Synthesis of Novel Poly 2-Vinylpyridine-Mixed Metal Complexes and Studying Their Effect as Antitumor Chemotherapeutic Agents, Part 2

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Received 14 January 2008; accepted 19 October 2008
DOI 10.1002/app.29720
Published online 22 March 2010 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: The poly2-vinylpyridine and cationic polymer-mixed metal complexes (P2VPMC) have been prepared and characterized by analytical measurement such as: molecular weight, elemental analysis, IR-spectroscopy, NMR-spectroscopy, XRD, and UV. The degree of *N*-alkylation of poly vinyl pyridine (P-2VP) was 10% determined by chlorine content according to elemental microanalysis. Through ICP instrument the complexation between P-2VPC and the mixed metal chlorides was proven. The structure of the samples was characterized using X-ray diffraction. It was found that the complexes have amorphous properties. The antitumor activity of this compound was examined *in vitro* on cell lines. The results reflect pronounced cytotoxicity of P-2VPMC against animal experimental EAC cells line, and human, HeLa, HCT116 and Hep-G2, cell lines. Antitumor activity of the novel compound as applied on mice bearing Ehrlich solid carcinoma, revealed delays tumor growth compared with untreated animals and decreases tumor volume. The antitumor activity of the P2VPMC might be due to its ability to pass through the membrane and interact with, DNA causing cross-linking action which might be the key factor for great antitumor activity of the P2VPMC compound. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 117: 501–508, 2010

Key words: poly2-vinylpyridine; quaternization; mixed metal chlorides complexes antitumor; chemotherapeutic agents

INTRODUCTION

Extensive studies were run during the last years to synthesis some new compound derivatives which possess anticancer effect with less toxicity and have the ability to increase the survival time. It has been suggested that the adhesion properties primarily depend upon the chemical composition of the outer plasma membrane.[1] A reduction in cohesive strength between tumor cells might be attributed to an excess negative charge on membrane surfaces that reflect structural-functional changes that have taken place in the course of neoplastic transformation.[2] This results in a greater electrostatic repulsive force between cells and disrupts the attractive force of contacting membranes that is caused by other reactions.[3] The negative charges on cell surfaces have been found to increase during carcinogenesis. It has been shown that with few exceptions, tumor cells[4] have greater negative charges than homologous normal tissues.[5] As the density of the negative charge increases, so does the transplant capability of tumor cells.[6] Metal ions or metal-based compounds are known to play an important role in cell regulation, cell growth, cell differentiation, and cell death.[7] Both natural and synthetic polymers have been used as drug carriers, and several bioconjugates have been clinically approved or are in human clinical trials. Natural polycations like polyamines have a role in facilitating cell death which might be partly mediated by the production of hydrogen peroxide during polyamine catabolism. A large body of data indicates that polyamine pathway can be a molecular target for therapeutic intervention in several types of cancers.[8]

Boyland[9] detected antitumor activity among some salts of aliphatic and aromatic bases. His study was the first to show that the polyamines had to have a specific positive charge to exhibit antitumor properties. Polycations were found to induce the rapid agglutination of Walker's carcinoma in a suspension. Such an effect was not produced by a nonionized compound of polysarcosine dimethylamides and the polyanion heparin. Poly ethylene and poly(L-Lysine) exhibited selected agglutinizing ability against tumor cells. As molecular weight of the compound increases, its toxicity increases against HeLa cells and its antitumor effect against Ehrlich's Ascites Carcinoma (EAC) are enhanced. The *in vitro* and *in vivo* experiments of low molecular weight of compound showed 20 times less activity than its high-molecular weight.[10] The first transition metal to be

