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**M.O. Yeshchenko¹, P.A. Virych^{1, 2}, M.S. Kostovskiy¹,
I.V. Raspertova¹, D.M. Khomenko¹, P.A. Virych^{1, 2}**

¹ Taras Shevchenko National University of Kyiv
Kyiv, Ukraine

² State Institution "O.S. Kolomiychenko Institute of Otolaryngology
of National Academy of Medical Science of Ukraine"
Kyiv, Ukraine
pavlo.virych@knu.ua

CYTOTOXICITY OF NEW PLATINUM COMPLEXES BASED ON 3-(2-PYRIDYL)-1,2,4-TRIAZOLE DERIVATIVES AGAINST SQUAMOUS CELL CARCINOMA

Platinum complexes are one of the key elements of anti-tumor chemotherapy. Currently, the efforts are focused on the development of novel Pt-complexes based on ligands of various chemical nature. The aim of the research was to study the anticancer activity of new platinum complexes based on ligands 2-(5-ethyl-1-methyl-1H-1,2,4-triazol-3-yl)pyridine (L^6) and benzyl 2-(5-benzyl-1-methyl-1H-1,2,4-triazol-3-yl)pyridine (L^{12}). **Methods.** The cytotoxicity of the $Pt(L^6)Cl_2$ and $Pt(L^{12})Cl_2$ complexes against the Hep-2 and MAEC cells was assessed. The catalytic activities of lactate dehydrogenase (LDH), succinate dehydrogenase (SDH), and glucose-6-phosphate dehydrogenase (G6PD) were determined using the nitroblue tetrazolium assay. The intracellular ROS level was determined by the 2',7'-dichlorofluorescein diacetate, and the mitochondrial potential ($\Delta\Psi_m$) was determined by Rhodamine 123. **Results.** The calculated EC_{50} for $Pt(L^{12})Cl_2$ against Hep-2 cells was $9.12 \pm 0.33 \mu M$. The LDH activity was decreased in both Hep-2 and MAEC cells, but no changes in the SDH activity were detected in Hep-2 cells. In Hep-2 cells, the treatment with the $Pt(L^{12})Cl_2$ complex resulted in decrease in G6PD activity, whereas the $Pt(L^6)Cl_2$ complex induced increase. An increase in the $\Delta\Psi_m$ and ROS was observed in Hep-2 cell. **Conclusions.** The Pt complexes have a cytotoxic effect on Hep-2 cells by reducing the activity of LDH, but without affecting SDH. Intracellular ROS level was changed weak, but $\Delta\Psi_m$ was increased.

Keywords: platinum complexes, cancer, reactive oxygen species, mitochondrial membrane potential, lactate dehydrogenase, succinate dehydrogenase.

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Introduction

Platinum-based complexes are used in approximately 50% of cancer chemotherapy. Cisplatin is the best-known representative of this group of drugs. Its mechanism of action involves the formation of DNA crosslinks, thereby blocking replication and transcription. Over time, researchers have developed several clinically applicable platinum complex compounds belonging to different generations [1]. Currently, the efforts are focused on the development of novel Pt-complexes based on ligands of various chemical nature to improve pharmacokinetic and pharmacodynamic properties and overcome cancer cell chemoresistance [2–4]. Metabolic reprogramming and the Warburg effect underlie several mechanisms of cancer drug resistance [5]. Lactate dehydrogenase (LDH) overexpression promotes accumulation of lactate in the intercellular space and a decrease in pH [6]. At the same time, in some types of cancer, succinate dehydrogenase (SDH) is suppressed, which is accompanied by the succinate accumulation [7]. Taken together, these changes are associated with

carcinogenesis, chemosensitivity, immune resistance, and prognosis. Metabolic reprogramming during malignant transformation is accompanied by alterations in redox homeostasis and anabolic metabolism. Glucose-6-phosphate dehydrogenase (G6PD) is the key enzyme of the pentose phosphate pathway. It is a source of NADPH and pentoses for the nucleic acids synthesis [8, 9]. The ROS levels play an important role in cancer progression. The mitochondrial electron transport chain is the main endogenous source of the cellular ROS. Maintaining physiological ROS levels is essential for cellular signaling and the normal functioning of cellular processes. Abnormally high mitochondrial membrane potential ($\Delta\Psi_m$) and dysregulated intracellular ROS levels are also characteristic features of malignant transformation [10, 11]. Thus, these indicators are interrelated, contribute to carcinogenesis, and can serve as indicators of the effectiveness of anticancer therapy.

Previously we reported cytotoxicity of two platinum complexes of general formula $\text{Pt}(\text{L}^{1,2})\text{Cl}_2$ [12] based on 2-(1-methyl-1H-1,2,4-triazol-5-yl)pyridine (L^1) and 2-(1-methyl-1H-1,2,4-triazol-3-yl)

