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Inhibition of C6 Glioma Cell Proliferation by Au(III) and Pt(II) Complexes of 1,10-Phenanthroline-5,6-dione

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In this study, we studied the antiproliferative effecs of Au(III) and Pt(II) metal complexes of 1,10-phenanthroline-5,6-dione and cisplatin on rat glioma C6 cells. The antiproliferative effects were evaluated by MTT ((3,4,5-dimethylthiazol-2-yl)-2-5-diphenyltetrazolium bromide) cell proliferation assay. We determined that Au(III) and Pt(II) metal complexes of 1,10-phenanthroline-5,6-dione and cisplatin have significant the time- and concentration-dependent antiproliferative effects on C6 glioma cells. Cell proliferation was significantly decreased by 5-100 µM of Au(III) and Pt(II) metal complexes at 24 and 48 h. Especially, an inhibition in the cancer cell proliferation was observed Au(III) metal complex being higher than that with Pt(II) metal complex. The present study demonstrates a powerful *in vitro* antitumor action of Au(III) metal complex of 1,10-phenanthroline-5,6-dione on C6 glioma cells.

Key Words: Au(III), Pt(II), Cisplatin, 1,10-Phenanthroline-5,6-dione, MTT.

INTRODUCTION

Metal ions are known to bind with nucleic acids and thereby alter their conformations and biological functions. The metal ion-base interaction depends on the nature of both metal and bases; a certain site of coordination is preferred. One of the most notable successes for inorganic drugs has been the effectiveness of platinum complexes against cancer. These advances have spurred a surge of investigations to identify new inorganic agents for use in chemotherapy with improved specificity and decreased toxic side effects. Au(I) and Au(III) complexes, the last isostructural and isoelectronic with platinum(II) complexes, are potentially attractive as anticancer agents. Au(I) and Au(III) complexes overcome some of these challenges by forming strong covalent attachments to targets. Au(III) isoelectronic with Pt(II)-d^8 system usually forms square planar complexes in solution. Since the square planar geometry of Pt(II) is important for its action as an anticancer drug, Au(III) compounds also can be used for the same purpose with the additional advantage of decreased toxicity. This, together with the recent finding that certain transitional metal complexes like Au and Pt complexes have been found to be potentially useful in cancer chemotherapy, created a renewed interest in the study of the interactions of metal ions with respect to the site of binding and the structure and stability of the complexes. Various studies in the past have shown that Au complexes are very attractive in view of their application as anticancer agents[1]. Au(III) complexes generally exhibit interesting cytotoxic and antitumor properties, but until now, their development has been heavily hampered by their poor stability under physiological conditions. Since enhance the stability of the Au(III) center, Messori *et al.*[2,3], prepared a number of gold(III) complexes with multidentate ligands-namely Au(en)(2)]Cl^{3-}, [Au(dien)Cl]Cl^{2-}, [Au(cyclam)](ClO_4)(2)Cl, [Au(terpy)Cl]Cl^{2-} and [Au(phen)Cl^{2-}]Cl- and analyzed their behaviour in solution. In contrast, the phenanthroline and terpyridine ligands turned out to be even more cytotoxic than the corresponding Au(III) complexes rendering the interpretation of the cytotoxicity profiles of the latter complexes less straightforward. The implications of the present findings for the development of novel Au(III) complexes as possible cytotoxic and antitumor drugs have been discussed elsewhere[2]. DNA represents a primary target for platinum antitumor metal complexes and is a probable target for newly developed cytotoxic Au(III) complexes. Notably, in all cases, the Au(III) chromophore is not largely perturbed by addition of calf thymus DNA ruling out occurrence of Au(III) reduction[3]. Au(III) compounds generally exhibit significant cytotoxic effects on cancer cell lines and are of potential interest as antitumor drugs. Marcon *et al.*[4], have reported that the interactions of [Au(bipy)(OH)(2)][PF_6] and [Au(bipy(c)-H)(OH)][PF_6] with calf thymus DNA were investigated *in vitro* by various

techniques to establish whether DNA represents a primary target for these compounds. Addition of saturating amounts of DNA does not affect appreciably the visible spectra of these Au(III) complexes. Some modifications of the CD spectra of calf thymus DNA and of the DNA melting parameters are observed; in any case, ultrafiltration experiments showed that binding of these Au(III) complexes to DNA is weak and reversible. There are lots of complexes formed with metal like Au and Pt have apoptotic effects on cancer cells and cytotoxic effects on cell proliferation[5-16].