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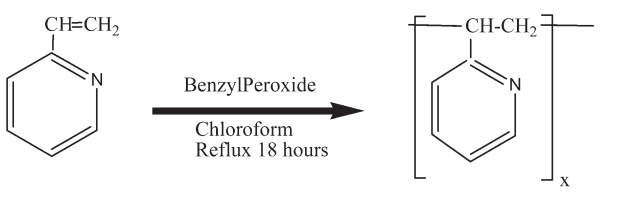
used successfully as an anticancer agent was platinum. It was used in a compound titled cisplatin [*cis*-$PtCl_2(NH_3)_2$], and its ability to inhibit tumors was discovered.[11,12] The polymer platinate AP5280 was designed to remain inactive while in the plasma but to be passively concentrated in the tumor extra cellular volume via the enhanced permeability and retention effect and subsequently activated to a cytotoxicity form by either extra cellular protease.[13] Thus, a polymer conjugate of a platinum-based drug would offer an attractive means of reducing toxicity, increasing solubility, and thus increasing passive tumor targeting via the Enhance Permeability and Retention (EPR) effect.[14] On the other hand, essential metals (like Fe) and therapeutic metal ions (like Pt, V, and others) that affect different targets are being used and studied as molecular therapies for cancer cell.[15,16] A polymer vanadium-based drug confirmed its potential as antineoplastic agent.[17] Liposoural surface-loading of water-soluble cationic iron(III) porphyrines allowed for a targeted necrosis of tumor cell.[18] Cobalt complexes exhibited selective effects on tumor tissue.[19] Recently reported, molybdate inhibited head and neck aqueous cell carcinoma, whereas some La(III) complexes had advantage than cisplatin against different cell lines.[20,21] For this reason, investigating the antitumor activity of mixed metal-polymer complexes represent a new, developing direction in the field of anticancer drugs. In this article, the synthesis of cationic polymer-mixed metal complexes, which have broad spectrum potential antitumor activity, was designed and formed through conjugating the polymer with more than one metal and evaluated for its efficiency as anticancer drug against EAC cells and other different human cell lines. The *in vivo* activity of this drug was investigated in Swiss albino mice bearing EAC cells through determination of tumor growth delay.

EXPERIMENTAL

Chemistry

Polymerization of 2-vinylpyridine

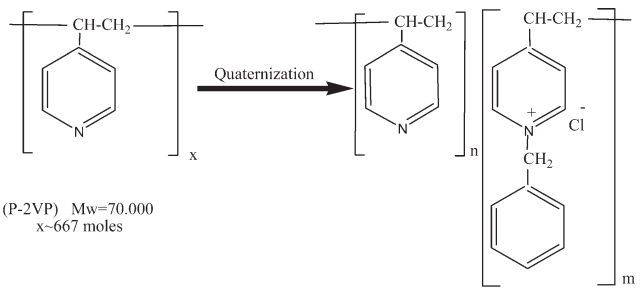
2-Vinylpyridine [105.14 g (1.0 mol) ≈ 107.8 mL] was placed in a round-bottomed flask. Chloroform (200 mL) and benzoyl peroxide (0.1 g) were added and refluxed gently for 18 h to give poly (2-vinylpyridine) (P2-VP) of Structure 1.



Structure 1 Polymerization of 2-Vinylpyridine.

Preparation of quaternary polycationic polymer

Poly2-vinylpyridine (P-2VP) [7 g (0.0001 mol)] of average molecular weight 70.000 in 50 mL of methyl alcohol was placed in a round-bottomed flask.[22] Benzyl chloride 3.8 g (0.03 mol) of benzyl chloride was added, and refluxed about 12 h, at 60°C. The resulting mixture was clear, viscous solution was evaporated to obtain the quaternary salt of poly (*N*-benzyl-2-vinylpyridinium chloride) (P-2VPC) as quaternary polycationic polymer which was filtered and washed with petroleum ether 40–60°C and dried. Analysis for chlorine content indicated that 10% of the nitrogen groups had been converted to the corresponding quaternary benzyl chloride derivative, the product was soluble in water (Structure 2).



Structure 2 Poly(N-benzyl-2-Vinylpyridinum chloride) Mw~78.500 (P -2VPC).

Cationic polymer-mixed metal complexes

Cisplatin (0.00004 mol) $(NH_3)_2PtCl_2$ and (0.001 mol) of each of the mixed metal chlorides $CoCl_2.6H_2O$, $SnCl_2.2H_2O$, $LaCl_3$, VCl_3, $MoCl_3$, and $FeCl_3$ were dissolved in conc. HCl. The dissolved mixed metal chlorides were added to 1 g of the quaternary polycationic polymer (P-2VPC) dissolved in 50 mL water in round-flask and stirred for 2 h at 60°C. Then the formed solution was concentrated by evaporation and cooled to form precipitate which was allowed to stand for 1 h, filtered, washed with ether, and dried at 60°C to give the corresponding cationic polymer-mixed metal complexes (P-2VPCMs) (Table I).

TABLE I
Metal Analysis of Polymer-Metal-Complexes

Metal salt	Metal% found	Metal salt mol. found	Metal salt Mw (gm mol)
$(NH_3)_2PTCl_2$	0.44	3	900
$CoCl_26H_2O$	0.21	5	1189
$SnCl_2.2H_2O$	9.88	130	29328
VCl_3	0.1	2	314
$FeCl_3$	0.2	3	486
$MoCl_3$	1.04	16	3237
$LaCl_3.7H_2O$	0	1	371
Total			35825

TABLE II
UV Adsorption Maxima of Polymers and Their Complexes

Compound	λ_{max} (nm)
P-2VP	627.50, 294.0, 233.00, 217.50
P-2VPc	295.50, 288.0, 262.50, 246.50, 227.0, 221.0, 210.50
P-2VPMc	689.0, 262.00, 234.0, 224.0

Analytical measurements

Molecular weight. Molecular weight determination was done by gel permeation chromatography (GPC). The number average molecular weight, Mw, for Structure 1 was found to be 70.000.