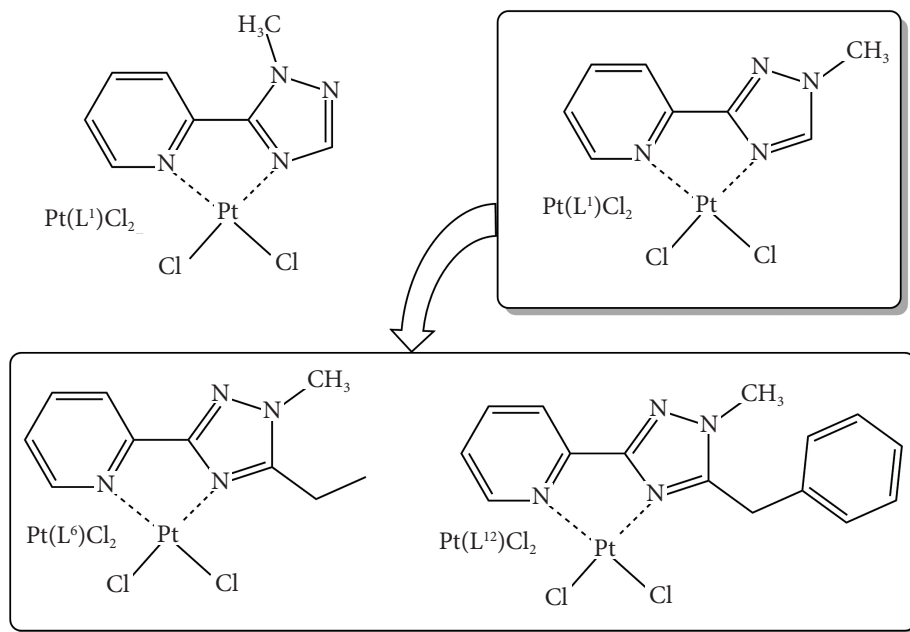


Fig. 1. Platinum complexes investigated in previous and present works

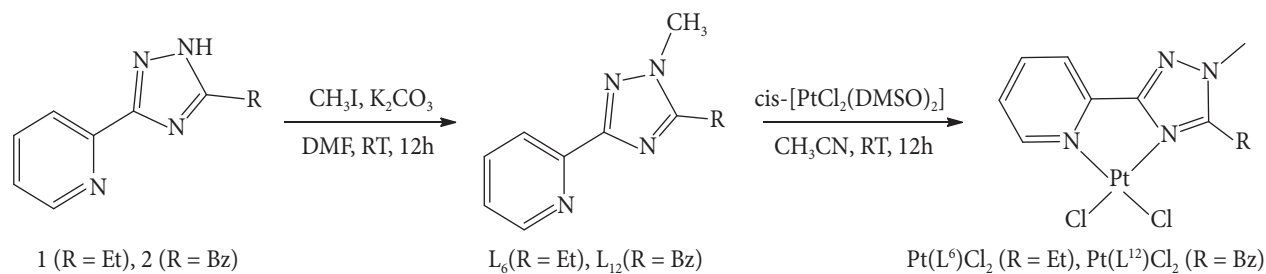


Fig. 2. Synthesis of ligands $L^{6,12}$ and corresponding coordination compounds $Pt(L^{6,12})Cl_2$

pyridine (L^2). One of the disadvantages of those compounds was bad solubility in all solvents that significantly complicated their investigation. Thus, we decided to introduce additional substituent to 3-(2-pyridyl)-1,2,4-triazole system to make compounds more soluble, without affecting of coordination abilities of ligands. Here we present investigation of two new platinum complexes which could be considered as 5C-substituted by ethyl (2-(5-ethyl-1-methyl-1H-1,2,4-triazol-3-yl)pyridine (L^6) and benzyl (2-(5-benzyl-1-methyl-1H-1,2,4-triazol-3-yl)pyridine (L^{12}) analogs of L^2 . The molecular structure of ligands and their complexes is shown in Fig. 1.

The aim of the research was to study the anticancer activity of above-mentioned platinum complexes $Pt(L^6)Cl_2$ and $Pt(L^{12})Cl_2$ against the squamous cell carcinoma cell line Hep-2, changes in key biochemical markers LDH, SDH, G6PD, intracellular ROS level and mitochondrial membrane potential.

Methods

General reagents and instrumentalations for chemicals analysis

K_2PtCl_4 was purchased from Sigma-Aldrich and used as received. $cis-[PtCl_2(DMSO)_2]$ [13] 2-(3-ethyl-1H-1,2,4-triazol-5-yl)pyridine (**1**) [14] and (2-(3-benzyl-1H-1,2,4-triazol-5-yl)pyridine (**2**) [15] are prepared as described previously. All solvents were laboratory reagent grade. Elemental analyses were carried out with Perkin-Elmer 2400 CHN Analyzer. Melting points ($^{\circ}C$, uncorrected) were measured with Opti Melt Automated Melting Point System (MPA 100). NMR spectra were recorded on a

VarianUnityPlus 400 spectrometer (at 400.4 MHz for ^1H nuclei). Internal standard — signal of residual solvent protons (CD_3CN — 1.94 ppm).

Synthesis of ligands and complexes

L^6 and L^{12} where obtained in one step started from **1** and **2** correspondingly using procedure described before for L^1 and L^2 [16]. Since present approach leads to the preparation of two isomeric compounds the relation of L^6 and L^{12} to proper regioisomers where confirmed by 1D NOE experiments (Fig. 2).

