoma cell lines (143B, CAL-72, HOS, MG-63, and SaOS-2). To varying degrees, 72-hour incubation with the test substance induced concentration-dependent cytotoxicity in all 5 cell lines, with the HOS cell line being the most sensitive (IC50 = 0.67 μm) and SaOS-2 being the least sensitive (IC50 = 5.93 μm). The authors believe that tropolone leads to activation of the unfolded protein response pathway (UPR), which in turn leads to induction of caspase-dependent cell death.

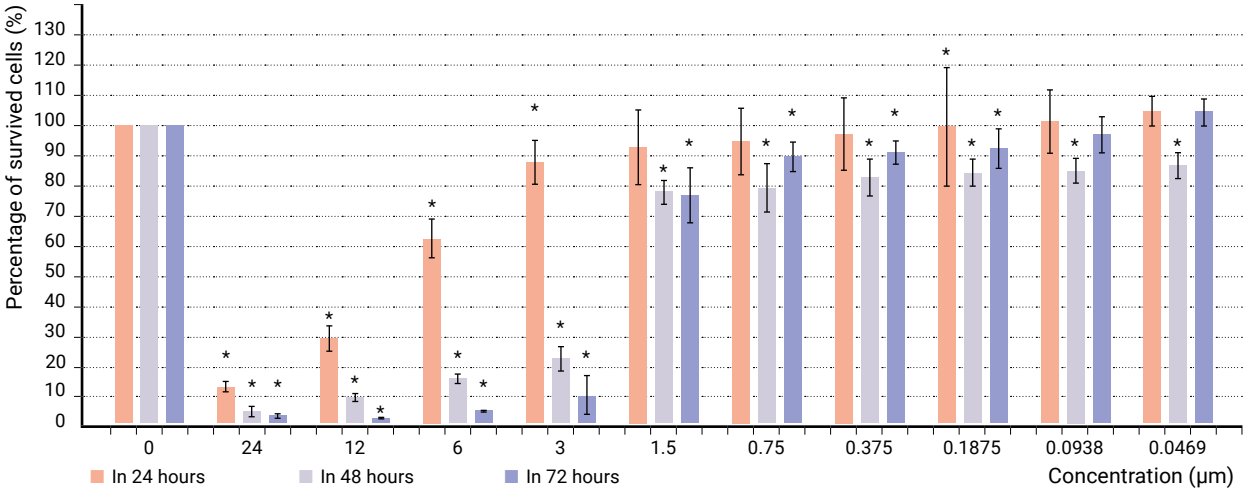

Fig. 1. The effect of tropolone JO-122 (2) on the survival of U87 tumor cells. The data is expressed as an average ± standard deviation.
Note: * – the differences are statistically significant at $p < 0.05$ compared to the control

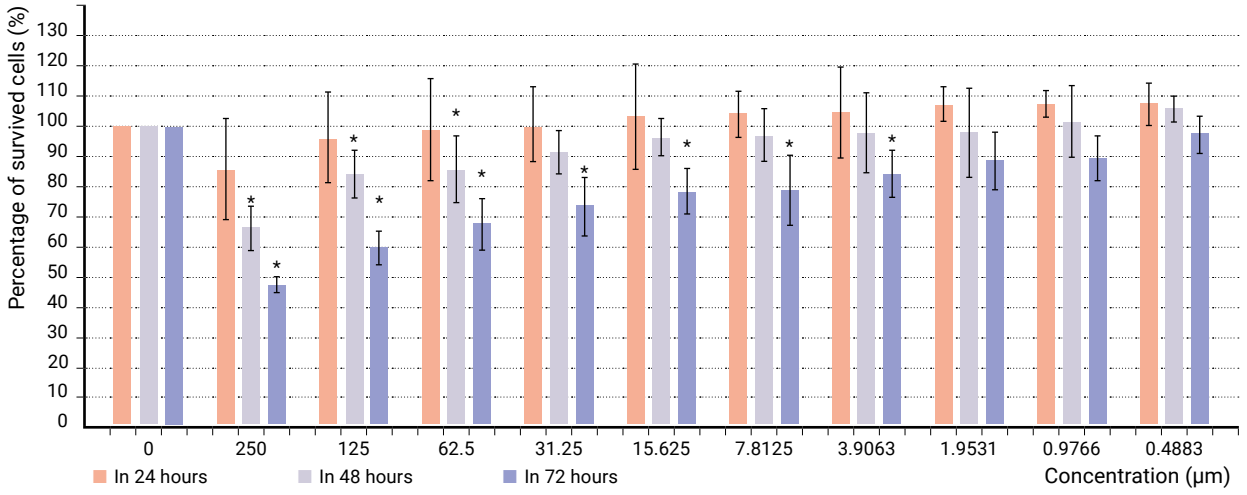

Fig. 2. The effect of Temozolomide on the survival of U87 MG tumor cells. The data is expressed as an average ± standard deviation.
Note: * – the differences are statistically significant at $p < 0.05$ compared to the control

CONCLUSION

According to the outcomes of the study, the cytotoxic activity of 2-(1,1-dimethyl-1h-benzo[e] indoline-2-yl)-5,6,7-trichloro-1,3-tropolone against U87 MG tumor cell culture has been studied, and an inhibitory IC50 concentration of the suggested compound has been obtained, which turned out to be lower than that for Temozolomide. The obtained data are of considerable scientific interest