Cisplatin (*cis*-diaminedichloroplatinum(II), [*cis*-$(NH_3)_2PtCl_2$]) is one of the most successful anticancer compound and widely used for the treatment of malignant brain tumours. Malignant gliomas are the most common malignant brain tumours and are usually incurable. The infiltrative growth pattern of these tumours precludes curative neurosurgery and tumour cells are usually resistant to irradiation, chemotherapy, or immunotherapy. Malignancy has been recognized to result not only from enhanced cell proliferation but also from decreased physiological apoptosis[17]. After the discovery of its activity, thousands of platinum complexes have been synthesized and evaluated for their possible anticancer activities. Research in the field of platinum-based cancer chemotherapy has shown that cisplatin and its analogous compounds exhibit similar patterns of antitumoral sensitivity and susceptibility to resistance, which means that most of them produce identical adducts with DNA[18,19].

Platinum(II)-based anticancer drug, cisplatin has been considered as one of the most effective chemotherapeutic agents, displaying clinical activity against a wide variety of solid tumors. The cytotoxicity of cisplatin is primarily ascribed to its interaction with nucleophilic N7 sites of purine bases in DNA to form DNA-protein and DNA-DNA interstrand and intrastrand crosslinks. The DNA adducts formed by interaction of cisplatin with DNA activate several signal transduction pathways, including those controlled by mitogen-activated protein kinases (MAPK), eventually culminating in the induction of apoptotic cell death. DNA damage-mediated apoptotic signals, however, can be attenuated by various mechanisms and the resistance that ensues is a major limitation of cisplatin-based chemotherapy[20].

Over the past few years, a renewed interest in Au(III) compounds as potential anticancer agents has developed, though a number of interesting Au(III) targets have been investigated[21]. The studies of square planar Au(III) complexes of 1,10-phenanthroline, terpyridine and bipyridine have suggested further that the interaction of these Au(III) compounds with DNA by intercalation may also play a role in their anticancer activities[21,22].

In this study, the antiproliferative effects of Au(III) and Pt(II) metal complexes of 1,10-phenanthroline-5,6-dione on rat glioma C6 cell lines are investigated. Antiproliferative effect was determined by the MTT method. The structure elucidation of the synthesized compounds was performed by IR, ^{1}H NMR and MASS spectroscopic data and elemental analyses results.

EXPERIMENTAL

Potassium tetrachloroplatinate $K_2[PtCl_4]$ and sodium tetrachloroaurate dihydrate $Na[AuCl_4]\cdot 2H_2O$ were purchased from Fluka. All other reagents were used as purchased without any further purification. Chemical analysis for C, H, N were performed on a Perkin-Elmer elemental analyzer. Infrared spectra were recorded in the 4000-200 cm^{-1} range on Perkin-Elmer FT-IR. KBr pellets were used to record spectra. ^{1}H NMR spectra were obtained in DMSO-d_6 solution on Bruker DX400 instrument. $[Au(dp)Cl_2]Cl$ and $[Pt(dp)]Cl_2$ derivatives were synthesised as reported[4,9]. The purity of the compounds was checked through elemental analysis and ^{1}H NMR spectroscopy. The ^{1}H NMR spectral data were also consistent with the assigned structures and all the protons were observed at expected regions. In the IR spectra, some significant stretching bands due N-H, C=O, C=N and C=C were at 3375-3105 and 1580-1486, respectively.

Synthesis: The mixture of (dp)1,10-phenanthroline-5,6-dione solution in EtOH-H_2O and $NaAuCl_4$ in H_2O was stirred at 30 ºC 2 h. The precipitate was filtered and washed several times with water and diethylether and dried in vacuum dessicator. The compound was characterised by IR, ^{1}H NMR and MASS spectroscopic data (Fig. 1).

