Role of chelates in treatment of cancer

REVIEW ARTICLE
Year : 2007 | **Volume** : 44 | **Issue** : 2 | **Page** : 62-71

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DOI: 10.4103/0019-509X.35813

PMID: 17938483

» Abstract

Chelates are used in cancer as cytotoxic agent, as radioactive agent in imaging studies and in radioimmunotherapy. Various chelates based on ruthenium, copper, zinc, organocobalt, gold, platinum, palladium, cobalt, nickel and iron are reported as cytotoxic agent. Monoclonal antibodies labeled with radioactive metals such as yttrium-90, indium-111 and iodine-131 are used in radioimmunotherapy. This review is an attempt to compile the use of chelates as cytotoxic drugs and in radioimmunotherapy.

Keywords: Chelates, cytotoxic agent, radioimmunotherapy

How to cite this article:
Tripathi L, Kumar P, Singhai AK. Role of chelates in treatment of cancer. Indian J

Cancer 2007;44:62-71

How to cite this URL:
Tripathi L, Kumar P, Singhai AK. Role of chelates in treatment of cancer. Indian J Cancer [serial online] 2007 [cited 2013 Jan 19];44:62-71. Available from: http://www.indianjcancer.com/text.asp?2007/44/2/62/35813

» Introduction

Trace quantities of several metals are essential constituents of the human body. This is because the activity of many enzymes depends on these metal ions. Though the amount of metals present in human body is approximately 0.3% of the body weight, but excess of any metal is harmful to the body. With industrial and technological advancements, metal pollution in the atmosphere has been increasing fast. Increased proportion of trace metals in atmosphere have laid down some serious toxic effects. One of the major toxicity induced by these metals is their ability to behave as carcinogens. Metals belong to the category of pro-carcinogens. These are chemicals that require metabolic activation for becoming potent 'ultimate' carcinogen. They are activated by mixed oxidase of cytochrome P-450 system located in the microsomal components of the endoplasmic reticulum or the nucleus, thus forming pro-carcinogens. These substances become electron-deficient i.e. electrophiles and bind to electron-rich portions in DNA causing mutagenesis, finally leading to cancer, e.g. metals like nickel, chromium, etc. cause lung cancer. [1]

Chelation refers to the formation of cyclic complex by coordination of a metal ion with a polydentate ligand. The resulting cyclic compound formed is known as a chelate. This complex formation results in precipitation of the metal or formation of a stable and a soluble compound. Controlled removal of undesirable metal ions can be achieved by the use of appropriate chelating agents. [2] A considerable number of metal complex compounds are known to possess antitumor activity. It is assumed that they deactivate either the carcinogenic metal or the enzymes necessary for the rapid growth of both healthy and malignant cells. [1]

Chelates can be useful in malignancy by the following ways:

- As cytotoxic drugs
- As radioactive agents in imaging studies
- In radioimmunotherapy (RIT)

This review is an attempt to compile the use of chelates as cytotoxic drugs and in RIT.

» Chelates as Cytotoxic Agent

Many chelates are shown to possess cytotoxic activity. The most widely used complex in chemotherapy is cis-dichlorodiamine platinum(II). Some rhodium and iridium complexes and analogs of the active platinum complexes (platinum(IV) complexes: [Pt (dmgly) $2Cl_2$], [Pt (sar) $2Br_2$] and [Pt (dmgly) $2Br_2$]) show antitumor activity. The role of tungstosilicic acid (TSA) as antitumor and antiviral agent is well established. From the data available on anticancer activity of metal chelates, it is generalized that:

- Metals used in such type of complexes should belong to group VII of the periodic table, like palladium, platinum, ruthenium and rhodium.
- Chelating agent should be lipophilic and should closely resemble a nutrient to ease its penetration in malignant cell across the cell membrane.
- The metal complex should be in cis-form.
- It should be sufficiently kinetically stable, so that it remains unchanged during circulation through body fluids. [3]

The following section discusses some of the latest advancements in use of metal chelates as cytotoxic agents [Table 1 in PDF].