Elemental analysis. Micro elemental analysis was performed in the Egyptian mineral resource authority by I.C.P. instrument. It was found the chlorine % in the quaternary polymer 10%, but in polymer-metal-complexes the chlorine % was calculated.

U.V spectra. UV spectra were recorded with a Perkin–Elmer S52 spectrophotometer. The quaternization and complex formation was confirmed by the appearance of new bands in UV spectra (Table II).[23]

The shift of the bands together with change in colors of the solutions denotes formation of polymer complexes.

FTIR spectra. IR spectra were recorded on Jusco FTIR 300E Fourier transform infrared spectrometer. It has been used to confirm the chemical reaction between P-4VPC with the mixed metal chlorides.[24]

There are characteristic bands at $\sim$ 1435 and 1473 cm^{-1} due to C—C stretching aromatic, and the peak at $\sim$ 3058 cm^{-1} is due to C—H stretching vibration of aromatic. However, the peak at $\sim$ 1296 cm^{-1} is due to C—N vibration aromatic tertiary for pyridine ring before quaternization and the peak at $\sim$ 1590 cm^{-1} is due to C=C aromatic. The vinyl chain was confirmed by band $\sim$ 3005 cm^{-1} due to C—H stretching and the peaks at $\sim$ 1703 and 992 cm^{-1} are due to C—C stretching and —CH2 bending, respectively. The band at $\sim$ 3046 cm^{-1} is due to presence of N—CH_2 aromatic quaternary ammonium salt. The peaks at $\sim$ 1296 cm^{-1} due to C—N vibration aromatic tertiary have almost disappeared. The strong band broad at $\sim$ 445 cm^{-1} is due to a single bridge compound polymeric association, due to the overlap of the *d*-orbital of the (N—Co) cobalt transitional element with the π-electron. The peak at $\approx$535 cm^{-1} stretching band vibration is due to N—Pt, and the peak at $\approx$ 410 cm^{-1} due to N—Fe. From all these facts, it is clear that there is a complexation between P-4VPC and the mixed metal chlorides.

Nuclear magnetic resonance NMR. Proton ^{1}H-NMR spectra measured in deuterated CH_3Cl containing tetramethyl silane as an internal standard was recorded on A Varian XL-GEM 200-MHZ. Instrument, chemical (g), all expressed in (PPM).[25]

At the NMR spectra, it is observed in Figure 1 and that there is a single absorption peak near 3.4 ppm due to the CH groups of the pyridine ring. The CH and CH_2 of the vinyl group are appear in the multiplet peak near 6.9 and 8.3 ppm, respectively, which confirm the Structure 1. The band of CH due to the benzene ring resulting of quaternization is near 2.5 ppm as shown in Figure 2.

X-ray diffraction. The structure of the samples was characterized using Brucker Axs-D8 Advance. It was found that the complexes have amorphous properties; due to the penetration and distribution of the mixed metals in the polymer.

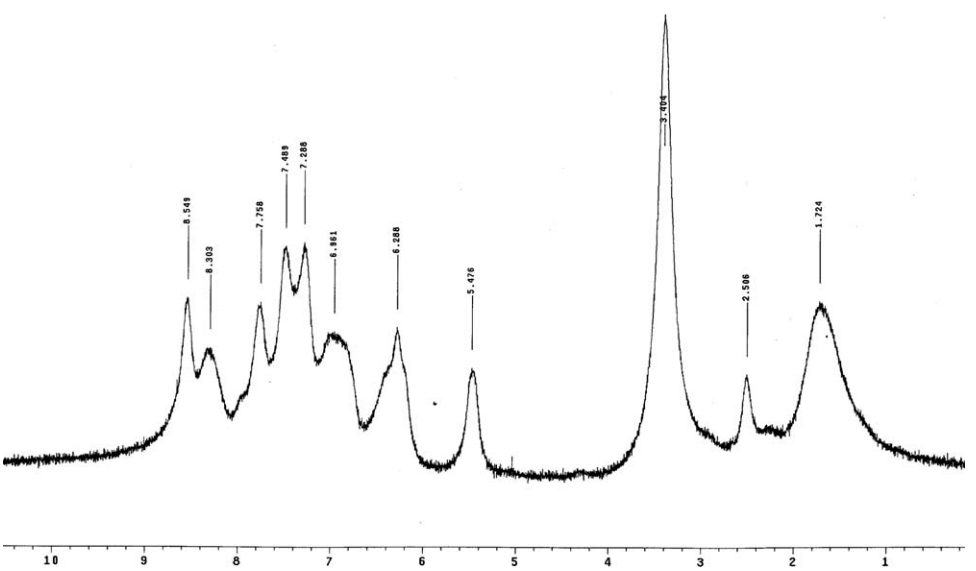


Figure 1 NMR Spectra of polymer (P-2VP).

