

# VITALITY AND MORPHOLOGY OF TUMOR CELLS TREATED WITH 4-TIAZOLIDINONE DERIVATIVES IMMOBILIZED ON NANOSCALE POLYMER CARRIER

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A nanoscale polymeric carrier was used for delivery of novel anticancer compounds — 4-tiazolidinone derivatives — to tumor cells of different lines. It was found that such way of delivery of the above mentioned compounds to target cells significantly (approximately 10 times) decreased acting cytotoxic dose of some of these compounds with preservation of similar level of their antineoplastic effect *in vitro* towards various mammalian tumor cells. The microscopic investigation of these cells demonstrated that under the action of some immobilized 4-tiazolidinone derivatives, there was an increase (up to 40%) of the part of apoptotic cells, as well as an appearance of 10% of cells with morphologically changed nucleus, and up to 35% of cells with an increased intensity of red fluorescence of acridine orange in the lysosomes, compared with such indicators observed under the action of free form of those compounds. Thus, the applied nanoscale carrier is a perspective polymer system for delivery of anticancer drugs to target cells.

**Key words:** 4-tiazolidinone derivatives, nanoscale polymer carrier.

The development of new systems for delivery of the antineoplastic drugs with low toxicity, capability of addressed transportation of drugs to the tumor target cells, and visualization of their action in the body is one of the major problems in modern biopharmaceutics. Despite an intensive work on creation of new anticancer drugs, the problem of cancer treatment has not been solved. The main reasons for that are the development of tumor cell resistance to known and new chemotherapeutic drugs and general toxicity in the body, resulting in damage of cells of normal tissues and organs [1]. One of the main mechanisms underlying acquired resistance of tumor cells to cytotoxic anticancer drugs is cell membrane transport that ensures removal of various xenobiotics, including drugs, from the target cells. This phenomenon has been called a multi-drug resistance (MDR) [2]. Therefore,

synthesis of new substances capable of killing cells resistant to anti-tumor drugs, and using special systems for delivery of these drugs are the priorities of the biopharmacology. The biocompatible and biodegradable polymers forming nanoscale particles possess high stability in the body, low toxicity and, because of their unique chemical structure, can be further functionalized in order to provide addressed delivery of the immobilized drugs to specific target cells and biomolecules. The use of these nanoscale systems can significantly reduce the effective therapeutic dose of the applied anticancer drug.

A number of synthetic polymers which can significantly enhance the biological effects of anticancer drugs *in vitro* and *in vivo* were described [3, 4]. Drug “Doxil”, which is a liposome functionalized polyethylene glycol with encapsulated anticancer drug

doxorubicin, is used in cancer chemotherapy [4]. A significant drawback of this polymeric carrier is difficulty of functionalization of liposomes for targeting action of the encapsulated anticancer drug.

In this work, we have used a biocompatible polymeric nanoscale carrier which has been previously shown to improve the efficacy of doxorubicin action for delivery of 4-tiazolidinone derivatives to the mammalian tumor cells [5–7]. A significant reduction of the acting dose of some of these drugs was a result of their delivery by the nanocarrier. Microscopic investigation of cell morphology showed an increase in number of apoptotic cells and cells with fragmented nuclei and damaged membranes under the influence of certain 4-tiazolidinone derivatives immobilized on the polymeric carrier compared with the effect of free drugs.

### Materials and Methods

*Synthesis of heterocyclic derivatives of 4-tiazolidinone with antitumor activity.* It was shown that synthetic derivatives of the heterocyclic 4-tiazolidinones possess a wide range of biological effects, including antibacterial, fungicidal, antiviral, anti-inflammatory, and anti-diabetic [8]. This class of compounds may contain promising antitumor drugs [8]. The results of experiments conducted under the screening program of new anticancer drugs at the National Cancer Institute (USA) can serve as a confirmation of that suggestion [9]. According to the results of previous studies of antitumor activity of some derivatives of 4-tiazolidinone, including pyrazolyne-substituted ones, it was found that pyrazoline-thiazolidinone-indoline conjugates (3288, 3833 and 3882) were the most active compounds which can be proposed for further pre-clinical trials [10–13]. These compounds were synthesized at the Department of Pharmaceutical, Organic and Bioorganic Chemistry of Danylo Halytsky Lviv National Medical University [14].