Ruthenium-based chelates

1. A series of mononuclear ruthenium complexes of the type [Ru(phen) $_2$ (nmit)]Cl $_2$ -(Ru1), [Ru(bpy) $_2$ (nmit)]Cl(2)-(Ru2), [Ru(phen)(2)(icpl)]Cl(2)-(Ru3), Ru(bpy)(2)(icpl)]Cl(2)-(Ru4){phen = 1, 10-phenanthroline; bpy = 2,2´-bipyridine; nmit = N-methyl-isatin-3 thiosemicarbazone, icpl = isatin-3-(4-Cl-phenyl)thiosemicarbazone}4-Cl-phenyl-(Ru10) and 4-Br-phenyl-(Ru11) show significant antitumor activity without adversely affecting the hematological profiles. They remarkably decreased the tumor volume, viable ascetic cell count and prolonged the lifespan of Ehrlich Ascetes Carcinoma (EAC) bearing mice. Tumor inhibition by the ruthenium chelates was followed by improvements in hemoglobin, RBC and WBC values. [4]
2. Bis(1,10-phenanthroline/2,2´-bipyridine) ruthenium(II) complexes contain 1-thiocarbamoyl-3,5-diphenyl-2-pyrazoline, 2-(3,5-diphenyl-4,5-dihydropyrazol-1-yl)-4-phenylthiazole, 2-hydroxyphenyl benzimidazole and benzoin thiosemicarbazone ligands coordinated with the metal through nitrogen, sulfur and oxygen atoms. They were shown to exhibit significant antitumor activity in EAC-bearing mice. [5]
3. New water-soluble bis(2-phenylazopyridine) ruthenium(II) complexes, namely 1,1-cyclobutanedicarboxylatobis(2-phenylazopyridine)ruthenium(II), alpha-[Ru(azpy)(2)(cbdca-O,O´)](1), oxalatobis(2-phenylazopyridine)ruthenium(II), alpha-[Ru(azpy)(2)(ox)](2) and malonatobis(2-phenylazopyridine)ruthenium(II), alpha-[Ru(azpy)(2)(mal)](3) display promising cytotoxicity with an activity comparable to that of cisplatin and even higher than the activity of carboplatin. Results further suggest that the activity of these compounds might not be influenced by the resistance mechanism that affects platinum anticancer agents. [6]
4. A novel class of ruthenium(III) complex of formulae K_2 [Ru(dmgly)Cl_4].$2H_2$ O, containing bidentate chelates N,N-dimethylglycine (dmgly) and additional chloro ligand, markedly inhibited the viability of non-confluent C6 cells and

confluent C6 cultures. Importantly, this complex was not toxic to primary rat astrocytes or macrophages, thus behaving as promising agent for developing drugs against astrocytomas. [7]

5. Fully coordinated 1,10-phenanthroline and 2,2´-bipyridine chelates of Ru(II) are lethal to lymphocytic leukemic cells. Lethal potency is greatest for Ru(II) chelates containing highly alkylated ligands. [8]
6. A group of four ruthenium chelates of the mixed hard/soft N-S donor ligand 2-formylpyridine (4-H/4-phenyl) thiosemicarbazone, namely bis[2-formylpyridine(phenyl)thiosemicarbazone]ruthe-nium(II)chloride], [2-formylpyridine(4-phenyl) thiosemicarbazone] Ruthenium(II)-trichloro (imidazole)ruthenium(III) monomethanolate, [2-formylpyridine(4-phenyl)thiosemicarbazone] dichloroimidazole ruthenium (II) and bis[2-formyl-pyridinethiosemicarbazone]ruthenium (II) perchlorate dihydrate were synthesized. Bis-chelates possessed greater cytotoxic properties toward primary tumor than the monochelates. The presence of two chelate rings around the ruthenium(II)/(III) acceptor center or the increase in the number of the soft (S) donor centers generate greater cytotoxic property in the corresponding ruthenium complexes. [9]
7. Organometallic ruthenium(II) complexes of the type [(eta(6)-arene)Ru(X)(Y)(Z)], where arene is benzene or substituted benzene; X, Y and Z are halide, acetonitrile or isonicotinamide or X, Y is ethylenediamine (en) or N-ethylethylenediamine were shown to have DNA binding properties; thus exhibiting anticancer activity. [10] These compounds show arene-nucleobase stacking and stereo-specific hydrogen bonding in guanine adducts. [11] They also induce cytostatic and cytotoxic effects on mammalian cancer cell lines through p53-dependent and p53-independent mechanisms. [12]

Copper(II)-based chelates

1. Substituted [phenylglyoxal bis(4-methyl-3-thiosemicarbazone)] copper(II) chelates show considerable cytotoxic activity. Electron-donating substituent enhanced the water solubility resulting in increased cytotoxicity. [13]
2. Anticarcinogenic activity of copper di-Schiff bases (two novel di-Schiff bases coordinated with active center analogs of Cu_2 Zn_2 superoxide dismutase) effectively catalyzes the production of hydroxyl radicals in the presence and absence of TPA-activated polymorphonuclear leukocytes, thus leading to reduction in tumor size, delay of metastasis and a significant increase in survival of the hosts. [14] In addition, Cu-67 chelates labeled with antibodies are developed and peptide linkers lead to modification of liver metabolism and improved tumor targeting of copper-67 labeled antibody fragments. [15]
3. Copper(II) complexes of N-1-isonicotinoyl-3-methyl-4-(p-hydroxybenzilidene)-2-pyrazolin-5-one (IMHBP) also show considerable activity against tumor. For the formation of these chelates, square-planar structure was assigned to the copper(II) complex. IMHBP acts as a neutral bidentate ligand in all these complexes by coordinating through the oxygen atoms of the amide group and carbonyl at position 5. Anions alone or anions and water molecules satisfy the other coordination sites. [16]