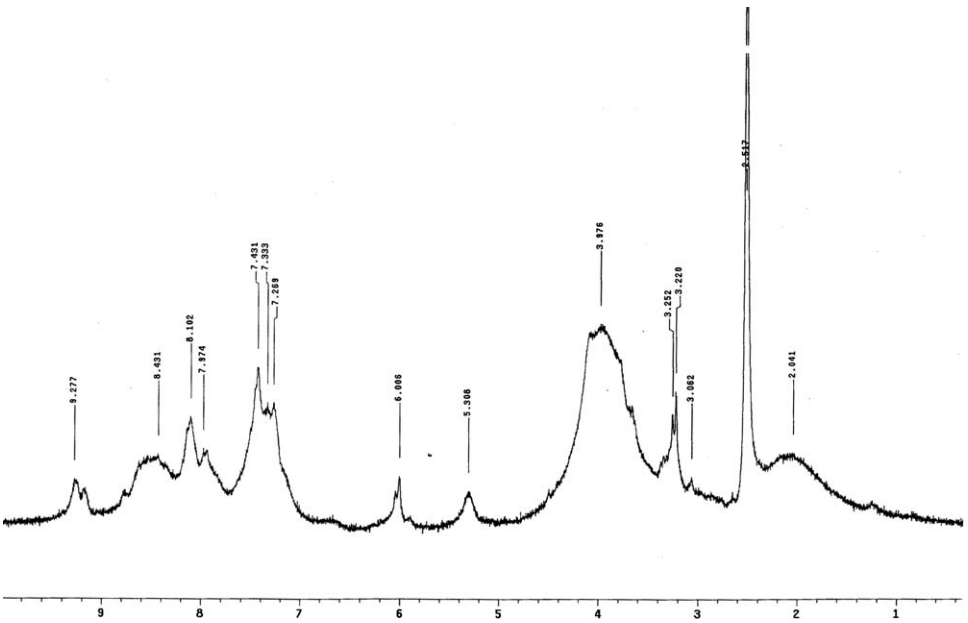


Figure 2 NMR Spectra of polymer complexes (P-2VPC).

Biology

In vitro study

In vitro *study in (EAC) cells.* A line of (EAC) cells used in this study had been kindly supplied from National Cancer Institute, Cairo Egypt, and maintained in female Swiss albino mice through weekly intraperitoneal (i.p.) transplantation of 2.5×10^6 tumor cells/mouse. EAC cells were obtained by needle aspiration with aseptic condition. The ascites fluid was diluted using a hemocytometer.[26]

In vitro study of this polymer complex (P-2VPCMs) was accomplished by mixing in a set of sterile test tubes 0.1 mL of tumor cells suspension, 0.8 mL RPMI 1640 media, and 0.1 mL of the tested compounds with different concentrations (0, 5, 10, 25, 50, 75, and 100 μg/tube) which corresponding to (0, 0.044, 0.089, 0.222, 0.445, 0.67, 0.89) 10^{-3} ηmol/tube. The test tubes were incubated at 37°C for 2 h and centrifuged. The cells were separated by the aspiration of supernatant, and stained with trypan blue. Percentage of Viable Cells (VC %) were calculated according to the method described[27] and survival percentage of tumor cells under different concentration of tested compound was calculated as follows:

$$\text{VC\%} = [\text{number of VC/total number of cells}]\ 100$$

In vitro *study in human cell lines.* In human cell lines application, the measurement of potential cytotoxicity by SRP assay was used according to the method of Shehen et al.[28] In brief, cells was plated in 96-multiwell plate (10^4 cells/well) for 24 h before treatment with the compound to allow attachment of cells to the wall of the plate. Different concentration of the tested compound ranged from (0, 5, 10, 25, 50, 75, and 100 μg/mL) which corresponding to (0, 0.044, 0.089, 0.222, 0.445, 0.67, 0.89) 10^{-3} ηmol/mL were added to the cell monolayer triplicate wells for each individual dose. Monolayer cells were incubated with the compound for 48 h at 37°C and in atmosphere of CO_2. After 48 h, cells were fixed, washed and stained with Sulfo-Rhodamine-B stain. Excess stain was washed with acetic acid and attached stain was recovered with Tris EDTA buffer. Color intensity was measured in an ELISA reader. The relation between surviving fraction and drug conc. is plotted to get the survival curve of each tumor cell line after the specified compound.