Anticancer cytotoxicity in vitro

The human larynx epidermal carcinoma cell line (Hep-2) and non-malignant mouse aortic endothelial cells (MAEC) were used. The cells were incubated in DMEM medium (L0103, Biowest, Nuaille, France) with 10% fetal bovine serum (Biowest), 40 $\mu g/mL$ gentamicin (Merck), 5% CO_2 atmosphere and 37 $^{\circ}C$. Incubation solutions with test compounds by double-dilution technics were prepared in the range of 1.56—100 μM for Pt-complexes and 15.625—1000 μM for respective ligands. The cells were incubated for 24 h. The cytotoxicity was determined photometrically by staining with 0.5% crystal violet in 70% methanol. The absorbance of the dye was recorded on a plate spectrophotometer Labsystems Multiskan PLUS (Vantaa, Finland) at 540 nm. The cytotoxicity of the compounds was assessed using the formula:

$$CD = (1 - D_s / D_c) \times 100\%$$

where CD is the relative changes in cell count as a percentage; D_s is the absorbance at 540 nm of experimental samples; and D_c is the absorbance at 540 nm of control samples. For compounds with cytotoxicity greater than 85% over the tested concentration range, the EC_{50} was calculated using the dose-response equation [17]. The experiment was repeated three times.

Intracellular enzymes activity

The cells were incubated with test substances for 24 h. The incubation medium was removed and the cells were frozen at -10°C for 10 min. The enzymes were assessed each individually. To determine lactate dehydrogenase (LDH) activity, cells were incubated (2 h, 37°C) in a mixture of the following composition: 10 mL 0.2 M PBS (pH 7.4, Calbiochem), 20 mL H_2O , 5 mg Nicotinamide adenine dinucleotide sodium salt (NAD-Na, Merck), 5 mg Nitro Blue Tetrazolium (Merck), 20 μL 50% Sodium Lactate (Merck). Succinate dehydrogenase (SDH) activity was studied after incubating cells (2 h, 37°C) in the following mixture: 10 mL 0.2 M Tris-HCl (pH 7.4, Merck), 15 mL H_2O , 300 mg sodium succinate (Merck), 5 mg Nitro Blue Tetrazolium (Merck). The cells were incubated (2 h, 37°C) in a mixture of the following composition to determine glucose-6-phosphate dehydrogenase (G6PH) activity: 20 mL 0.2 M Tris-HCl (pH 7.4, Merck), 20 mL H_2O , 40 mg glucose-6-phosphate (Merck), 10 mg NADPH (Merck), 5 mg Nitro Blue Tetrazolium (Merck). After incubation, the reaction mixture was replaced with distilled water. Cell staining was investigated using an Olympus IX71 inverted microscope with a DP72 camera. For each variant, at least 10 fields of view were snapped. The studies were repeated three times.

Mitochondrial functionality and ROS detection in vitro

The cells were incubated with EC_{50} for Pt-complexes and same concentrations for their ligands for 24 h. Cells were stained with 15 μM 2',7'-di-

chlorofluorescein diacetate (Thermo Fisher Scientific, Waltham, MA, USA) in PBS for intracellular ROS detection. The cells were incubated at 37°C for 30 min and then washed with saline for 2 min. The cells were incubated with 1 μM Rhodamine 123 in PBS for 10 min. The cells were washed in saline for 1 min. Fluorescence was studied under an Olympus BX53 microscope (Japan) with an XCite Series 120 Q luminescence block and an Olympus DP72 camera. Excitation with blue light filter, emission was green light filter, snap exposition was 10 ms for 2',7'-dichlorofluorescein diacetate and 20 ms for Rhodamine 123. The experiment was repeated three times.

Data processing

The images were processed by ImageJ software. The background luminescence values were subtracted from the values of the cells' integrated density for determination of ROS and mitochondrial membrane potential. The values of the cells' integrated density were subtracted from the background illumination to determine the activity of LDH, SDH and G6PH. Statistical data processing was carried out using the Kruskal-Wallis Test ($p < 0.05$). Data was presented as median and interquartile range (Me, 25—75%).

Results and Discussion

Two Pt-complexes based on 3-(2-pyridyl)-1,2,4-triazole derivatives were tested against the Hep-2 laryngeal carcinoma cell line. The maximum cytotoxicity against cancer cells was determined to be 86% for the $\text{Pt}(\text{L}^{12})\text{Cl}_2$ complex and 63% for the $\text{Pt}(\text{L}^6)\text{Cl}_2$ complex at a concentration of 100 μM (Fig. 3, b).

The calculated EC_{50} for $\text{Pt}(\text{L}^{12})\text{Cl}_2$ was $9.12 \pm 0.33 \mu\text{M}$ against Hep-2 cells. The EC_{50} for reference Cisplatin was $12.02 \pm 0.10 \mu\text{M}$ (Fig. 3, b). The cytotoxicity of the structure-forming ligands was much lower and amounted to 19 and 38% for L^6 and L^{12} , respectively at concentration 1000 μM (Fig. 3, a). The number of MAEC cells was decreased by