4. Copper chelates of synthetic curcuminoids show enhanced antitumor activity. Four synthetic curcuminoids, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione(curcumin-1); 1,7-bis(piperonyl)-1,6-heptadiene-3,5-dione(piperonyl curcumin); 1,7-bis(2-hydroxy naphthyl)-1, 6-heptadiene-2,5-dione(2-hydroxy naphthyl curcumin); 1,1-bis(phenyl)-1, 3, 8, 10-undecatetraene-5,7-dione(cinnamyl curcumin), and their copper(II) complexes were investigated for their possible cytotoxic and antitumor activities. Copper complexes of curcuminoids with a hydroxy group on the ring such as 2-hydroxy naphthyl curcumin were found to be most active. Copper complex of cinnamyl curcumin, which has an extended conjugation, showed considerable activity in increasing the life span (ILS = 78.6%) of ascites tumor bearing animals, whereas complex of piperonyl curcumin showed least antitumor activity. Copper chelates of curcuminoids showed a significant reduction ($P < 0.001$) of solid tumor volume in mice. [17]
5. Copper(II) complexes of N-Salicyloyl-N´-p-hydroxythiobenzohydrazide and N-benzoyl-N´-thiobenzohydrazide show significant inhibition of 3H-thymidine and 3H-uridine incorporation in DNA and RNA, respectively. In-vivo administration of these complexes resulted into prolongation of life span of Dalton's Lymphoma (DL) bearing mice. [18]
6. L-ascorbic acid inhibits the growth of mouse neuroblastoma and human endometrial carcinoma cells at concentrations greater than 100 mM. The antitumor activity of ascorbate can be greatly potentiated by combination with copper ions. The exposure of normal and tumor cells to the mixtures of ascorbate and copper chelates, especially Cu^{2+} -o-phenanthroline and Cu^{2+} -2,9-dimethyl-o-phenanthroline complexes resulted in the killing of a large proportion of cell populations. These copper chelates in combination with ascorbate showed different degrees of DNA-scission and antiproliferative activity. [19] In addition, mixed chelate copper-based anticancer drug, casiopeinas, was found to bind to DNA and degrade DNA and RNA in the presence of reducing agents, e.g. ascorbic acid. [20]
7. Exogenous copper in the form of chelate increases the growth of a copper-requiring tumor system. The growth promoting activity of exogenous copper in the B16 melanoma system involves both enhanced copper nutrition and concomitant alteration of host reactions to tumors. [21] This exception was observed in cuprous chelate of neocuproine ($NC\text{-}Cu^{+1}$) that enhanced tumorogenicity of s.c. tumors. [21],[22] But, cupric chelate of nitrilotriacetic acid ($NTA\text{-}Cu^{2+}$) inhibited pigmentation in s.c. tumors. [21] Further, it was concluded that the growth-promoting activity of $NC\text{-}Cu^{+1}$ on tumors is related to the oxidation state of copper in chelates and enhanced copper nutriture of tumors. [22]
8. Copper(II) complex of N´-[(2-hydroxy phenyl) carbonothioyl] pyridine-2-carbohydrazide inhibits the expression of c-Src, a non-receptor tyrosine kinase, which plays a significant role in the growth-mediated signaling pathway, thus showing cytotoxicity against the colon cancer cell line. [23]
9. Tris-(hydroxymethyl)phosphine copper(I) complexes containing the new bis(1, 2, 4-triazol-1-yl)acetate ligand showed in-vitro antitumor activity similar or better than that of cisplatin, the most used metal-based antitumor drug. Copper(I) complexes were able to overcome cisplatin resistance, supporting the hypothesis of a different mechanism of action compared to that exhibited by the reference drug. It is hypothesized that the cytotoxic activity of the new copper(I)

complex may be correlated to its ability to trigger paraptosis, a non-apoptotic mechanism of cell death. [24]

10. Cytotoxic effects are shown by copper(I) phosphane complexes of dihydridobis(3-nitro-1, 2, 4-triazolyl)borate, [25] copper(II) complex of N-Nicotinoyl-N´-o-hydroxythiobenzhydrazide, [26] copper(II)-doxorubicin chelate [27] and copper(I) complexes of 1,2-bis(diphenylphosphino) ethane (DPPE). [28] Copper(II) chelate of trans-bis(salicylaldoximato) showed cytotoxicity comparable to that of adriamycin by inducing cell cycle arrest and apoptosis. [29]

Zinc-based chelates

1. Substituted phenylglyoxal-bis-(4-methyl-3-thiosemicarbazone) zinc chelates behave as potential antineoplastic agents. Fourteen para-substituted phenylglyoxal-bis-(4-methyl-3-thiosemicarbazone) zinc chelates were shown to be cytotoxic against Ehrlich ascites tumor cells. Quantitative comparative analysis suggests that this selective action against the tumor cell system can be improved by substitution with groups having electron withdrawing and lipophilic nature. [30]
2. Beta-thujaplicin metal chelates act as promising anticancer agents. The cytotoxic effects of beta-thujaplicin and five kinds of metal chelates were examined on mouse melanoma B16BL6 cells by cell viability and lactate dehydrogenase (LDH) release assay. Beta-thujaplicin-zinc chelate and beta-thujaplicin-copper chelate had higher cytotoxic effects than beta-thujaplicin. In addition, the zinc chelate induced DNA ladder formation; as shown by the DNA fragmentation assay, suggesting that cell death induced by the zinc chelate is apoptosis. These chelates induce apoptotic cell death in various other tumor cell lines also. Thus, it is a potent antitumor agent for tumor cells including malignant melanomas. [31]