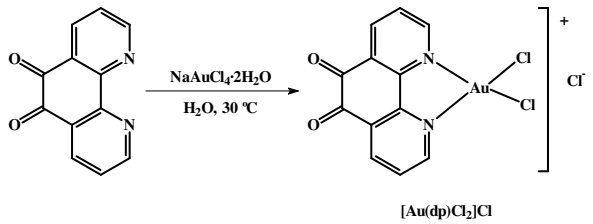


Fig. 1. Synthesis of the $[Au(dp)Cl_2]Cl$ compound

$Au(dp)Cl_2]Cl$: Selected IR (KBr, ν_{max}, cm^{-1}): 3148, 3110, 3075 (Ar C-H), 1645, 1630, 1450, 1391 (C=O, C=N, C=C), 325 (M-Cl), 287 (M-N). ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 7.52-9.25 (6H, m). MS (ES): m/z: 477 [M + 1].

The mixture of (dp)1,10-phenanthroline-5,6-dione solution in EtOH-H_2O and K_2PtCl_4 in H_2O was stirred at 30 ºC 12 h. The precipitate was filtered and washed several times with water and diethylether and dried in vacuum dessicator. The compound was characterised by IR, ^{1}H NMR and MASS spectroscopic data (Fig. 2).

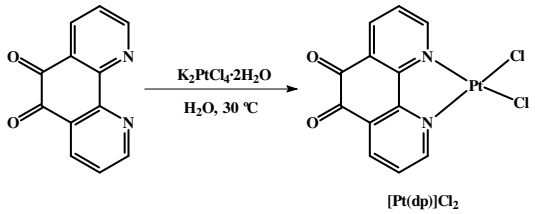


Fig. 2. Synthesis of the $[Pt(dp)]Cl_2$ compound

$[Pt(dp)]Cl_2$: Selected IR (KBr, ν_{max}, cm^{-1}): 3148, 3100, 3087 (Ar C-H), 1640, 1632, 1456, 1392 (C=O, C=N, C=C), 327 (M-Cl), 289 (M-N). ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 7.60-9.20 (6H, m). MS (ES): m/z: 475 [M + 1].

Cell culture: The rat glioma C6 cells were obtained from American Type Culture Collection (ATCC number CCL-107). In view of the common use of the C6 rat glioma cell line in experimental studies, it appeared desirable to compare the

results of *in vitro* MTT cytotoxicity testing of human gliomas with the chemosensitivity of the same antineoplastic agents against the C6 glioma cell line[23]. C6 cells were maintained as a monolayer culture in DMEM medium with 10 % FCS in the presence of penicillin (100 U/mL) and streptomycin (100 g/mL) at 37 ºC in a humidified atmosphere of 5 % CO_2 in air. Subculture was made by using 0.05 % trypsin with 0.02 % EDTA every 3-4 days.

Cisplatin, [Au(dp)Cl_2]Cl and [Pt(dp)]Cl_2 were dissolved in dimethyl sulfoxide (DMSO) as a stock solution and the stock solution was diluted to the required concentrations. Cisplatin used to positive control. The results of [Au(dp)Cl_2]Cl and [Pt(dp)]Cl_2 were compared to cisplatin.

Cell proliferation assay: The proliferation of the cells was assessed by MTT (3,4,5-dimethylthiazol-2-yl)-2-5-diphenyltetrazolium bromide) assay, which is based on the reduction of yellow-coloured MTT by the mitochondrial dehydrogenase of living intact cells to a purple formazan product. This reduction takes place only when mitochondrial reductase enzymes are active and therefore conversion can be directly related to the number of viable (living) cells[24,25].

C6 glioma cells (5×10^4 cells/mL; 100 µL/well) were seeded in 96-well microtiter plates, incubated at 37 ºC for 24 h and treated with 5, 10, 25, 50 and 100 µM concentration of cisplatin, [Au(dp)Cl_2]Cl and [Pt(dp)]Cl_2 for 24, 48 and 72 h. Also, control (medium) and DMSO control (0.1 % DMSO in medium) groups were consisted. *In vitro* growth inhibition was measured by 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl tetrazolium bromide (MTT) (Sigma, St. Louis, MO, USA) reduction assay[24]. After incubations, MTT solution was added to cell cultures in final concentration of 0.5 mg/mL and mixed by tapping gently on the side of wells; the cells were incubated at 37 ºC for 4 h in the CO_2 incubator. Then, the medium with MTT was removed from the wells and the purple MTT-formazan crystals was dissolved by adding 100 µL DMSO (100 %) (Sigma Chemical Co., St. Louis, MO) to each well. The absorbance of the samples was measured with an ELISA reader (wavelength 570 nm). MTT reduction is used to estimate cell numbers at the end of the assay. In the experiment, each group was performed in 8 wells. The proliferation of cells was determined by calculating the absorbance of the test wells as the percentage of the control well. The results presented as the average of three independent experiments.