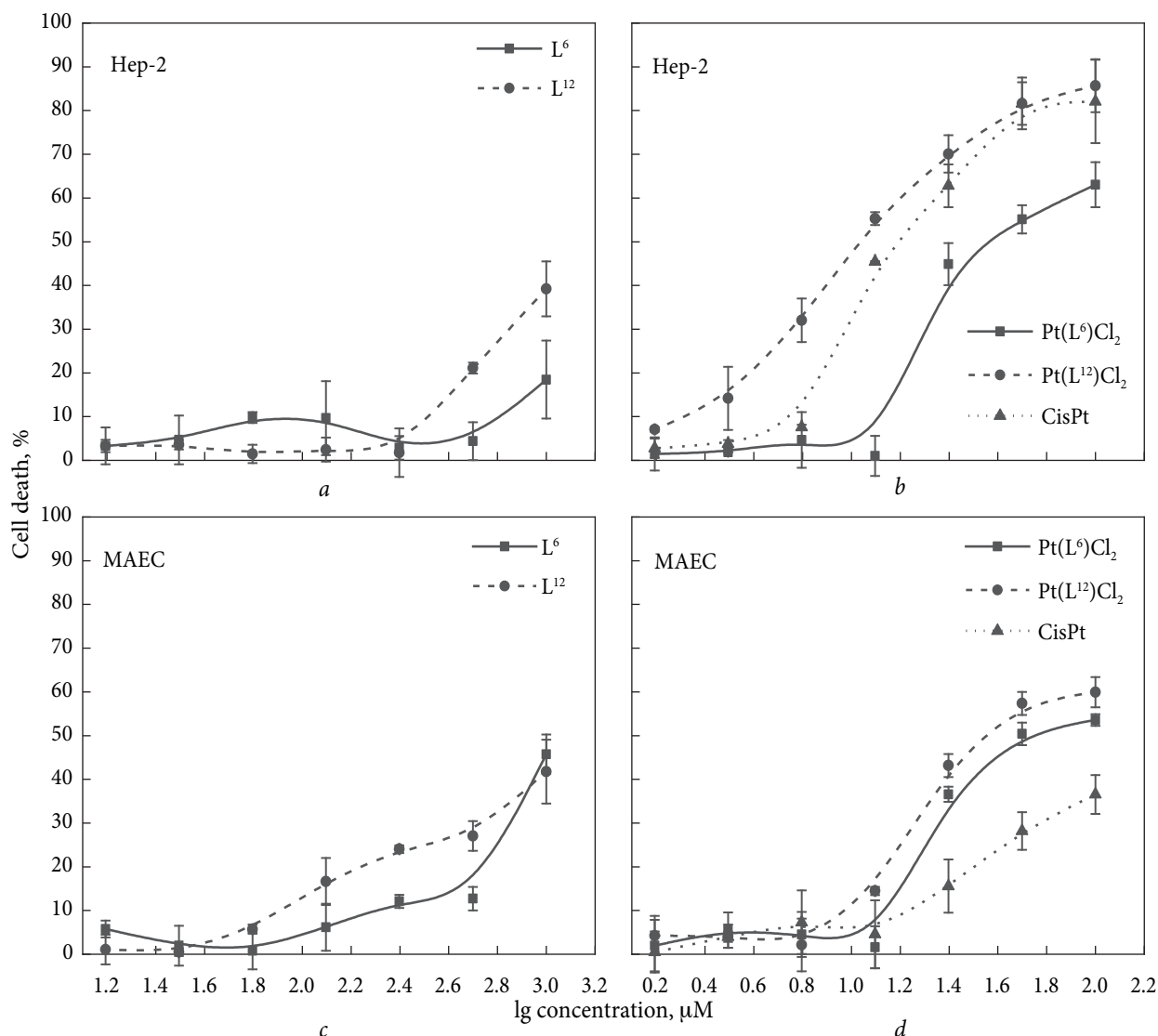


Fig. 3. Cytotoxicity of ligands (a, c) and their Pt-complexes (b, d) against laryngeal squamous cell carcinoma Hep-2 and non-malignant MAEC cells; reference compound was cisplatin (CisPt); $M \pm SD$, $n = 3$

approximately 40% when incubated with L^6 and L^{12} ligands (Fig. 3, c). These changes did not differ from those observed in cancer cells. At the same time, the cytotoxicity against MAEC cells of the $Pt(L^6)Cl_2$ and $Pt(L^{12})Cl_2$ complexes was 50–60% at a concentration of 100 μM (Fig. 3, d). The cytotoxicity of Cisplatin against MAECs was slightly lower in this concentration range (Fig. 3, d).

The development of novel platinum-based anti-cancer complexes remains an active area of re-

search. The azide-appended trinuclear platinum complex N3-TriplatinNC with anticancer activity against the MDA-MB-231 breast cancer cell line was synthesized. It possessed DNA-binding properties and anti-cancer cytotoxicity [18]. Platinum complexes containing 1,3-diphenyl-1,3-propanedione and distyryl-BODIPY-appended acetylacetone ligand were synthesized. They exhibit cytotoxicity and inactivate the mitochondria of cancer cells after exposure to red light [19].