Gold(I)-based chelates

1. Some tetrahedral bis(di-phosphino) gold(I) chelates were found to be most active against P388 leukemia, M5076 sarcoma and B16 melanoma. Chelates were ionic, tetrahedral, bischelated gold diphosphine complexes of the type $[Au1(R_2 PYPR_{2'})_2]X$, where $Y = (CH_2)_2$, $(CH_2)_3$ or cis-CH = CH. The anion (X = Cl, Br, I, CH_3SO_3, NO_3, PF_6) had little effect upon activity. [32]
2. Antitumor agents gold-monophosphine and gold-diphosphine derivatives show activity against non-small lung, colon, CNS, renal, prostate, breast and ovarian cancer. [33]
3. Two newly synthesized gold(III) derivatives of methylsarcosinedithiocarbamate, containing a sulfur chelating ligand that is able to bind the metal center strongly acts as a potent anticancer agent against human acute myeloid leukemia cells by exerting antiproliferative and apoptotic effects. [34]
4. Six dinuclear gold(III) oxo complexes with bipyridyl ligands showed in-vitro antitumor effects against human ovarian carcinoma cell line due to antiproliferative effects and DNA- and protein-binding properties. [35]

5. Gold(III) derivatives of N,N-dimethyldithiocarbamate and ethylsarcosinedithiocarbamate proved to be much more cytotoxic in-vitro than cisplatin and rules out the occurrence of cross-resistance phenomena. [36]

Organocobalt(III)-based chelates

Organocobalt(III) chelates containing a sigma-bonded organyl group and a mixed tridentate ligand derived from a Schiff base are proposed for combined cancer therapy. These complexes generate free radicals due to the action of protons in physiological ranges of pH and temperature and hence are conceivably capable of selectively attacking a malignant neoplasm that is slightly acidic and can be made even more by introducing some means of intensifying glycolysis. [37]

Platinum-based chelates

Diamine platinum(II) complexes bearing an N,N-bis(phosphonomethyl) glycine ligand, [38] cis-bis-(2-chloroethylamine) platinum(II) and platinum(IV) complexes, [39] cis-diamine-1,1-cyclobutane dicarboxylato platinum(II) complexes show significant activity against leukemia and ovarian tumor. [40] Platinum(II) complexes of cyclopentanecarboxylic acid hydrazide [41] and platinum(II) and (IV) complexes of 1,3-diaminepropane and 1,4-diaminebutane were found active against ovarian tumor cells. [42] Platinum(II) complexes of 2-benzoylpyrrole [43] and octahedral (1,4-butanediamine) platinum(IV) complexes were found active against L1210 leukemia/B16 melanoma. [44] Lipophilic cis-dichloro-bis(2-aminohexadecanol) platinum(II) complex [45] and transamine dichlorodihydroxo platinum(IV) and tetrachloroplatinum(IV)/(II) complexes show significant activity against murine plasmacytoma and advanced stage human ovarian carcinoma. [46] The other platinum-based chelates reported to possess cytotoxic activity are platinum(II) complexes of diaminocarboxylic acids (D,L-2,3-diaminopropionic acid and D,L-2,4-diaminobutyric acid) and their ethyl-ester derivatives, [47] [2-substituted-4,5-bis(aminomethyl)-1,3-dioxolane] platinum(II) complexes, [48] [(2R)-aminomethylpyrrolidine](1,1-cyclobutanedicarboxylato) platinum(II) complexes [49] and polynuclear platinum(II) chelates with biogenic polyamines. [50] The platinum-based chelates were reported to have significant activity against leukemia and ovarian tumors. The reported mode of action is their ability to bind with DNA and inhibition of apoptosis.

Palladium- and platinum-based chelates

1. Cytotoxic action of palladium and platinum complexes [51] of 6-mercaptopurine and thioguanine - $Pd(MP)_2 \cdot 2H_2O$, $Pt(MP)_2 H_2O$ (MPH = 6-mercaptopurine), $Pt(AMP)_2 \cdot 3H_2O$ and $Pd_3(AMP)4Cl_2(AMPH) \cdot 4H_2O$ (AMPH = thioguanine) - showed marked antitumor activity against L-1210 lymphoid leukemia test system. [52]
2. Cis-dichloropalladium(II) complexes with diaminosuccinic acid and its diethyl esters show significant antitumor activity against human cancer cell lines. [53],[54]

Miscellaneous chelates

1. Cobalt and nickel chelates of 5-dimethylaminomethyl-2-thiouracil were found more active than the parent compound. Cobalt(II) complexes were found to be four coordinates, among which the bromo, iodo and nitrato complexes were polymeric. The nickel(II) isothiocyanato complex exhibited four-coordinate geometry and the remaining nickel(II) complexes were six coordinates. The order of activity was influenced by the chelate geometry and thermal stability. The activity increased with a decrease in coordination number and increase in thermal liability. [55]
2. Cobalt(II), copper(II), nickel(II) and zinc(II) complexes with furanylmethyl- and thienylmethyl dithiolenes [1,3-dithiole-2-one and 1,3-dithiole-2-thione] show prominent cytotoxic activity. [56]