Structural formulas of the compounds 3288, 3833 and 3882 are shown in Fig. 1. It can be seen that a combination of thiazolidine, pyrazoline and 2-oxoindoline fragments in tricyclic 3-[2-(3,5-diaryl-4,5-dihydropyrazole-1-yl)-4-oxo-4H-thiazole-5-ylidene]-1,3-dihydroindole-2 structure made it possible to achieve a significant cytostatic effect towards 9 groups of 60 cancer cell lines of human tumors without an expressed selectivity of their action [11, 14]. The analysis of patterns

of “structure-antitumor activity” proved that the introduction of Halogen atom in the 5th position of indolyn fragment contributes to a significant strengthening of antitumor activity [15]. The molar masses of synthetic compounds under study are 559.44 (for 3288), 530.61 (for 3882) and 609.51 g/mol (for 3833 compound). Structural differences of these heterocyclic derivatives are the presence of Brom atom in the 5th position isatin fragment of 3288 and 3833 compounds and the replacement of the phenyl radical (3288 compound) in the 3rd position of pyrazoline cycle of the naphthyl fragment (3833 and 3882 compounds). We suggested that these structural fragments might influence the cytotoxic effect of the compounds. Therefore, for further detailed study three synthesized compounds (3288, 3833 and 3882) were chosen. They are structurally similar and belong to the groups of patented pyrazoline-thiazolidinone-isatins which possess the antineoplastic activity *in vitro* and relatively low toxic effects in laboratory rats, compared with such action of the doxorubicin [11, 14, 16, 17].

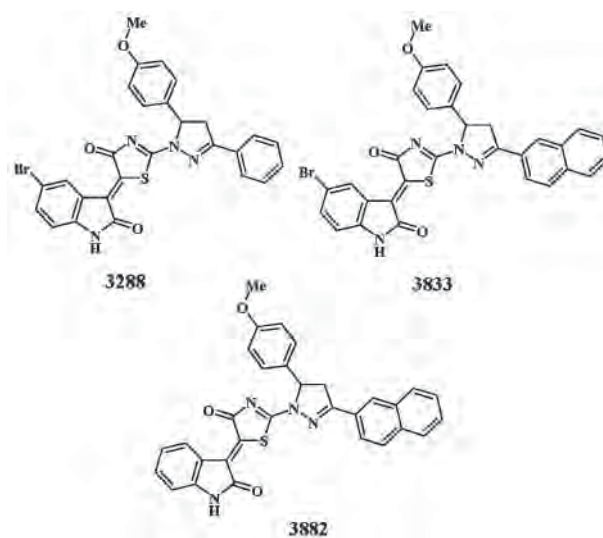


Fig. 1. Structure of synthetic 4-tiazolidinone derivatives — compounds 3882, 3288 and 3833

*Synthesis of the polymeric carriers for drug delivery systems.* Polymer poly(VEP-co-GMA)-graft-PEG was synthesized at the Department of Organic Chemistry (Lviv National Polytechnic University) under the supervision of Dr. Alexander Zaichenko. The carrier is a water-soluble comb-like polymer poly(VEP-co-GMA)-graft-PEG (A24PEG) with a backbone based on the copolymer of unsaturated peroxide 5-*tert*butylperoxy-5-methyl-1-hexen-

3-yne (VEP) and glycidyl methacrylate (GMA) and polyethylene glycolic side chains [18]. Its general structure is shown in Fig. 2.

Synthesis of the polymeric A24PEG carrier was performed in two stages. At the first stage, the linear poly(VEP-co-GMA) copolymer was obtained by the radical polymerization. At the second stage, this copolymer was modified by the polyethylene glycol methyl ether (mPEG) with a molecular mass of 750 g/mol due to the interaction of the epoxide groups of the copolymer with the hydroxylic groups of mPEG.

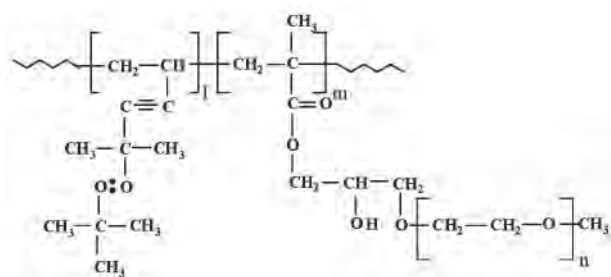


Fig. 2. Chemical structure of the poly(VEP-co-GMA)-graft-PEG

Water-based sample of A24PEG was prepared by transferring the polymer from the organic phase into the inorganic one. To do this, the polymer sample was dissolved in the dimethyl sulfoxide (DMSO) and added drop by drop to water containing 0.9% NaCl. Subsequently, the solution was sonicated for 20 sec.