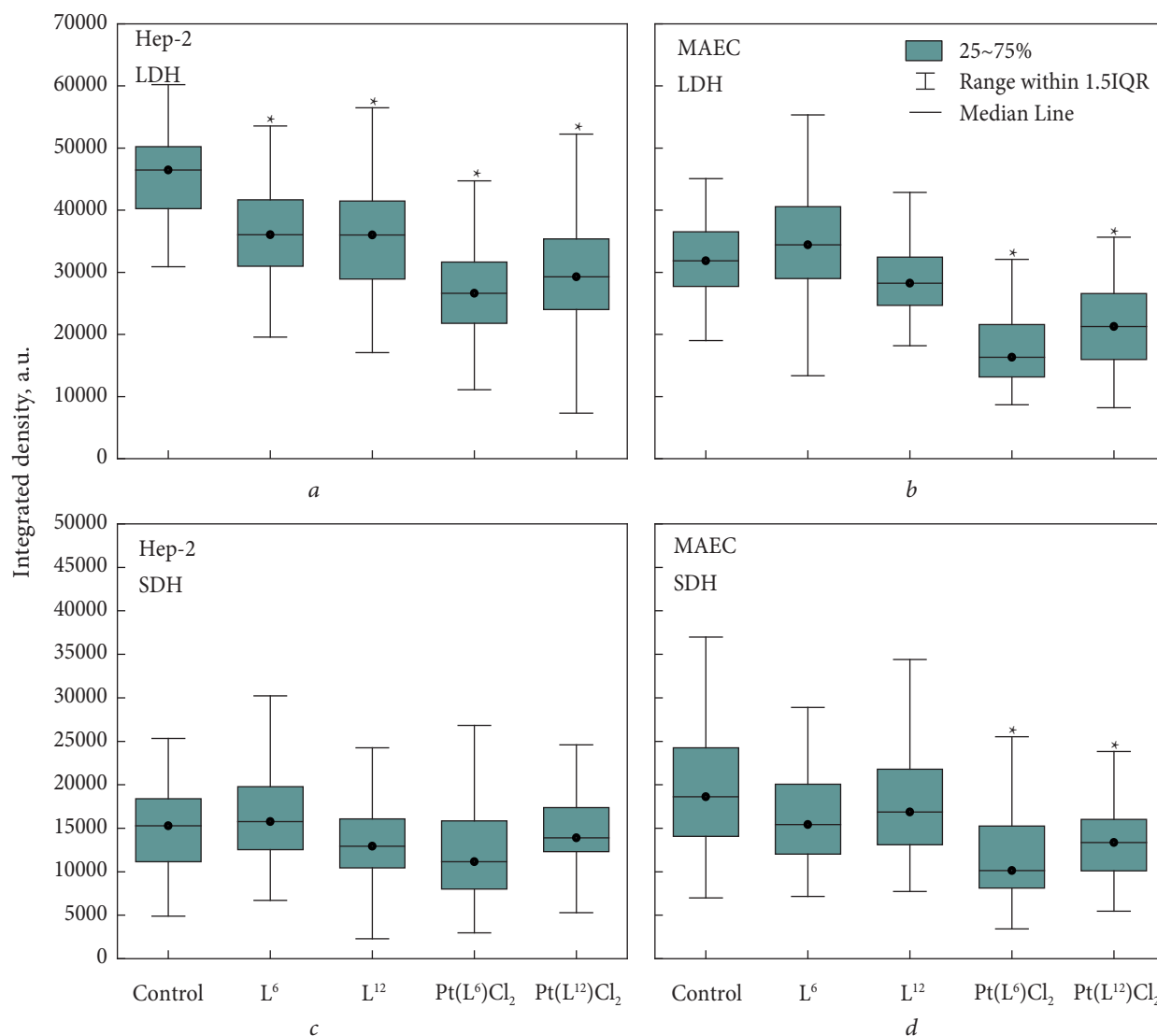


Fig. 4. Catalytic activity of lactate dehydrogenase (a, b) and succinate dehydrogenase (c, d) in Hep-2 and MAEC cell lines after 24 h incubation with L⁶ and L¹² ligands and their Pt complexes; Me, 25–75%, Kruskal-Wallis test, * p < 0.05 comparison with non-treated cells

Thus, the ligands cytotoxicity was approximately the same for malignant and non-malignant cells. No differences in inhibition of both cell lines by the Pt(L⁶)Cl₂ complex were found. However, differences were identified in the effects of the Pt(L¹²)Cl₂ complex on the cell growth.

Lactate dehydrogenase and succinate dehydrogenase are important indicators of cancer progression. The restructuring of cancer cell metabolism is ac-

companied by hyperexpression of the enzyme and the lactate accumulation [20]. A decrease in LDH levels in response to platinum-based chemotherapy has been shown to be associated with a favorable treatment prognosis [21]. Lactate dehydrogenase activity in untreated cancer Hep-2 cells was higher than in non-malignant MAEC cells (Fig. 4, a, b).

No statistically significant changes in this parameter were identified in MAEC cells after 24 h of