» Chelates in RIT

Radioimmunotherapy [51] is a promising approach for treating metastatic breast cancer and non-Hodgkin's lymphoma (NHL). Approximately 55,400 new cases of NHL are diagnosed each year, with the overall prevalence of the disease now estimated to be 243,000. Based on the results of several clinical trials, the chimeric monoclonal antibody Rituximab has now been approved by the US-FDA for treatment of patients with relapsed or refractory, low-grade or follicular, B-cell NHL. Several other monoclonal antibodies in conjugated and unconjugated forms have been evaluated in the treatment of NHL [Table 2]. Ibritumomab, the murine counterpart to Rituximab, radiolabeled with 90Y (Zevalin), is presently being evaluated in clinical trials. The success of RIT is dependent upon the appropriate choice of antibody, isotope and chelator-linker. The Ibritumomab antibody targets the CD20 antigen. The antibody is covalently bound to the chelator-linker tiuxetan (MX-DTPA), which tightly chelates the isotope 90Y. To date, two Phase I/II Zevalin clinical trials have been completed in patients with low-grade, intermediate-grade and mantle cell NHL. The overall response rate was 64% in the first trial and 67% in the later trial. Phase II and III trials are ongoing. [57] Yttrium-90 Ibritumomab tiuxetan (IDEC-Y2B8) is a murine immunoglobulin G1 kappa monoclonal antibody that covalently binds MX-DTPA (tiuxetan), which chelates the radioisotope yttrium-90. The antibody targets CD20, a B-lymphocyte antigen Zevalin, which consists of a murine anti-CD20 monoclonal antibody (Ibritumomab), conjugated to the linker-chelator tiuxetan, which securely chelates 111-Indium for imaging and dosimetry and yttrium-90 for RIT. [58] Previous trials involving rituximab-naive patients have demonstrated excellent targeting of Zevalin to $CD20^{+}$ B-cell NHL with minimal uptake in normal organs. Zevalin treatment of rituximab-refractory follicular NHL patients at 0.4 mCi/kg resulted in acceptable estimates of absorbed radiation dose to organs, similar to those observed in other Zevalin-treated populations. [59]

90Y-labeled humanized LL2 (hLL2) monoclonal antibody (mAb) prepared with the

DOTA chelate represents an improved agent for RIT of NHL, with an in-vivo model demonstrating a large reduction in bone-deposited yttrium, as compared with 90Y-hLL2 agents prepared with open-chain DTPA-type chelating agents. Dosimetry suggests that this benefit will result in a substantial toxicologic advantage for a DOTA-based hLL2 conjugate. [60]

Initial clinical trials using 131-I radioimmunoconjugates and more recent studies employing 90Y have demonstrated objective, although transient, antitumor effects in heavily pretreated metastatic breast cancer patients with minimal toxicity. Antibodies targeting unique epitopes of epithelial glycoprotein mucin (MUC-1) on breast cancer cell surfaces that have been studied in patients include BrE-3 (murine and humanized) and m170 (murine). Both antibodies react with at least 90% of breast cancers. In these and other RIT trials, myelosuppression has been the dose-limiting toxicity. However, this toxicity has been successfully circumvented with the use of autologous peripheral blood stem cell transplantation, and recent clinical trials have escalated 90Y doses up to 50 mCi/m(2). [61]

» Conclusion

Chelates are inorganic agents that have good clinical effects in treatment of various types of cancer as cytotoxic agent and in RIT. It is suggested that they deactivate either the carcinogenic metal or the enzymes necessary for the rapid growth of both healthy and malignant cells. The cis-form of complex of metals belonging to group VII of the periodic table, such as palladium, platinum, ruthenium and rhodium, shows significant cytotoxic activity. The use of monoclonal antibodies labeled with radioactive metals, such as yttrium-90, indium-111 and iodine-131, in treatment of malignancies is an evolving field. New therapeutic approaches are rapidly emerging, and further research may help in designing more specific chelates that would spare the normal tissues, have less adverse effects and improve patient's quality of life.

» References

1. Kumar V, Cotran RS, Robbins SL. Robins Basic Pathology, 7th edn. Saunder; 2003. pp. 197-8.
2. Cotton FA, Wilkinson G, Murillo CA. Advanced Inorganic Chemistry, 7th edn. Manfred Bochmann Press; 2003. pp. 32-3.
3. Huhery JE, Keiter EA, Keiter RL. Inorganic Chemistry - Principles of Structure and Reactivity, 6th edn. Pearson Education; 2005. pp. 955-8.
4. Mazumder UK, Gupta M, Karki SS, Bhattacharya S, Rathinasamy S, Thangavel S. Synthesis, anticancer and antibacterial activity of some novel mononuclear Ru (II) complexes. Chem Pharm Bull (Tokyo) 2004;52:178-85. [PUBMED] [FULLTEXT]
5. Rathinasamy S, Karki SS, Bhattacharya S, Manikandan L, Prabakaran SG, Gupta M, et al. Synthesis and anticancer activity of certain mononuclear Ru (II) complexes. J Enzyme Inhib Med Chem 2006;21:501-7.
6. Hotze AC, Bacac M, Velders AH, Jansen BA, Kooijman H, Spek AL, et al. New cytotoxic and water-soluble bis-phenylazopyridine) ruthenium (II) complexes. J Med Chem 2003;46:1743-50. [PUBMED] [FULLTEXT]
7. Djinovic´ V, Momcilovic´ M, Grguric´-Sipka S, Trajkovic´ V, Mostarica Stojkovic´