Composition of PEGylated polymeric A24PEG carrier was determined by CNH elemental analysis and calculated by using described methods [19].

The molecular weight of A24PEG was determined basing on the average molecular weight of poly(VEP-co-GMA) which is 61,100 g/mol, and the number and molecular weight of grafted PEG chains which is 245,000 g/mol. The average molecular weight of poly(VEP-co-GMA) was measured by gel-penetration chromatography on a Styragel HR1 (THF) column (Waters GPC/HPLC Instrument, Waters, USA). Tetrahydrofuran (THF) was used as eluent, and polystyrene of known molecular mass was used as a standard. The flow rate was 0.3 ml/min.

The structure of the obtained copolymers was confirmed by the IR and NMR spectroscopy. The composition and molecular weight characteristics of the synthesized polymer are presented in Table 1.

Table 1. Molecular characteristics of the PEG-containing carrier

Composition of the initial copolymer, % mol		Composition of the modified copolymer, % mol			Mn A24PEG, g/mol
VEP	GMA	VEP	GMA	PEG	
2.0	98.0	1.4	69.1	29.5	245,000

The diameter of the particles of the polymeric carrier determined according to the data of transmission electron microscopy (TEM) was 61 nm. It was confirmed by a dynamic light scattering on a Zetasizer Nano ZS (Malvern Instruments GmbH, Stuttgart, Germany) and photon correlation spectra using NIBS (Non-Invasive Back Scatter) technology at 25 °C [18].

**Cell culture.** The human T-leukemia Jurkat cell line, mouse leukemia L1210 cell line and mouse transformed fibroblasts of L929 line were used in the experiments. Cell lines were obtained from the collection of the Kavetsky Institute of Experimental Oncology, Pathology and Radiobiology, of the National Academy of Sciences of Ukraine (Kyiv, Ukraine). All three cell lines were cultured in Dulbecco's modified Eagle's medium (DMEM, Sigma, USA) supplemented with 10% fetal bovine serum (Sigma, USA). Cells were grown in CO<sub>2</sub>-incubator at 37 °C, 5% CO<sub>2</sub> and 95% humidity. The reseeding of cells was performed at a ratio of 1: 5 once in 2-3 days.

**The effect of 4-tiazolidinone derivatives and their complexes with a polymeric carrier.** The concentration of complexes was calculated by the content of antitumor agent, and the effects of free 4-tiazolidinones and their complexes with the carrier were compared. The ratio carrier : drug in the complexes was 30:1. We used 4-tiazolidinone derivatives (free or immobilized on the carrier) at the concentrations of 0.01, 0.1, and 1 µg/ml. To evaluate the action carrier, it was added in 30-fold higher concentration, corresponding to its amount in its complex with the drug. The effectiveness of action of these substances was determined by counting cell number comparing to the control (untreated cells).

**Determination of cytotoxic action of studied substances.** Cells were seeded in 96- and 24-well plates (Greiner bio-one, USA). The substances were added at various concentrations immediately after cell seeding without the adaptation period. Counting of cell number was carried out at regular intervals in the hemocytometer (counting chamber) using

Trypan Blue dye (DV-T10282, Invitrogen, Life Technologies Corporation) at 0.01% final concentration 2 min after its addition to cell suspension.

After 72 h of drug treatment, the part of viable cells was determined by the MTT assay in accordance with the manufacturer's recommendations (Sigma, USA). Purple product of the reaction (formazan crystals dissolved in the DMSO) was quantitatively determined in a multi-channel microphotometer VioTek 76 883 (VioTek, USA) at 620 nm wavelength.

**Light and fluorescence microscopy.** The experimental living, apoptotic and necrotic cells were viewed on the inverted light microscope Biolam (LOMO). Images were processed with a fluorescent microscope Zeiss (Carl Zeiss, Germany) using AxioImager A1 camera, by ~400 times magnification in the relevant sections of the excitation and emission.

L929 cells were seeded on glass microscopic slides in the 24-well plates (Greiner bio-one, USA). The substances were added in different concentrations 24 hours after cell seeding. Cell nucleus was stained with the DNA-specific fluorescent Hoechst 33342 dye (Sigma, USA). Cells were stained by the polyspecific dye acridine orange (AO, Sigma, USA) [21]. Fluorochromes were added to cells at following final concentrations: AO — 0.3–1.0 µg/ml, Hoechst 33342 — 0.2–0.5 µg/ml, and incubated for 20–30 min.