Statistical analysis: Data were expressed as mean ± standard error of mean (SEM) of three determinations. Statistical differences between experimental groups were determined by one-way analysis of variance (ANOVA), Tukey's test. Differences were considered significant if $p < 0.05$ ($p < 0.05$*, $p < 0.01$**, $p < 0.001$***).

RESULTS AND DISCUSSION

As shown by the MTT reduction assay (Figs. 3-5), treatment of C6 glioma cells with 5-100 µM cisplatin, [Au(dp)Cl_2]Cl and [Pt(dp)]Cl_2 complexes for 24 and 48 h resulted in a concentration-dependent decrease in the cell proliferation.

When C6 glioma cells exposed to 5, 10, 25, 50 and 100 µM cisplatin for 24 h, the cell proliferations decreased to 84, 78, 77, 78 and 65 %, respectively, compared to control ($p < 0.001$).

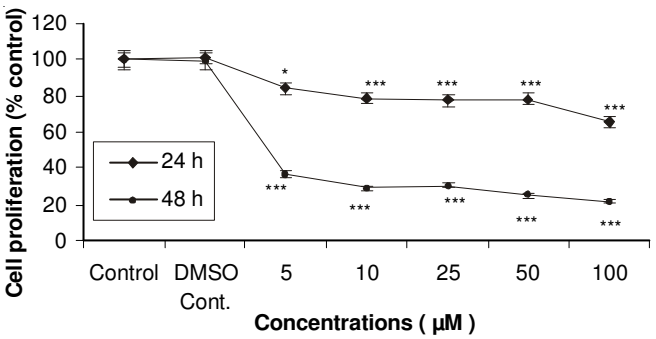


Fig. 3. Cytotoxicity analysis of the cisplatin in different concentrations against C6 glioma cells for 24 and 48 h. Cell proliferation (%) as presented as mean ± SEM from three independent experiments $p < 0.05$*, $p < 0.01$**, $p < 0.001$*** compared with control

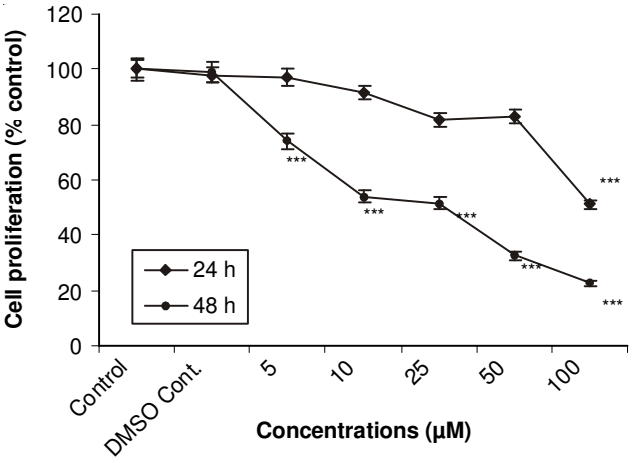


Fig. 4. Cytotoxicity analysis of the [Au(dp)Cl_2]Cl compound in different concentrations against C6 glioma cells for 24 and 48 h. Cell proliferation (%) was presented as mean ± SEM from three independent experiments $p < 0.05$*, $p < 0.01$**, $p < 0.001$*** compared with control

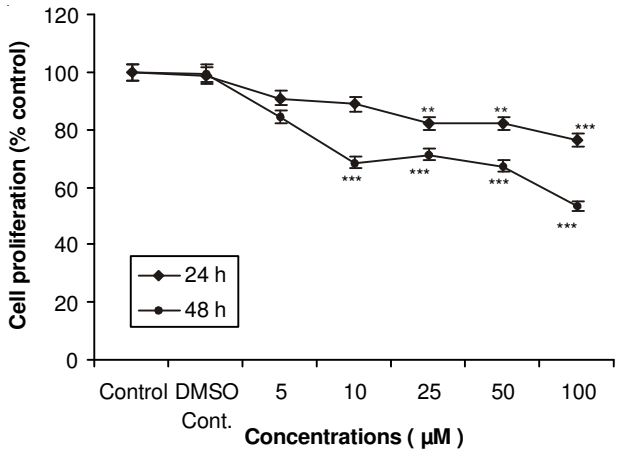


Fig. 5. Cytotoxicity analysis of the [Pt(dp)]Cl_2 compound in different concentrations against C6 glioma cells for 24 and 48 h. Cell proliferation (%) was presented as mean ± SEM from three independent experiments $p < 0.05$*, $p < 0.01$**, $p < 0.001$*** compared with control