M, Miljkovic´ D, et al. Novel ruthenium complex K2 [Ru(dmgly)Cl4]: 2H2O is toxic to C6 astrocytoma cell line, but not to primary rat astrocytes. J Inorg Biochem 2004;98:2168-73.
8. Shulman A, Laycock GA. Action of 1,10-phenanthroline transition metal chelates on P388 mouse lymphocyte leukaemic cells. Chem Biol Interact 1977;16:89-99. [PUBMED]
9. Bregant F, Pacor S, Ghosh S, Chattopadhyay SK, Sava G. Effects of some ruthenium chelates on MCa mammary carcinoma and on TLX5 lymphoma in mice. Anticancer Res 1993;13:1011-7. [PUBMED]
10. Morris RE, Aird RE, Murdoch Pdel S, Chen H, Cummings J, Hughes ND, et al. Inhibition of cancer cell growth by ruthenium (II) arene complexes. J Med Chem 2001;44:3616-21.
11. Chen H, Parkinson JA, Parsons S, Coxall RA, Gould RO, Sadler PJ. Organometallic ruthenium(II) diamine anticancer complexes: Arene-nucleobase stacking and stereospecific hydrogen-bonding in guanine adducts. J Am Chem Soc 2002;124:3064-82. [PUBMED] [FULLTEXT]
12. Gaiddon C, Jeannequin P, Bischoff P, Pfeffer M, Sirlin C, Loeffler JP. Ruthenium (II)-derived organometallic compounds induce cytostatic and cytotoxic effects on mammalian cancer cell lines through p53-dependent and p53-independent mechanisms. J Pharmacol Exp Ther 2005;315:1403-11. [PUBMED] [FULLTEXT]
13. Coats EA, Milstein SR, Holbein G, McDonald J, Reed R, Petering HG. Comparative analysis of the cytotoxicity of substituted (phenylglyoxal bis-methyl-3-thiosemicarbazone)) copper (II) chelates. J Med Chem 1976;19:131-5. [PUBMED]
14. Miesel R, Weser U. Anticarcinogenic reactivity of copper-di-schiff bases with superoxide dismutase-like activity. Free Radic Res Commun 2006;11:39-51.
15. Novak-Hofer I, Zimmermann K, Schubiger PA. Peptide linkers lead to modification of liver metabolism and improved tumor targeting of copper-67-labeled antibody fragments. Cancer Biother Radiopharm 2001;16:469-81. [PUBMED] [FULLTEXT]
16. Kuncheria J, Aravindakshan KK. Synthesis, characterization and antitumour studies of metal chelates of N1-isonicotinoyl-3-methyl-4-(p-hydroxybenzilidene)-2-pyrazolin-5-one. J Chem Technol Biotechnol 1993;57:43-7. [PUBMED]
17. John VD, Kuttan G, Krishnankutty K. Anti-tumour studies of metal chelates of synthetic curcuminoids. J Exp Clin Cancer Res 2002;21:219-24. [PUBMED]
18. Singh NK, Singh SB, Singh N, Shriviastav A. Synthesis, characterization and antitumor studies of N-aroyl-N¢-thioaroylhydrazines and their Co(II), Ni(II), Cu(II) and Zn(II) complexes. Biometals 2003;16:471-7. [PUBMED] [FULLTEXT]
19. Chiou SH, Ohtsu N. Antiproliferative and DNA-scission activities of L-ascorbic acid in the presence of copper chelates. Proc Natl Sci Counc Repub China B 1985;9:275-80. [PUBMED]
20. Rivero-Maller A, De Vizcaya-Ruiz A, Plant N, Ruiz L, Dobrota M. Mixed chelate copper complex, Casiopeina IIgly, binds and degrades nucleic acids: A mechanism of cytotoxicity. Chem Biol Interact 2007;165:189-99.
21. Pierson HF. Pharmacological perturbation of murine melanoma growth by copper chelates. Cancer Lett 1985;26:221-33. [PUBMED] [FULLTEXT]
22. Pierson HF. Enhancement of tumorigenicity of B16 melanoma in heterogenetic mice by administration of copper chelates. Cancer Treat Rep 1985;69:1283-91. [PUBMED]