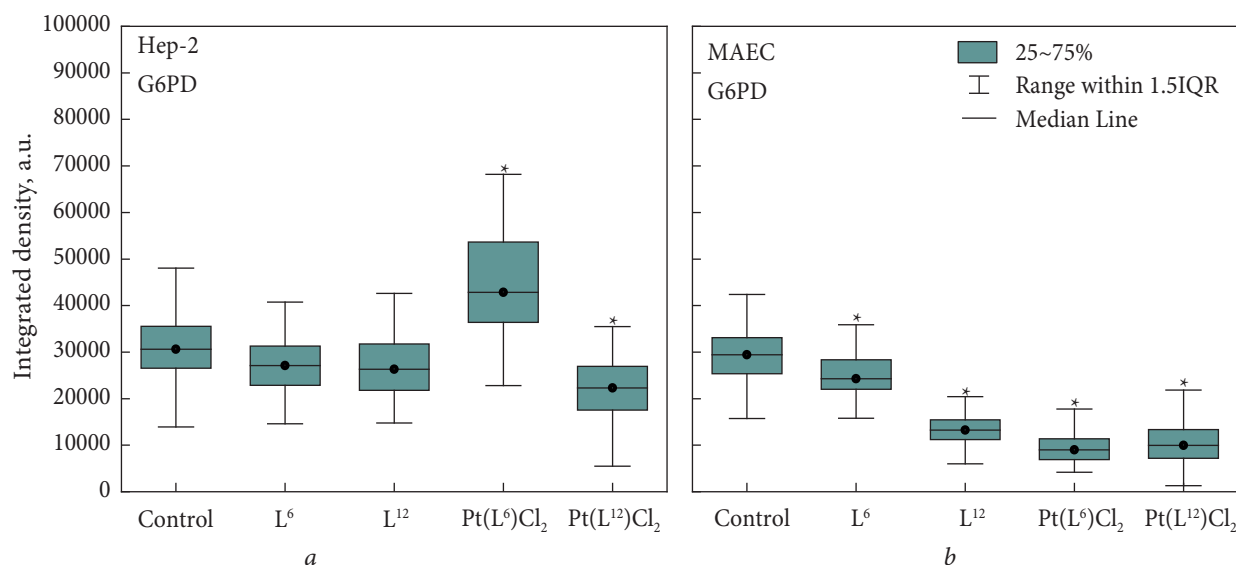


Fig. 5. Catalytic activity of glucose-6-phosphate dehydrogenase in Hep-2 (a) and MAEC (b) cell lines after 24 h incubation with L^6 and L^{12} ligands and their Pt complexes; Me, 25–75%, Kruskal-Wallis test, * $p < 0.05$ comparison with non-treated cells

treatment with L^6 and L^{12} ligands (Fig. 4, b). Under these conditions, LDH activity in Hep-2 cells was decreased by 1.3-fold for both ligands (Fig. 4, a). The enzyme activity was reduced 1.6-fold after 24 h of incubation of Hep-2 cells with the $Pt(L^6)Cl_2$ and $Pt(L^{12})Cl_2$ complexes. LDH activity was decreased 2-fold and 1.5-fold after treatment of MAEC cells with $Pt(L^6)Cl_2$ and $Pt(L^{12})Cl_2$ complexes, respectively. No significant differences in the SDH catalytic activity were detected between untreated Hep-2 and MAEC cells (Fig. 4, c, d). No significant changes in the catalytic activity of SDH were detected in Hep-2 cells after incubation with the $Pt(L^6)Cl_2$ and $Pt(L^{12})Cl_2$ complexes or their corresponding ligands. A 1.8-fold and 1.4-fold decrease in the enzyme activity in MAEC cells was calculated after treatment with $Pt(L^6)Cl_2$ and $Pt(L^{12})Cl_2$, respectively (Fig. 4, d).

SDH dysfunction in cancer cells is accompanied by the succinate accumulation [7]. The mechanisms of cisplatin-induced cell death involve mitochondrial pathways for initiating apoptosis. SDH activity is required for the successful induction of cell death [22]. However, many types of cancer are characterized by reduced SDH activity. This may

be one of the reasons for tumor chemo-resistance and low treatment effectiveness [23].

Although the expression of G6PD varies among different cancer types, it plays a crucial role in tumor invasion, metastasis, and chemoresistance [24]. G6PD is also involved in cisplatin chemoresistance pathways [25]. Significant differences in G6PD activity were found between Hep-2 and MAEC cells following treatment with the tested compounds. No changes in G6PD activity were observed in Hep-2 cells after 24 h of incubation with the L^6 and L^{12} ligands. In contrast, treatment with the $Pt(L^{12})Cl_2$ complex resulted in a 1.3-fold decrease in G6PD activity, whereas the $Pt(L^6)Cl_2$ complex induced a 1.4-fold increase (Fig. 5, a).

A decrease in the G6PD activity was observed in non-malignant MAEC cells. A 1.2-fold and 2.2-fold decrease in the activity of this enzyme was calculated after 24 h of MAEC incubation with ligands L^6 and L^{12} , respectively (Fig. 5, b). A further reduction in the G6PD activity was observed following treatment with the corresponding platinum complexes. Thus, the response of malignant and non-malignant cells to treatment with platinum complexes differed. No differences were