After 48 h, 5-100 µM cisplatin concentrations significantly decreased the cell proliferation ($p < 0.001$). The percentages of cell proliferation for 48 h were determined at the concentrations of 5, 10, 25, 50 and 100 µM cisplatin as 36, 28, 30, 24 and 21 %, respectively. It is found that cytotoxic effect was

significantly increased by 5-100 µM cisplatin in C6 glioma cells for 48 h ($p < 0.001$) (Fig. 3).

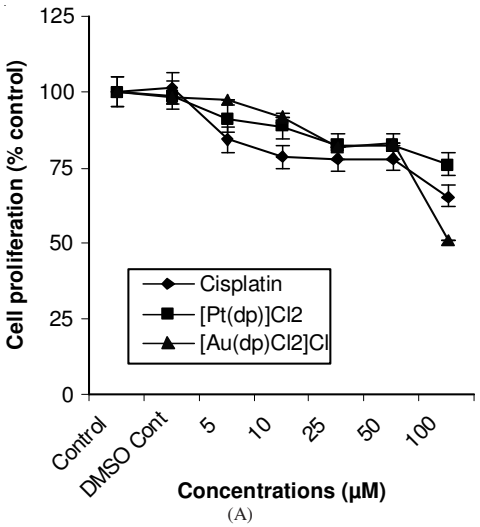
For 24 h, [Au(dp)Cl_2]Cl compound at the concentrations of 5, 10, 25, 50 and 100 µM reduced cell proliferations to 97, 91, 81, 83 and 51 %, respectively, compared to control. After the incubation with [Au(dp)Cl_2]Cl compound at the concentrations of 5-100 µM for 48 h, the percentages of cell proliferation were determined as 74, 53, 51, 32 and 22 %, respectively (Fig. 4) ($p < 0.001$). Both cisplatin and [Au(dp)Cl_2]Cl compound exhibited cytotoxic effect on C6 glioma cells in the concentration range of 5 and 100 µM. Although 5 µM cisplatin reduced the number of proliferative cells to 84 % after 24 h and 36 % after 48 h, 5 µM concentration of [Au(dp)Cl_2]Cl decreased to the number of proliferative cells to 97 and 74 %, respectively. For the [Au(dp)Cl_2]Cl compound, the most important cytotoxic effect was determined at 100 µM concentration in C6 cells for 48 h ($p < 0.001$).

For 24 h, [Pt(dp)]Cl_2 compound at the concentrations of 5, 10, 25, 50 and 100 µM reduced cell proliferations to 90, 88, 82, 82 and 76 %, respectively, compared to control. The concentrations of 5-100 µM concentrations of [Pt(dp)]Cl_2 for 48 h, the percentages of cell proliferation were determined as 84, 68, 71, 67 and 53 %, respectively (Fig. 5). [Pt(dp)]Cl_2 compound exhibited cytotoxic effect on C6 glioma cells being similar to cisplatin and [Au(dp)Cl_2]Cl compound. Although 5 µM cisplatin reduced the number of proliferative cells to 84 % after 24 h and 36 % after 48 h, 5 µM [Pt(dp)]Cl_2 decresed the number of proliferative cells to 90 and 84 %, respectively. For the [Pt(dp)]Cl_2 compound, the most important cytotoxic effect was determined at 100 µM concentration in C6 glioma cells for 48 h ($p < 0.001$).

When compared to the cytotoxic effects of cisplatin, [Au(dp)Cl_2]Cl and [Pt(dp)]Cl_2 after 24 h, the cisplatin's inhibitory effect on C6 glioma cell proliferation in a concentration intervals from 5-50 µM was more than [Au(dp)Cl_2]Cl and [Pt(dp)]Cl_2 compounds. It was determined that the inhibitory effects of [Au(dp)Cl_2]Cl and [Pt(dp)]Cl_2 compounds on C6 glioma cell proliferation were similar to each other at the concentration range from 5-50 µM. It was found that cell proliferations at 100 µM concentrations of cisplatin, [Au(dp)Cl_2]Cl and [Pt(dp)]Cl_2 for 24 h were 65, 51 and 76 %, respectively. In addition, the cytotoxic effect of [Au(dp)Cl_2]Cl concentration at 100 µM on C6 glioma cells was more than that of [Pt(dp)]Cl_2 and cisplatin (Fig. 6).