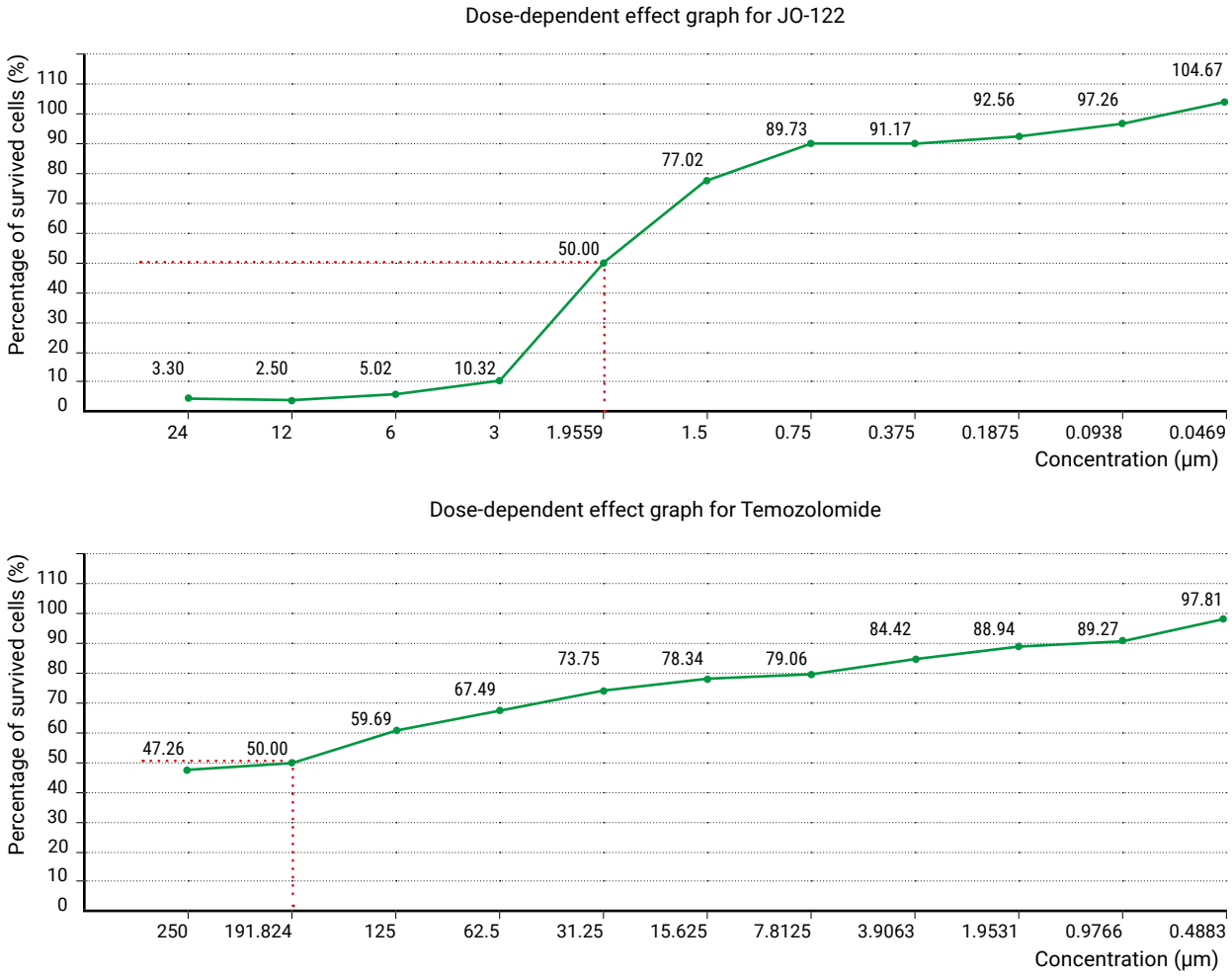

Fig. 3. comparison of IC50 tropolone JO-122 (2) with temozolomide

Table 1. Distribution of the U87MG cell population by cell cycle phases in the control group and 24 hours after the addition of the tested tropolone. The data is expressed as mean ± standard deviation

Group	Cell cycle phases		
	G1	S	G2/M
Control	71.77 ± 0.91	6.79 ± 0.54	17.63 ± 0.83
JO-122 (2) – 2 μm	28.08 ± 1.02*	10.63 ± 1.70	58.56 ± 0.83*
JO-122 (2) – 1 μm	29.71 ± 0.67*	11.81 ± 0.77	56.61 ± 0.54*
JO-122 (2) – 0.5 μm	34.45 ± 1.55*	9.06 ± 0.65	52.65 ± 1.56*

Note: * – the differences are statistically significant at $p < 0.05$ compared to the control

and indicate the prospects for further research on 2-(1,1-dimethyl-1h-benzo[e]indoline-2-yl)-5,6,7-trichloro-1,3-tropolone. One possible direction is to study the effect of JO-122(2) on other cell lines, including evaluation of the proliferative activity of tumor cells and the cell cycle, as well as CDX and PDX models, which will allow us to more fully assess the effect of tropolone on glioblastoma.

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