**Data analysis and statistics.** All experiments were repeated three times with three parallels in each variant. All data are expressed as a mean ± SD [22]. Statistical analysis was performed using either two-sided Student's t test.  $P \leq 0.05$  was considered statistically significant.

## Results and Discussion

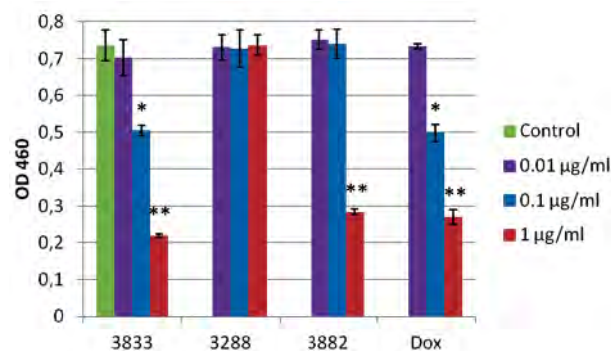
### *The effect of 4-tiazolidinones on the viability of mouse leukemia L1210 cells and human T-leukemia Jurkat T cells*

The influence of 4-tiazolidinones on the viability of leukemic cells was studied by using the MTT test. The principle of action of this reagent is based on determination of the ability of mitochondrial dehydrogenases of living cells to reduce the uncolored form 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) to formazan purple detected photometrically.

Free and immobilized on polymer carrier substances were added to the incubation medium at 0.01, 0.1 and 1 µg/ml

concentrations. Doxorubicin ("gold standard" in cancer chemotherapy) was used at 0.01, 0.1 and 1 µg/ml concentrations as a positive control. It was shown that effect of doxorubicin after its immobilization on the polymeric carrier was significantly enhanced [5–7]. The results of the MTT test after 72 hours of incubation are shown on Fig. 2–5.

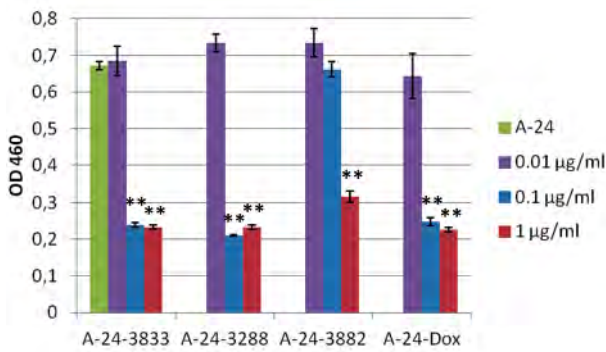
It was shown that substances 3833 and 3882 were effective only at 1 µg/ml concentration, whereas substance 3288 did not affect the viability of murine leukemia cells of L1210 line at all (Fig. 3).



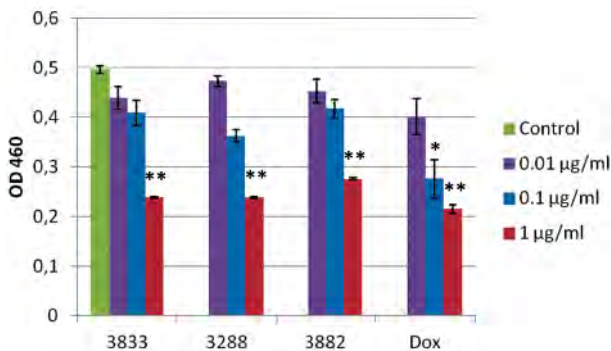
**Fig. 3. The effect of 4-tiazolidinones — 3833, 3288, 3882 — on the viability of murine leukemia L1210 cells at 72 hours treatment**  
Hereinafter: \* —  $P \leq 0.05$ ; \*\* —  $P \leq 0.01$

The substances immobilized on the nanoscale polymeric A-24 carrier demonstrated a significant enhancement of their effects towards treated tumor cells. That enhancement was observed for substances 3833 at 0.1 µg/ml concentration and for 3288 — at 0.1 µg/ml and 1 µg/ml concentrations. At these concentrations, the applied substances reduced a survival of murine leukemia L1210 cells to extent comparable with the action of free doxorubicin at 1 µg/ml concentration (Fig. 4). It should be noted that empty carrier was not toxic for studied cells in all variants of the experiment (green column at the graphs).