In vivo study

Animals. Female Swiss albino mice weighing 25–30 g obtained from (The holding company of biological products and vaccines, Cairo, Egypt) were used in this study. Mice were housed at a constant temperature (24°C ± 2°C) with alternating 12 h- light and dark cycles and fed standard laboratory food and water *ad libitum*.

Transplantation of solid tumor. Solid tumors were produced by intramuscular inoculation with 0.2 mL of EAC cells, which contained 2.5×10^6 viable EAC cells, in the right thigh of the lower limb of each mouse. Mice with a pulbable solid tumor mass (100 mm^3) that developed within 10 days after inoculation were used in the study. The change in tumor volume (TV) was measured at different time intervals during the experimental period (days 10, 13, 16, 20, 23, 27, 30, 34, 38, 41, and 44) using a Vernier

TABLE III
The Antitumor Activity of P-2VPMc on Ehrlich Ascites Carcinoma Cells Line

Concentrations of the new polymeric metal complex(P-2VPMc)		
μg/mL	ηmol/mL	Surviving fraction
0.0	0.0	0.98
5	0.000044	0.84
10	0.000089	0.70
25	0.000222	0.45
50	0.000445	0.18
75	0.00067	0.11
100	0.00089	0.05

caliper and calculated by the following formula according to Osman et al.[29] as follows:

$$\text{Tumor volume } (\text{mm}^3) = 0.52\ AB^2$$

where A is the minor axis and B is the major axis.

Preparation of polymer complex (P-2Vpcms) for biological application. Tested compound was dissolved in dimethylsulfoxide (DMSO) and given to mice by intraperitoneal injection (i.p.). Toxicity of the present compound was determined in normal mice (didn't bear tumor) and the LD50 was calculated and found to be 2 mg/kg body weight. The maximum tolerated dose (1.0 mg P-2VPMc/kg body weight) was administered twice a weak for a total of 11 injections during 34 days began after 10 days from tumor transplantation as described by Osman et al.[29]

Experimental design. At the beginning of the experiment, mice were divided into three groups. The 1st one was the untreated control group, the 2nd group was inoculated with solid Ehrlich carcinoma cells in left thigh of animals to form solid tumor, and the 3rd group was inoculated with Ehrlich cells as in 2nd group and treated with tested compound.

Groups are divided as followed (10 animals per group):

1. *Control:* Animals served as untreated control group.
2. *ESC:* Mice bearing Ehrlich Solid Carcinoma.
3. *Treated group:* Mice bearing Ehrlich Solid Carcinoma and injected with (P-2Vpmc).

Statistical analysis. Student's test was used for the evaluation of tumor volume (TV) and other data were analyzed using the same programmed analysis. The data were expressed as mean ± standard error. Differences were considered significant at $P < 0.05$ level.

RESULTS AND DISCUSSION

In vitro study

A tumorcidal effect of the present compound was evaluated in EAC cells line. The drug was applied at different concentration, 0, 5, 10, 25, 50, 75, and 100 μg/mL corresponding to (0, 0.044, 0.089, 0.222, 0.445, 0.67, and 0.89) 10^{-3} ηmol/mL, respectively, as presented in Table III and Figure 3. The present compound induced pronounced antitumor activity against EAC cells line recording 99.6%, 84.4%, 71.4%, 44.1%, 18.6%, 10.4%, and 4.2% of viable cells at previous concentrations with very low doses IC_{50} approximately about 0.00018 ηmol/mL.