23. Shrivastav A, Singh NK, Tripathi P, George T, Dimmock JR, Sharma RK. Copper(II) and manganese(III) complexes of N¢-[-hydroxy phenyl) carbonothioyl] pyridine 2-carbohydrazide: Novel therapeutic agents for cancer. Biochimie 2006;88:1209-16.
24. Marzano C, Pellei M, Colavito D, Alidori S, Lobbia GG, Gandin V, et al. Synthesis, characterization and in vitro antitumor properties of tris(hydroxymethyl)phosphine copper(I) complexes containing the new bis,2,4-triazol-1-yl)acetate ligand. J Med Chem 2006;49:7317-24. [PUBMED] [FULLTEXT]
25. Marzano C, Pellei M, Alidori S, Brossa A, Lobbia GG, Tisato F, et al. New copper (I) phosphane complexes of dihydridobis-nitro-1,2,4-triazolyl)borate ligand showing cytotoxic activity. J Inorg Biochem 2006;100:299-304. [PUBMED] [FULLTEXT]
26. Shrivastav A, Singh NK, Singh SM. Synthesis, characterization and antitumor studies of Mn(II), Ni(II), Cu(II) and Zn(II) complexes of N-nicotinoyl-N¢-o-hydroxythiobenzhydrazide. Biometals 2003;16:311-20. [PUBMED] [FULLTEXT]
27. Monti E, Paracchini L, Piccinini F, Malatesta V, Morazzoni F, Supino R. Cardiotoxicity and antitumor activity of a copper (II)-doxorubicin chelate. Cancer Chemother Pharmacol 1990;25:333-6. [PUBMED]
28. Sanghamitra NJ, Phatak P, Das S, Samuelson AG, Somasundaram K. Mechanism of cytotoxicity of copper (I) complexes of 1,2-bis (diphenylphosphino) ethane. J Med Chem 2005;48:977-85. [PUBMED] [FULLTEXT]
29. Elo H. Uniform potent activity of the antiproliferative metal chelate transbis (resorcylaldoximato) copper (II) against a large panel of human tumor cell lines in vitro. Chemotherapy 2004;50:229-33. [PUBMED] [FULLTEXT]
30. Coats EA, Milstein SR, Pleiss MA, Roesener JA, Sc hmidt J, McDonald J, et al. Comparative analysis of cellular respiratory inhibition by substituted phenylglyoxal-bis--methyl-3-thiosemicarbazone) zinc chelates. Farmaco Sci 1983;28:143-52.
31. Ferry G, Boutin JA, Hennig P, Genton A, Desmet C, Fauchθre JL, et al. A zinc chelator inhibiting gelatinases exerts potent in vitro anti-invasive effects. Eur J Pharmacol 1998;351:225-33.
32. Berners-Price SJ, Girard GR, Hill DT, Sutton BM, Jarrett PS, Faucette LF, et al. Cytotoxicity and antitumor activity of some tetrahedral bis(diphosphino)gold(I) chelates. J Med Chem 1990;33:1386-92. [PUBMED]
33. Caruso F, Rossi M, Tanski J, Pettinari C, Marchetti F. Antitumor activity of the mixed phosphine gold species chlorotriphenylphosphine-1,3 bis(diphenylphosphino)propanegold(I). J Med Chem 2003;46:1737-42. [PUBMED] [FULLTEXT]
34. Aldinucci D, Lorenzon D, Stefani L, Giovagnini L, Colombatti A, Fregona D. Antiproliferative and apoptotic effects of two new gold (III) methylsarcosinedithiocarbamate derivatives on human acute myeloid leukemia cells in-vitro. Anticancer Drugs 2007;18:323-32. [PUBMED] [FULLTEXT]
35. Casini A, Cinellu MA, Minghetti G, Gabbiani C, Coronnello M, Mini E, et al. Structural and solution chemistry, antiproliferative effects and DNA and protein binding properties of a series of dinuclear gold(III) compounds with bipyridyl ligands. J Med Chem 2006;49:5524-31. [PUBMED] [FULLTEXT]
36. Ronconi L, Giovagnini L, Marzano C, Betta F, Graziani R, Pilloni G, et al. Gold dithiocarbamate derivatives as potential antineoplastic agents: Design,