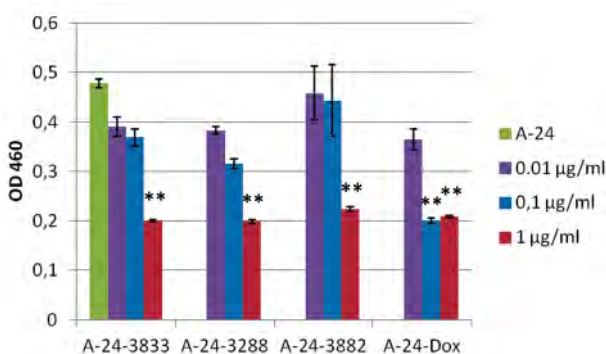
In another series of experiments, the studied substances were tested in free form and after immobilization on the nanoscale polymeric carrier for their influence on human T-leukemia Jurkat cells. We did not observe significant changes in cell viability under the effect of 4-tiazolidinones at 0.01 µg/ml concentration, however, we detected inhibition of cell growth at 0.1 and 1 µg/ml concentrations (Fig. 5, 6).



**Fig. 4.** The effect of 4-tiazolidinones — 3833, 3288, 3882 — immobilized on the nanoscale polymeric A-24 carrier on the viability of murine leukemia L1210 cells at 72 hours treatment



**Fig. 5.** The effect of 4-tiazolidinones — 3833, 3288, 3882 — on the viability of human T-leukemia Jurkat cells at 72 hours treatment



**Fig. 6.** The effect of 4-tiazolidinones — 3833, 3288, 3882 — immobilized on the nanoscale polymeric A-24 carrier on the viability of human T-leukemia Jurkat cells at 72 hours treatment

Thus, the effect of using nanoscale polymeric carrier for delivery of 4-tiazolidinones depends on the type of target cells. The growth inhibitory action of these substances towards murine leukemia L1210 cells is more prominent than their action towards human T-leukemia Jurkat cells.

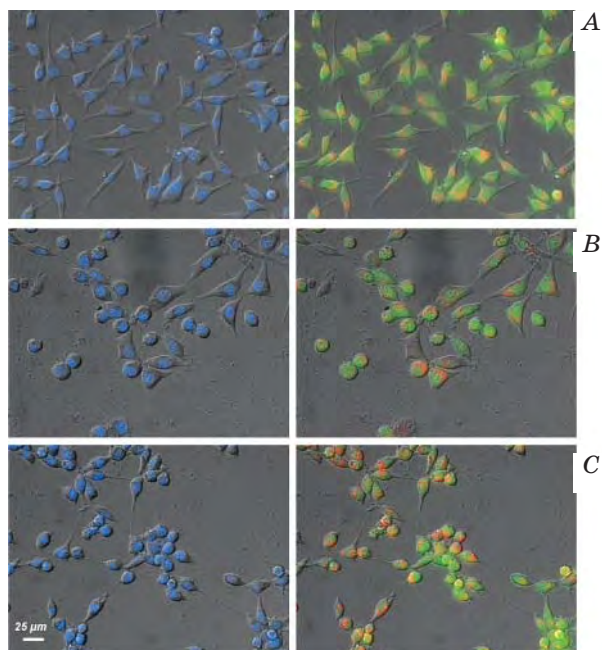
We were not successful when using the MTT test for evaluation of the cytotoxic action of 4-tiazolidinones in murine transformed fibroblasts of L929 line (data not shown). It is known that most tumors with high level of cell transformation possess Warburg effect at which the contribution of mitochondria in cell energy support stays insignificant [23]. We suggest that those fibroblasts have lower malignant transformation level compared with the above mentioned leukemia cells. Therefore, the MTT test based on measuring activity of mitochondrial dehydrogenases is not significant in murine transformed fibroblasts of L929 line.

*Morphological changes in murine transformed fibroblasts of L929 line under the influence of 4-tiazolidinones*

In previous studies using 4-tiazolidinones, it was found that leukemia cells are the most sensitive to such treatment among different tumor cell lines [11, 17]. To study concentration dependence of the cytotoxic effect of these substances we used MTT-testing of human T-leukemia Jurkat cell line and murine leukemia L1210 cell line. However, since the leukemic cells have relatively small volume of cytoplasm and irregular shape of nucleus, it was difficult to conduct their cytomorphological study focused at distinguishing between chromatin condensation and nucleus fragmentation. That is why, in order to obtain presentable micrographs, we used murine transformed fibroblasts of L929 line which have enough cytosol and are well spread on the surface of culture flask. Thus, changes in their morphology can be better visualized than that of the leukemic cells.