When compared to the cytotoxic effects of cisplatin, [Au(dp)Cl_2]Cl and [Pt(dp)]Cl_2 for 48 h, the cisplatin's inhibitory effect on C6 glioma cell proliferation was more than those of [Au(dp)Cl_2]Cl and [Pt(dp)]Cl_2 compounds depending on the concentration. It was also determined that the inhibitory effect of Au(dp)Cl_2]Cl on C6 glioma cell proliferation was higher than that of [Pt(dp)]Cl_2 compound. It was found that cell proliferations at 100 µM concentration of cisplatin, [Au(dp)Cl_2]Cl and [Pt(dp)]Cl_2 after 48 h were 21, 22 and 53 %, respectively. In addition, it was detected that the cytotoxic effect of 100 µM [Au(dp)Cl_2]Cl on C6 glioma cells were similar to 100 µM cisplatin and higher than that of [Pt(dp)]Cl_2 concentration (Fig. 7).

In the present work, Au(III) and Pt(II) metal complexes of 1,10-phenanthroline-5,6-dione were tested *in vitro* on antiproliferative activity using rat glioma cell line (C6) and



(A)

	Cisplatin-[Pt(dp)]Cl_2	Cisplatin - [Au(dp)Cl_2]Cl	Pt(dp)]Cl_2-[Au(dp)Cl_2]Cl
Control	n.s.	n.s	n.s
DMSO Control	n.s.	n.s	n.s
5 µM	$p < 0.01^{**}$	$p < 0.001^{***}$	n.s
10 µM	$p < 0.001^{***}$	$p < 0.001^{***}$	n.s
25 µM	n.s	n.s	n.s
50 µM	n.s	n.s	*n.s*
100 µM	$p < 0.01^{**}$	$p < 0.001^{***}$	$p < 0.001^{***}$

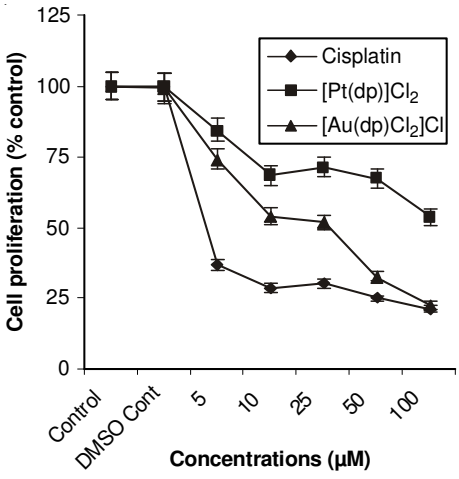
(B)

Fig. 6. Inhibitory effects of cisplatin, [Pt(dp)]Cl_2 and [Au(dp)Cl_2]Cl ompounds on C6 glioma cell proliferation for 24 h (A) and results of statistical analyses (B). Cell proliferation (%) was presented as mean ± SEM from three independent experiments $p < 0.05$*, $p < 0.01$**, $p < 0.001$***, n.s.: non-significant for the comparison within the same concentration groups

compared with the original Pt-based drug cisplatin. C6 glioma cells have been demonstrated to have high chemosensitivities to all of the drugs (cisplatin, doxorubicin and mitomycin C[23]. Caspase-3-dependent and -independent cell death pathways have been reported in cisplatin-treated human ovarian cancer cell lines[17,26].

The mode of tumor cell death could be very important for the outcome of cancer therapy. While anticancer drugs mainly promote apoptotic cell death, the resistance to chemotherapy-induced apoptosis seems to be a hallmark of most common cancers. Moreover, numerous data describing the immunostimulatory properties of necrotic cell products have fostered a hypothesis that necrosis might be more efficient than apoptosis in inducing tumor regression[20].