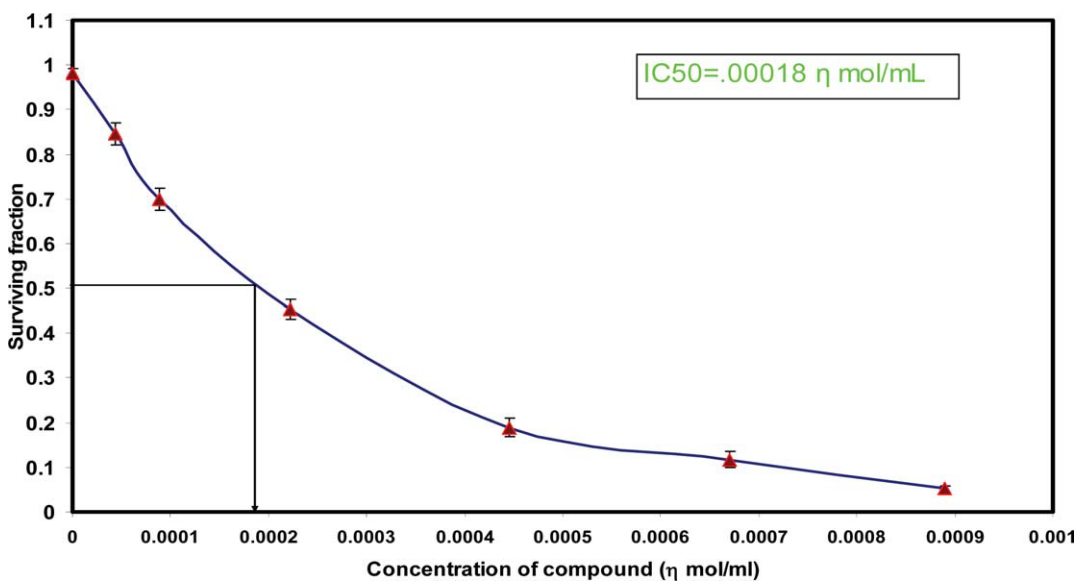


Figure 3 The antitumor activity of P-2VPMc (0–0.9 × 10^{-3}) ηM/mL on Ehrlich Ascites Carcinoma (2.5 × 10^6 cells/mL). The survival fractions measured using trypan blue technique. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

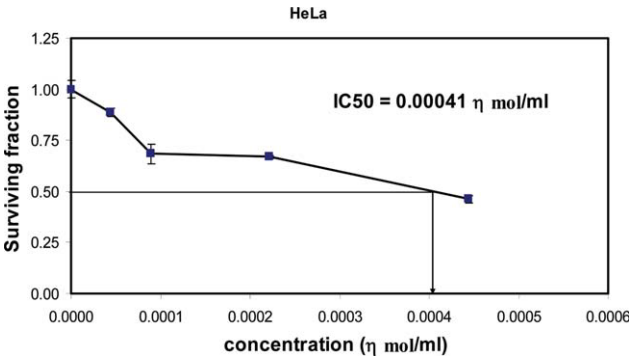


Figure 4 Represents the antitumor activity of P-2VPMc (0–0.5 × 10^{-3}) η*M*/mL was evaluated in Cervix carcinoma cell line (HeLa) (10^3 cells/mL). The survival fractions measured using MTT and detected by Elisa technique. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Human cell line

Cervix carcinoma cell line (HeLa). Antitumor effect of P-2VPMc was evaluated in Cervix carcinoma cell line (HeLa).The compound was applied with concentration of 0, 5, 10, 25, and 50 μg/mL, which corresponding to (0, 0.044, 0.089, 0.222, 0.445) 10^{-3} ηmol/mL and cytotoxic activity against Cervix carcinoma cell line (HeLa) was presented in Figure 4.

The data showed antitumor activity with IC_{50} 46.6 μg which corresponding to (0.41 × 10^{-3} ηmol/mL).

Colon carcinoma cell line (HCT116). Antitumor effect of P-2VPMc was evaluated in colon carcinoma cell line (HCT116). The compound was applied with concentration of 0, 25, 50, 75, and 100 μg/mL which corresponds to (0, 0.222, 0.445, 0.67, 0.89) 10^{-3} ηmol/mL. Cytotoxic activity against colon carcinoma cell line (HCT116) is presented in Figure 5. The data show antitumor activity with IC_{50} 98.8 μg/mL corresponding to (0.87 × 10^{-3} ηmol/mL).

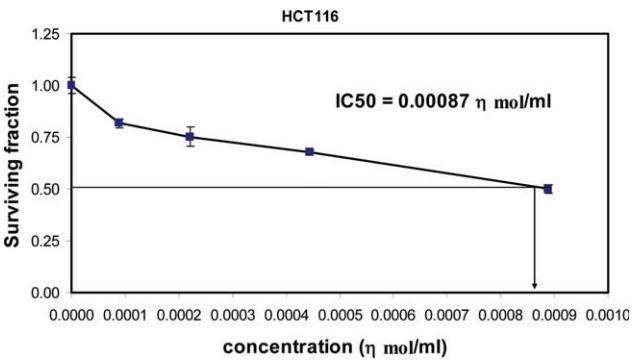


Figure 5 Represents the antitumor activity of P-2VPMc (0–0.5 × 10^{-3}) η*M*/mL was evaluated in colon carcinoma cell line (HCT116) (10^3 cells/mL). The survival fractions measured using MTT and detected by Elisa technique. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