The micrographs presented on Fig. 7–11 show that the studied substances, depending on their type and concentration, cause changes in the state of cytoplasm and nucleus of murine transformed fibroblasts of L929 line. The cytotoxic effect of these substances results in a loss of elongated form of cells that is characteristic for the fibroblasts, cell rounding, and increase of the intensity of red fluorescence of acridine orange in the cytoplasm which suggests enhancement in the lysosome functioning [21]. The effect of

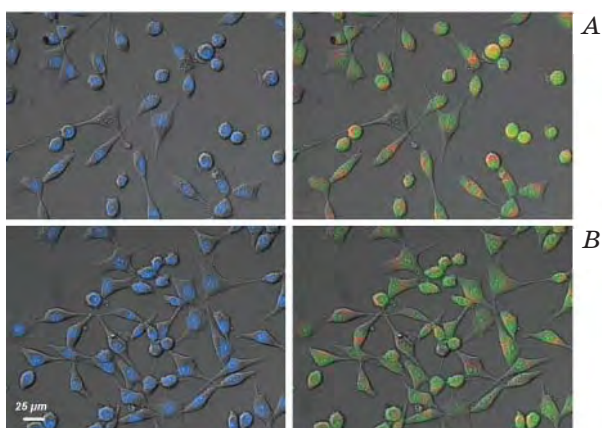
substances 3288 (1 µg/ml), 3833 (1 µg/ml), 3882 (1 µg/ml) (Fig. 9–11) and of doxorubicin (Fig. 7, 8), both in free form and immobilized on A-24 carrier, leads to appearing of such signs of apoptosis as fragmentation of the nucleus and/or cells.



**Fig. 7. Effect of doxorubicin on morphology of murine transformed fibroblasts of L929 line at 18 h treatment**

Control (A), free doxorubicin (B), and doxorubicin (1 µg/ml) immobilized on the carrier (C).

Hereinafter: the blue color — cell staining with fluorescent dye Hoechst 33342, red and green color — staining with polyspecific acridine orange dye

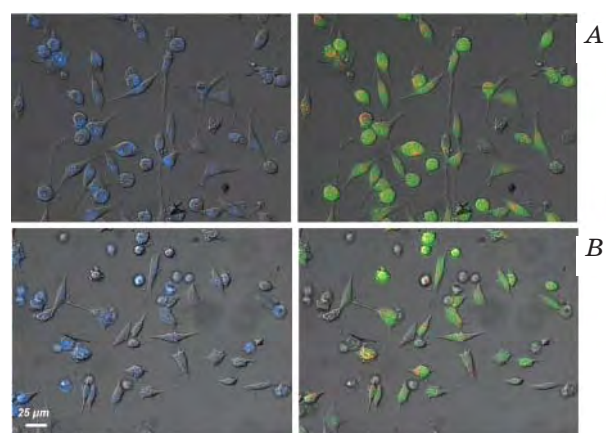


**Fig. 8. Effect of doxorubicin on morphology of murine transformed fibroblasts of L929 line at 18 h treatment:**

Free doxorubicin (A) and doxorubicin (0.1 µg/ml) immobilized on the carrier (B)

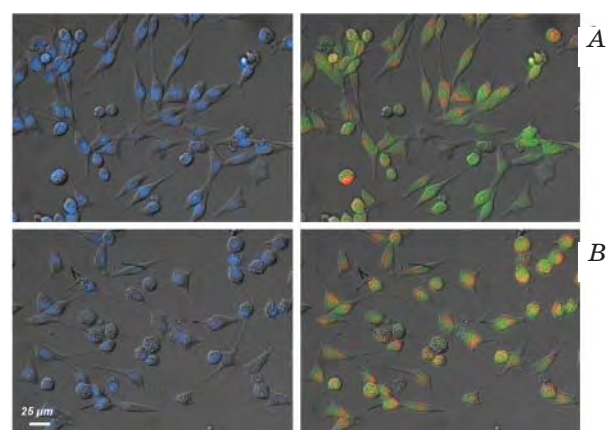
As shown in Fig. 9, a cytotoxic effect of the compound 3833 is significantly increased after its immobilization on the polymeric carrier. The increase in number of cells with condensed nucleus is observed, and in general, treated cells look more damaged. These data correlate with the results of MTT-testing (Fig. 4) showing that the compound 3833 immobilized on the polymeric carrier affects the viability of malignant cells more significantly than the free form of this compound does.