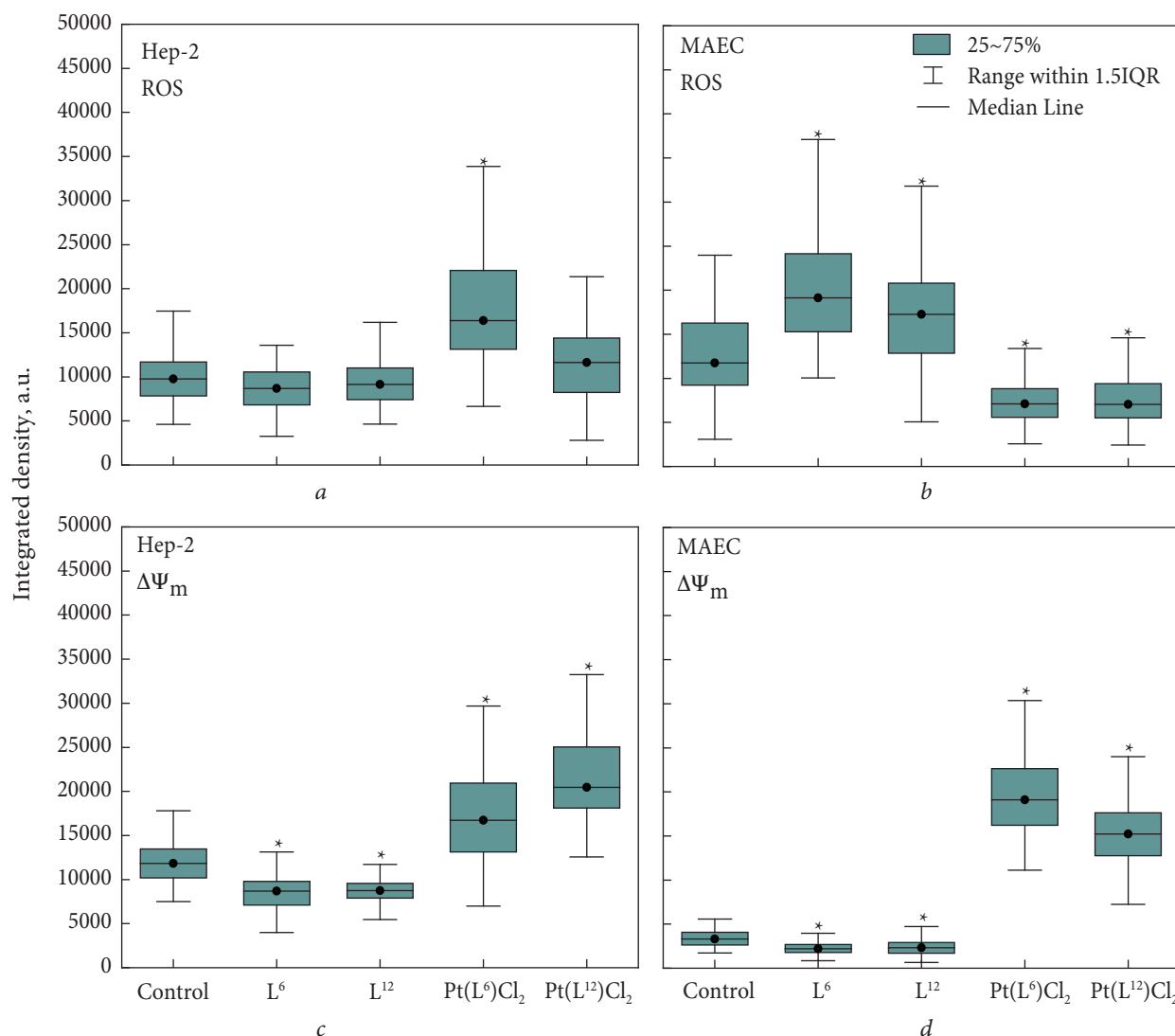


Fig. 6. Changes in reactive oxygen species (ROS; *a, b*) and mitochondrial membrane potential ($\Delta\Psi_m$; *c, d*) in Hep-2 cells and MAEC cell lines after 24 h of incubation with L⁶ and L¹² ligands and their Pt complexes. Me, 25–75%, Kruskal-Wallis test, * $p < 0.05$ comparison with non-treated cells

found in the baseline ROS levels of Hep-2 and MAEC cells (Fig. 6, *a, b*). Intracellular ROS were increased 1.7-fold after treatment of cancer cells with the Pt(L⁶)Cl₂ complex (Fig. 6, *a*).

No significant changes in ROS were induced after treatment of Hep-2 cells with the other test compounds. ROS in MAEC cells increased 1.6-fold and 1.5-fold after 24 h of incubation with ligands L⁶ and L¹², respectively (Fig. 6, *b*). ROS levels were reduced 1.7-fold after treatment of non-ma-

lignant cells with the corresponding platinum complexes. Thus, the patterns of ROS changes in response to treatment with the novel platinum complexes differed between malignant and non-malignant cells. The mitochondrial membrane potential of Hep-2 cells was increased 3.5-fold compared to MAEC (Fig. 6, *c, d*). A 1.4-fold decrease in $\Delta\Psi_m$ was calculated in both cell lines after 24 h of incubation with ligands L⁶ and L¹². A 1.4-fold and 1.7-fold increase in the parameter was

observed in Hep-2 cells following treatment with the $\text{Pt}(\text{L}^6)\text{Cl}_2$ and $\text{Pt}(\text{L}^{12})\text{Cl}_2$ complexes, respectively (Fig. 6, c). In non-malignant MAEC cells, a significant increase in mitochondrial membrane potential was also detected, amounting to 5.8-fold for the $\text{Pt}(\text{L}^6)\text{Cl}_2$ complex and 4.6-fold for the $\text{Pt}(\text{L}^{12})\text{Cl}_2$ complex (Fig. 6, d). Thus, in MAEC cells, a simultaneous increase in mitochondrial membrane potential and a decrease in ROS levels were detected. This is likely attributable to adaptive responses to the toxic effects of the platinum complexes and the more efficient functioning of antioxidant systems in MAEC cells compared with Hep-2 cells.

Combined platinum-based chemotherapy and radiotherapy are used to treat laryngeal cancer [28]. The efficacy of platinum-based anticancer therapy in patients with metastatic or recurrent oral squamous cell carcinoma depends on the development of treatment resistance and the interval between chemotherapy cycles [29]. Despite this, there is a risk of reduced sensitivity to platinum-based compounds. Therefore, the search for new platinum ligands remains a relevant task. The efficacy of platinum complexes with benzimidazole ligands against the Hep-2 cell line has been reported [30]. Their ability to bind DNA has also been established, and a dependence of their cytotoxicity on ligand structure has been observed across different cancer cell lines. The anticancer activity of anionic platinum complexes against the oral squamous cell carcinoma cell lines OSC-19 and OSC-20 has been demonstrated [31]. The efficacy of these compounds was confirmed *in vivo* against bone metastases of OSC-19 cells.