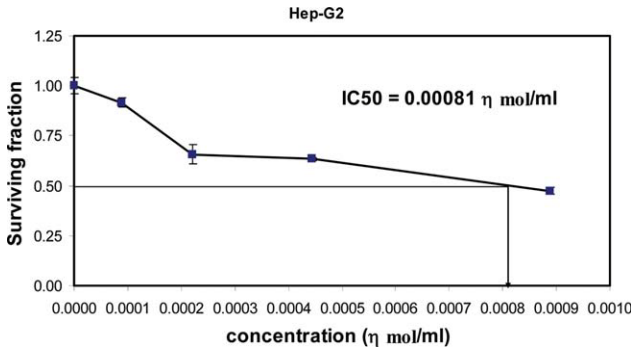


Figure 6 Represents the antitumor activity of P-2VPMc (0–0.5 × 10^{-3}) η*M*/mL evaluated in liver carcinoma cell line (Hep-G2) (10^3 cells/mL). The survival fractions measured using MTT and detected by Elisa technique. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Liver carcinoma cell line (Hep-G2). Antitumor effect of P-2VPMc was evaluated in liver carcinoma cell line (Hep-G2).The compound with was applied with concentration of 0, 25, 50, 75, and 100 μg/mL corresponding to (0, 0.222, 0.445, 0.67, 0.89) 10^{-3} ηmol/mL. Cytotoxic activity against liver carcinoma cell line (Hep-G2) is presented in Figure 6. The data show antitumor activity with IC_{50} 92 μg corresponding to (0.81 × 10^{-3} ηmol/mL).

In vivo study

Tumor growth delay in mice bearing EAC

When mice were inoculated with 2.5 × 10^6 cell/mouse EAC without further treatments, tumor volume gradually increased from (392.19 mm^3) at day 10 after tumor inoculation and reached to (4303.6 mm^3) at day 44 postinoculation as represented in Figure 7.

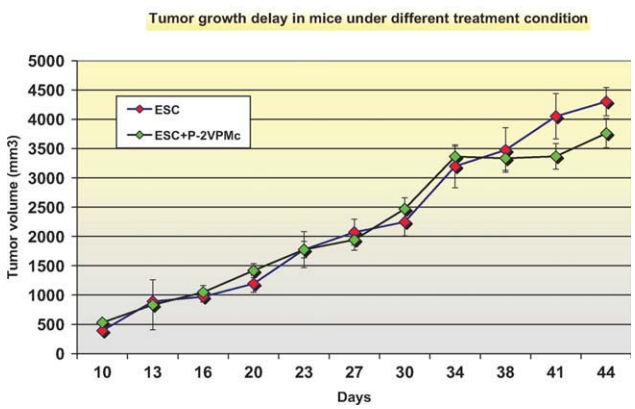


Figure 7 Tumor volume delay in group of mice ($n = 10$/group) bearing tumor without treatment (ESC) and group of mice bearing tumor and subjected to P-2VPMc with dose of 1 mg/Kg body weight (ESC+ P-2VPMc). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

On the other hand, when animals bearing Ehrlich tumor treated with metals complex P-2VPMc (1.0 mg/kg b.w) with repeated doses began 10 days after tumor transplantation and continued to the end of experiments. Tumor growth delay was recorded a quite linear with time. The measurement of tumor size delay was not statistically significance in the period from 10 to 38 days post-tumor inoculation, whereas significant delayed of tumor growth compared with control group injected with EAC without treatment were detected during the period ranging from 38 to 44 days post-tumor inoculation as shown in Figures 7, 8.

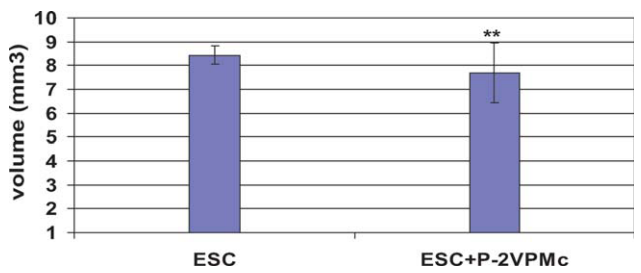


Figure 8 Change in tumor volume (mm^3) in group of mice (10 mice/group) bearing tumor without treatment (ESC) and group of mice bearing tumor and subjected to 1 mg/Kg body weight of P-2VPMc (ESC+ P-2VPMc) subjected 10 days after tumor inoculation and measured at the end of experiment (44) days. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Net final body weight in mice bearing Ehrlich carcinoma tumor

As shown in Figure 9, when animals treated with (P-2VPMC) using repeated doses beginning 10 days after tumor transplantation and continued to the end of experiments, significant increase of body weight were record compared with the control group.