In contrast to the effect of the compound 3833, the action of compound 3288 (Fig. 10) towards studied target cells did not significantly differ from that in the control (no treatment). In case of the effect of the



**Fig. 9. Effect of 4-tiazolidinone compound 3833 on morphology of murine transformed fibroblasts of L929 line at 18 h treatment:**

Free drug (A) and drug (1.0 µg/ml) immobilized on the carrier (B)



**Fig. 10. Effect of 4-tiazolidinone compound 3288 on morphology of murine transformed fibroblasts of L929 line at 18 h treatment:**

Free drug (A) and drug (1 µg/ml) immobilized on the carrier (B)

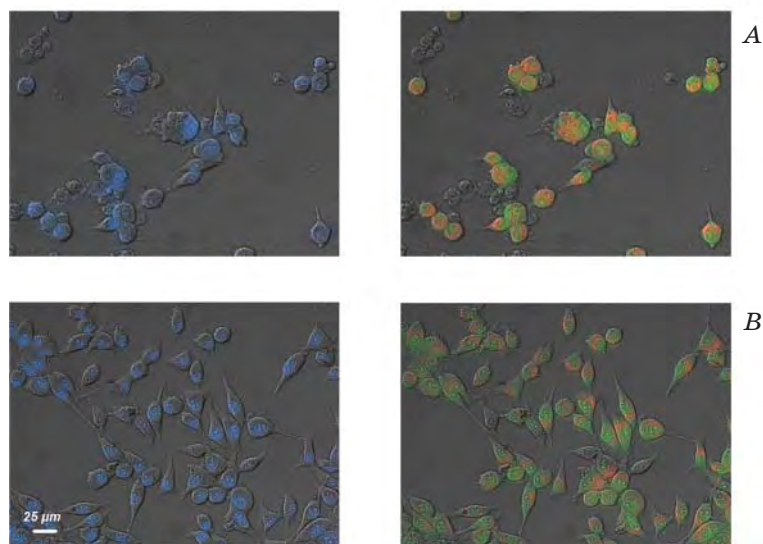
compound 3288 immobilized on the carrier, the part of rounded cells was increased and the intensity of red fluorescence of the acridine orange in lysosomes was also elevated.

It should be noted that changes in the morphology of L929 cells under the effect of compound 3882 (Fig. 11) in free form and being immobilized on the carrier differed significantly from the effect of compounds 3833 and 3288. It was established that compound 3882 in free form caused more noticeable cytomorphological changes compared with its negligible influence when used in the immobilized form. In the first case, the majority of cells got rounded shape, increased size, protrusions of plasma membrane, and increased fluorescence of lysosomes. After combining with the carrier, that compound caused much less changes in the morphology of target cells.

Table 2 presents the results of quantitative characteristics of the morphological changes in target cells under the effect of 4-tiazolidinone compared with the effect of doxorubicin and the control. The field of view on photography was selected taking into account the density of uniform location of 40–70 cells on the surface of the microscopic slides. We photographed

4–6 fields of view depending on the density of cell location, and counted the number of cells in these fields at different experimental conditions. The Table 2 shows a typical field of view for each variant of experiment (generally all experimental data were reliable comparing to the control).

Summarizing, it should be noted that under the effect of 4-tiazolidinone *in vitro*, the viability of tumor cells is reduced and the pro-apoptotic morphological changes are observed. These changes were significantly amplified by the immobilization of studied substances on the polymeric carrier. Changes were especially noticeable in the morphology of murine transformed fibroblasts of L929 line, and an increase in number of cells with condensed nucleus (a sign of apoptosis), rounding of cells, and the intensification of red fluorescence of acridine orange in cytoplasm (indicates an increased functioning of lysosomes) were observed. In general, the treated cells looked more damaged. Besides, under the influence of compound 3882 in free form towards L929 transformed fibroblasts, the giant tumor cells were observed. This phenomenon suggests an abnormal course of cell cycle, and the



**Fig. 11. Effect of 4-tiazolidinone compound 3882 on morphology of murine transformed fibroblasts of L929 line at 18 h treatment:**  
Free drug (A) and drug (1 µg/ml) immobilized on the carrier (B)

Table 2. Quantitative characteristics of the morphological changes in murine transformed fibroblasts of L929 line under the effect of studied anticancer substances compared to the control