In this study, [Au(dp)Cl_2]Cl and [Pt(dp)]Cl_2 complexes and cisplatin showed potent antitumor activity. Moreover, [Au(dp)Cl_2]Cl) complexes was markedly more efficient than corresponding [Pt(dp)]Cl_2 complex. It has been known for a long time that gold(III) compounds possess antitumor activities. However, most of the reported cytotoxic gold(III) complexes are unstable in physiologic conditions and have marginal or moderate *in vivo* antitumor activity against human carcinoma xenografts[4,11,27,28]. Shuiping *et al.*[29] have observed that gold 1a exhibited significant cytotoxicity against different colon cell



(A)

	Cisplatin-[Pt(dp)]Cl_2	Cisplatin-[Au(dp)Cl_2]Cl	Pt(dp)]Cl_2-[Au(dp)Cl_2]Cl
Control	n.s.	n.s	n.s
DMSO Control	n.s.	n.s	n.s
5 μM	$p < 0.001^{***}$	$p < 0.001^{***}$	n.s
10 μM	$p < 0.001^{***}$	$p < 0.001^{***}$	$p < 0.05^{*}$
25 μM	$p < 0.001^{***}$	$p < 0.01^{**}$	$p < 0.01^{**}$
50 μM	$p < 0.001^{***}$	n.s	$p < 0.001^{***}$
100 μM	$p < 0.001^{***}$	n.s	$p < 0.001^{***}$

(B)

Fig. 7. Inhibitory effects of cisplatin, [Pt(dp)]Cl_2 and [Au(dp)Cl_2]Cl ompounds on C6 glioma cell proliferation for 48 h (A) and results of statistical analyses (B). Cell proliferation (%) was presented as mean ± SEM from three independent experiments $p < 0.05$*, $p < 0.01$**, $p < 0.001$***, n.s.: non-significant for the comparison within the same concentration groups

lines with 8.7-fold to 20.8-fold greater potency than that of cisplatin. The mechanisms responsible for the antitumor activity of gold (III) complex still are largely unknown. It is believed generally that the cytotoxic effects of metal complexes are the consequences of direct damage to nuclear DNA[29]. However, some studies have demonstrated that gold(III) complex interactions with DNA are not as tight as platinum interactions[3,4]. Gold(III) compounds inhibit DNA and RNA syntheses and have only minimal cross-resistance to cisplatin, suggesting a different mechanism of action. It has been reported that cisplatin caused G2/M cell cycle arrest and inhibition of DNA synthesis in a panel of human cancer cell lines[29,30]. These novel Au(III) complexes are isoelectronic and isostructural with clinically important Pt(II) complexes. This provides a motivation for investigation of these compounds as potential candidates through which Pt(II) drug resistance may be overcome. Studies are currently underway to investigate the manner by which these complexes kill cells (*i.e.*, apoptosis versus necrosis) and the extent that they bind to DNA[2,21].

It is found that [Au(dp)Cl_2]Cl and [Pt(dp)]Cl_2 complex used as such also exhibit important cytotoxic properties. Complexes of [Au(dp)Cl_2]Cl and [Pt(dp)]Cl_2 demonstrated significant cytotoxicity against glioma cancer cell line (C6) with values of per cent proliferation comparable to that observed for cisplatin. Palanichamy *et al.*[21] have reported that the cytotoxic activity imparted by Pt(II) complexes may be due to the intercalation of the compounds with DNA and/or reactivity with proteins through a Au(III)/Au(I) mediated redox process[21].

It should be noted that the cytotoxic effect of the Pt(II) complex was much lower compared to that of cisplatin and Au(III) complex[19]. Giovagnini *et al.*[31] have reported the synthesis and *in vitro* cytotoxic activity of new palladium(II) derivatives of methylsarcosinedithiocarbamate and its S-methyl ester. The biological activity of these compounds, as determined by growth inhibition and apoptosis induction, has been investigated in both human leukemic promyelocites HL60 and human squamous cervical adenocarcinoma HeLa cell lines and their activity has been compared to the well-known platinum-based anticancer agent cisplatin[31].

Conclusion

In summary, the present study demonstrated a powerful *in vitro* antitumor action of Au(III) metal complex of 1,10-phenanthroline-5,6-dione on C6 glioma cells. Gold compounds have the potential to form the basis of new chemotherapeutic. By further investigating gold interactions with other potential biological targets in cancer cells and identifying them, more potent and more specific gold-based drugs could be designed, synthesized and, hopefully in near future, developed for treatment of cancers.

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