The tested compounds offer several advantages over the parent compound, cisplatin. Replacing the amine ligands of cisplatin with an N,N-donor chelating ligand alters its mode of interaction with the DNA double helix. Pyridyl-triazole derivatives are among such ligands. They provide an additional mode of interaction with DNA, namely intercalation, which distinguishes platinum complexes containing these ligands from cisplatin [32]. 1,2,4-Triazole ligands can be readily modified chemically by introducing various substituents, enabling control

over the physicochemical properties of the resulting chelate complexes.

The proposed platinum complexes have a cytotoxic effect on Hep-2 cells by reducing the catalytic activity of LDH, but without affecting SDH. At the same time, intracellular ROS levels changed only slightly despite the increase in mitochondrial membrane potential. Presumably, this is associated with different mechanisms of cell protection from toxicants, as well as the intensity of metabolic activity [26, 27]. Also, it is likely that the proposed complexes involve mechanisms of cell death initiation that differ from cisplatin, which requires further study. This may be an advantage in overcoming chemoresistance in cancer cells.

Conclusions

The cytotoxicity of platinum complexes $\text{Pt}(\text{L}^6)\text{Cl}_2$ and $\text{Pt}(\text{L}^{12})\text{Cl}_2$ ($\text{EC}_{50} = 9.12 \pm 0.33 \mu\text{M}$) against Hep-2 laryngeal squamous cell carcinoma cells and non-malignant MAEC cells was demonstrated. A reduction in LDH activity, but no change in SDH activity, was observed following treatment of cancer cells with the platinum complexes. The changes in intracellular G6PD activity depended on the structure-forming ligand, highlighting the importance of this component in the development of anticancer platinum complexes. The treatment of Hep-2 cells with the $\text{Pt}(\text{L}^6)\text{Cl}_2$ complex resulted in increased ROS levels, accompanied by an increase in mitochondrial membrane potential. Incubation of Hep-2 cells with the $\text{Pt}(\text{L}^{12})\text{Cl}_2$ complex did not lead to the significant changes in ROS levels, although mitochondrial membrane potential was increased. Thus, the new platinum-based complexes exhibit anticancer activity against the Hep-2 laryngeal squamous cell carcinoma cells. The structure-forming ligands influence the cytotoxicity of the Pt-complexes. However, the ligands themselves have only a weak effect on the viability of cancerous and non-malignant cells.

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Єщенко М.О.¹, Вірич П.А.^{1,2}, Костовський М.С.¹,

Распертова І.В.¹, Хоменко Д.М.¹, Вірич П.А.^{1,2}

¹ Київський національний університет імені Тараса Шевченка

Київ, Україна

² ДУ «Інститут отоларингології ім. проф. О.С. Коломійченка НАМН України»

Київ, Україна

ЦИТОТОКСИЧНІСТЬ НОВИХ ПЛАТИНОВИХ КОМПЛЕКСІВ НА ОСНОВІ ПОХІДНИХ 3-(2-ПІРИДИЛ)-1,2,4-ТРІАЗОЛУ ПРОТИ ПЛОСКОКЛІТИННОЇ КАРЦИНОМИ

Платинові комплекси є одним з ключових елементів протиракової хіміотерапії. Наразі зусилля зосереджені на розробці нових Pt-комплексів на основі лігандів різної хімічної природи. **Метою** дослідження було вивчення протиракової активності нових платинових комплексів на основі лігандів 2-(5-етил-1-метил-1Н-1,2,4-тріазол-3-іл)піридину (L^6) та бензил-(2-(5-бензил-1-метил-1Н-1,2,4-тріазол-3-іл)піридину (L^{12})). **Методи.** Була оцінена цитотоксичність комплексів $Pt(L^6)Cl_2$ та $Pt(L^{12})Cl_2$ проти клітин Нер-2 та МАЕС. Каталітичну активність лактатдегідрогенази (ЛДГ), сукцинатдегідрогенази (СДГ) та глюкозо-6-фосфатдегідрогенази (Г6ФД) визначали за допомогою нітросинього тетразолію. Внутрішньоклітинний рівень активних форм кисню (АФК) визначали за допомогою 2',7'-дихлорфлуоресцеїну діацетату, а мітохондріальний потенціал ($\Delta\Psi_m$) – за допомогою родаміну 123. **Результати.** Розрахована EC_{50} для $Pt(L^{12})Cl_2$ проти клітин Нер-2 становила $9,12 \pm 0,33$ мкМ. Активність ЛДГ була знижена як у Нер-2, так і в МАЕС, але змін активності СДГ у клітинах Нер-2 не виявлено. У клітинах Нер-2 обробка комплексом $Pt(L^{12})Cl_2$ призвела до зниження активності Г6ФД, тоді як комплекс $Pt(L^6)Cl_2$ індукував її підвищення. У клітинах Нер-2 спостерігалось збільшення $\Delta\Psi_m$ та АФК. **Висновки.** Комплекси Pt мають цитотоксичну дію на клітини Нер-2, знижуючи активність ЛДГ, але не впливаючи на СДГ. Внутрішньоклітинні рівні АФК змінювалися слабо, але $\Delta\Psi_m$ збільшувався.

Ключові слова: платинові комплекси, рак, активні форми кисню, мітохондріальний мембранний потенціал, лактатдегідрогеназа, сукцинатдегідрогеназа.