Substance	Number of cells in the field of view	Rounded cells (% to number of cells in the field of view)	Cells with morphological changes in nucleus (% to number of cells in the field of view)	Cells with increased intensity of red fluorescence (% to number of cells in the field of view)
Control	72	3 (4.2%)	–	–
Doxorubicin, 1 µg/ml	39	17 (43.6%)	3 (7.7%)	4 (10.3%)
Doxorubicin + A24, 1 µg/ml	62	27 (43.6%)	4 (6.5%)	19 (30.7%)
Doxorubicin, 0.1 µg/ml	40	15 (37.5%)	2 (5.0%)	6 (15.0%)
Doxorubicin + A24, 0.1 µg/ml	51	17 (33.3%)	7 (13.7%)	8 (15.7%)
3833, 1 µg/ml	48	20 (41.7%)	4 (8.3%)	2 (4.2%)
3833 + A24, 1 µg/ml	39	15 (38.5%)	8 (20.5%)	2 (5.1%)
3288, 1 µg/ml	63	15 (23.8%)	4 (6.4%)	5 (7.9%)
3288 + A24, 1 µg/ml	50	26 (52.0%)	3 (6.0%)	20 (40.0%)
3882, 1 µg/ml	41	26 (63.4%)	3 (7.3%)	17 (41.5%)
3882 + A24, 1 µg/ml	42	19 (45.2%)	–	7 (16.7%)

appearance of polyploid and giant cells may indicate a formation of special protective mechanisms against the effect of extreme agents including anticancer drugs [23-25].

Thus, the delivery of 4-tiazolidinone compounds 3288, 3882 and 3833 by the nanoscale polymeric carrier increases their

cytotoxic effect which is accompanied by a reduction of the viability of tumor cells (murine leukemia L1210 cells and human T-leukemia Jurkat cells), as well as the appearance of the pro-apoptotic morphological changes (murine transformed L929 fibroblasts).

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**ЖИТТЄЗДАТНІСТЬ І МОРФОЛОГІЯ  
ПУХЛИННИХ КЛІТИН ЗА ДІЇ ПОХІДНИХ  
4-ТІАЗОЛІДИНОНОВОГО РЯДУ,  
ІММОБІЛІЗОВАНИХ  
НА НАНОРОЗМІРНОМУ ПОЛІМЕРНОМУ  
НОСІЄВІ**

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Метою роботи було використати полімерний наночіп для доставлення протипухлинних препаратів 4-тіазолідинового ряду в пухлинні клітини різних ліній. З'ясовано, що таке доставлення до клітин-мішеней дає змогу суттєво (майже в 10 разів) знизити дію цитотоксичну дозу деяких із них за збереження подібного за рівнем антинеопластичного ефекту *in vitro* щодо різних пухлин ссавців. Мікроскопічне дослідження клітин цих ліній показало, що за дії деяких іммобілізованих на носіїв препаратів 4-тіазолідинового ряду спостерігається вища (до 40%) частка апоптичних клітин, а також більше (до 10%) клітин із морфологічними змінами в ядрі та 35% клітин із підвищеною інтенсивністю червоного свічення акридинового оранжевого в лізосомах, порівняно з показниками, що їх фіксували за дії вільних препаратів цього типу. Використаний нами нанорозмірний носій є перспективною полімерною системою для доставлення протипухлинних препаратів у клітини-мішені.

**Ключові слова:** похідні 4-тіазолідинону, нанорозмірний полімерний носій.

**ЖИЗНЕСПОСОБНОСТЬ И МОРФОЛОГИЯ  
ОПУХОЛЕВЫХ КЛЕТОК  
ПОД ДЕЙСТВИЕМ ПРОИЗВОДНЫХ  
4-ТІАЗОЛІДИНОНОВОГО РЯДА,  
ИММОБИЛИЗОВАННЫХ  
НА НАНОРАЗМЕРНОМ ПОЛІМЕРНОМ  
НОСИТЕЛЕ**

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Целью работы было использовать полимерный наночип для доставки противоопухолевых препаратов 4-тиазолідинового ряда в опухолевые клетки разных линий. Показано, что такая доставка в клетки-мишени позволяет существенно (почти в 10 раз) снизить действующую цитотоксическую дозу некоторых из них при сохранении подобного по уровню антинеопластического эффекта *in vitro* относительно различных опухолевых клеток млекопитающих. Микроскопическое исследование клеток этих линий показало, что под воздействием некоторых иммобилизованных на носителе препаратов 4-тиазолідинового ряда наблюдается более высокая (до 40%) доля апоптических клеток, а также больше (до 10%) клеток с морфологическими изменениями в ядре и 35% клеток с повышенной интенсивностью красного свечения акридинового оранжевого в лизосомах, по сравнению с показателями, наблюдаемыми под воздействием препаратов этого типа в свободном состоянии. Использованный нами наноразмерный носитель является перспективной полимерной системой для доставки противоопухолевых препаратов в клетки-мишени.

**Ключевые слова:** производные 4-тиазолідинона, наноразмерный полимерный носитель.