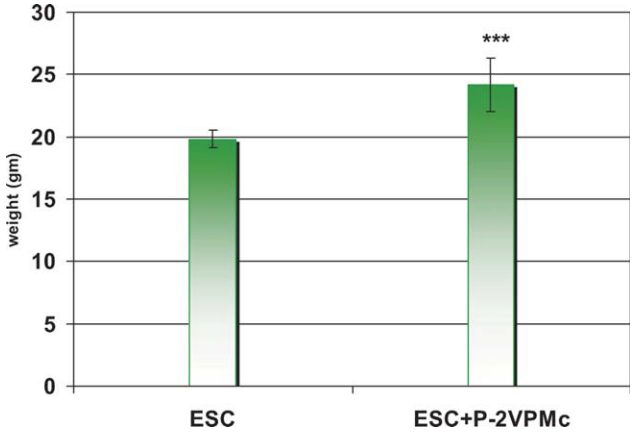


Figure 9 Net final body weight (gm) in group (10 mice/group) of mice bearing tumor without treatment (ESC) and group of mice bearing tumor and subjected to 1 mg/Kg body weight of P-2VPMc (ESC+ P-2VPMc) subjected 10 days after tumor inoculation and measured at the end of experiment (44) days. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

DISCUSSION

The present investigation, succeeded in synthesizing new compound bearing seven different metals. The structure of this novel compound was proved by accurate and standard methods. The degree of *N*-alkylation of poly vinyl pyridine (P-2VP) was 10% determined by chlorine content according to elemental microanalysis. Thus, the formation of 10% quaternary ammoniums moieties might present a significant role in the increase of positive charges. The antitumor activity of this compound was examined *in vitro* on different human cell lines and in experimental animals' cell line. The results reflect pronounced cytotoxicity of cationic poly2-vinylpyridine metal complexes (P-2VPMC) against EAC cells, and cell lines of Cervix carcinoma (HeLa), colon carcinoma (HCT116), and liver carcinoma (Hep-G2). Antitumor activity of the novel compound as applied on mice bearing Ehrlich solid carcinoma ESC cells, delays tumor growth compared with untreated animals and decreases tumor volume.

Interaction of metal ions with the water-soluble cationic polymers is mainly due to electrostatic forces and the formation of coordination bonds.[30] Other weak interactions may appear such as trapping metal ions in the bulk of the polymer phase. There has been great interest in studying the interactions between polyions and metal ions (counter ions) around the polyions.[31,32] The polymer P-2VP retained significantly the seven metals cations. From Table I, it seams that according to metal % found that remarkable counter ions binding specifications were noted by the increase in metal retention profile % in the following order:

$$Sn^{2+} > Mo^{3+} > Pt^{2+} > Co^{2+} > Fe^{3+} > V^{3+} > La^{3+}$$

In general, cationic polymers did not show interactions with metal ions because of the electrostatic repulsion between the charges.[33] The first interaction between a compound and the tumor cells is at the cell-wall level The basis for this interaction is in the strong attraction on positively charged compounds such as polycations. Since, polycations can form bond complexes or interact electro statically with the tumor cell wall; it is very probably that they will, together with the loaded metal ions, show antitumor activity. These polymer-metal complexes could pass through the membrane and interact with the tumor cell membranes, producing changes that would

finally cause cytotoxicity. It is possible that these complexes achieve cytoplasm bonding with important compounds such as DNA, avoiding replication of the tumor cells.

Another probable mechanism is that the polymer-metal complex would block the ion exchange channels, inhibiting tumor growth and producing cell death. One important aspect of the cytotoxic metal ion complexes is the presence of a positive charge close to the backbone, which increased the charge density and hence also increased their antitumor activity. The polycations may be placed near the cell wall or penetrate the cell wall blocking the ion channels producing a total blocking of the ionic transport and causing the death of tumor cells. Polymer as drug carriers has been investigated to achieve efficient delivery of anticancer agents to tumor cells. In most cases, the water soluble polymer metal complexes exhibit a cationic polyelectrolyte behavior in aqueous solution. For this reason they are potentially biologically active compounds. Since Ambrose and his co-workers[33] reported that tumor cells have a higher-negative surface charge than the components' cell, many different types of quaternary ammonium compounds have been screened for their antitumor activity[34] Moreover, Gastand and co-workers indicated that halogenic quaternary ammoniums induced a present growth inhibitory activity on different cancer cell lines.[36] Recently, Soug et al.[37] reported that DNA interact and its cross-linking action might be the key factor to inhibit transcription by quaternary ammonium compounds.

CONCLUSIONS

Cationic polymer metal complexes offer a significant role in the increase of positive charges which allow the polymer-metals complexes to penetrate the tumor cells, blocking the ion channels, producing a total blocking of ionic transport, DNA interact cross-linking action and causing tumor cell death.

From an industry viewpoint, one of the great challenges for drug delivery from cationic polymers is the design of genetic amphiphilic polymers that will form highly stable supramolecular assemblies. In the future, modeling studies focusing on the compatibility between different mixed metal ions and other important issues, such as long- term toxicity, control over the release rate, and the targeted delivery, should still be addressed before cationic polymer become the first choice for drug delivery.

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