spectroscopic properties and in vitro antitumor activity. Inorg Chem 2006;44:1867-81.
37. Osinsky SP, Levitin IY, Bubnovskaya LN, Ganusevich II, Tsikalova MV, Istomin YP, et al. Modifying effect of organocobalt complexes on the tumour response to anticancer treatments. Anticancer Res 1997;17:3457-62. [PUBMED]
38. Galanski M, Slaby S, Jakupec MA, Keppler BK. Synthesis, characterization and in vitro antitumor activity of osteotropic diam(m)ineplatinum(II) complexes bearing a N,N-bis-(phosphonomethyl)glycine ligand. J Med Chem 2003;46:4946-51. [PUBMED] [FULLTEXT]
39. Khokhar AR, Xu Q, Newman RA, Kido Y, Siddik ZH. Synthesis, characterization and antitumor activity of new chloroethylamine platinum complexes. J Inorg Biochem 1992;45:211-9. [PUBMED] [FULLTEXT]
40. Swinnen LJ, Ellis NK, Erickson LC. Inhibition of cis-diammine-1, 1-cyclobutane dicarboxylatoplatinum(II)-induced DNA interstand cross-link removal and potentiation of cis-diammine-1,1-cyclobutane dicarboxylatoplatinum(II) cytotoxicity by hydroxyurea and 1-beta-D-arabinofuranosylcytosine. Cancer Res 1991;51:1984-9. [PUBMED] [FULLTEXT]
41. Kushev D, Gorneva G, Taxirov S, Spassovska N, Grancharov K. Synthesis, cytotoxicity and antitumor activity of platinum (II) complexes of cyclopentanecarboxylic acid hydrazide. Biol Chem 1999;380:1287-94. [PUBMED]
42. Alvarez-Valdes A, Perez JM, Lopez-Solera I, Lannegrand R, Continente JM, Amo-Ochoa P, et al. Preparation and characterization of platinum (II) and (IV) complexes of 1,3-diaminepropane and 1,4-diaminebutane: Circumvention of cisplatin resistance and DNA interstrand cross-link formation in CH1cisR ovarian tumor cells. J Med Chem 2002;45:1835-44.
43. Rubino S, Petruso S, Pierattelli R, Bruno G, Stocco GC, Steardo L, et al. Synthesis, characterization and cytotoxic activity of copper (II) and platinum (II) complexes of 2-benzoylpyrrole and X-ray structure of bis [2-benzoylpyrrolato(N,O)]copper (II). J Inorg Biochem 2004;98:2071-9. [PUBMED] [FULLTEXT]
44. Kwon YE, Whang KJ, Park YJ, Kim KH. Synthesis, characterization and antitumor activity of novel octahedral Pt (IV) complexes. Bioorg Med Chem 2003;11:1669-76. [PUBMED] [FULLTEXT]
45. Kokotos G, Theodorou V, Constantinou-Kokotou V, Gibbons WA, Roussakis C. Synthesis and in vitro cytotoxicity of lipophilic platinum (II) complexes. Bioorg Med Chem Lett 1998;8:1525-30. [PUBMED] [FULLTEXT]
46. Bloemink MJ, Prez JM, Heetebrij RJ, Reedijk J. The new anticancer drug [(R)-aminomethylpyrrolidine], 1-cyclobutanedicarboxylato) platinum(II) and its toxic S enantiomer do interact differently with nucleic acids. J Biol Inorg Chem 2006;4:554-67.
47. Moradell S, Lorenzo J, Rovira A, Robillard MS, Avils FX, Moreno V, et al. Platinum complexes of diaminocarboxylic acids and their ethyl ester derivatives: The effect of the chelate ring size on antitumor activity and interactions with GMP and DNA. J Inorg Biochem 2007;96:493-502.
48. Kim DK, Kim G, Gam J, Cho YB, Kim HT, Tai JH, et al. Synthesis and antitumor activity of a series of [2-substituted-4,5-bis(aminomethyl)-1,3-dioxolane] platinum (II) complexes. J Med Chem 2004;37:1471-85.
49. Bloemink MJ, Perez JM, Heetebrij RJ, Reedijk J. The new anticancer drug [R)-aminomethylpyrrolidine], 1-cyclobutanedicarboxylato) platinum (II) and its toxic S enantiomer do interact differently with nucleic acids. J Biol Inorg Chem

1999;4:554-67.
50. Teixeira LJ, Seabra M, Reis E, da Cruz MT, de Lima MC, Pereira E, et al. Cytotoxic activity of metal complexes of biogenic polyamines: Polynuclear platinum (II) chelates. J Med Chem 2004;47:2917 25. [PUBMED] [FULLTEXT]
51. Perk LR, Visser GW, Vosjan MJ, Stigter-van Walsum M, Tijink BM, Leemans CR, et al. (89)Zr as a PET surrogate radioisotope for scouting biodistribution of the therapeutic radiometals (90)Y and (177)Lu in tumor-bearing nude mice after coupling to the internalizing antibody cetuximab. J Nucl Med 2005;46:1898-906. [PUBMED] [FULLTEXT]
52. Visser GW, Perk LR, Vosjan MJ. Zr as a PET surrogate radioisotope for scouting biodistribution of the therapeutic radiometals Y and 7Lu in tumor-bearing nude mice after coupling to the internalizing antibody cetuximab. J Nucl Med 2006;46:1907-12.
53. Navarro-Ranninger C, Zamora F, Prez JM, Lpez-Solera I, Martanez-Carrera S, Masaguer JR, et al. Palladium (II) salt and complexes of spermidine with a six-member chelate ring: Synthesis, characterization and initial DNA-binding and antitumor studies. J Inorg Biochem 1992;46:267-79.
54. Matilla A, Tercero JM, Dung NH, Viossat B, Prez JM, Alonso C, et al. cis-dichloro-palladium (II) complexes with diaminosuccinic acid and its diethyl ester: Synthesis, molecular structure and preliminary DNA-binding and antitumor studies. J Inorg Biochem 1994;55:235-47.
55. Kamalakannan P, Venkappayya D. Synthesis and characterization of cobalt and nickel chelates of 5-dimethylaminomethyl-2-thiouracil and their evaluation as antimicrobial and anticancer agents. J Inorg Biochem 2002;90:22-37. [PUBMED] [FULLTEXT]
56. Chohan ZH, Shaikh AU, Supuran CT. In-vitro antibacterial, antifungal and cytotoxic activity of cobalt (II), copper (II), nickel (II) and zinc (II) complexes with furanylmethyl- and thienylmethyl-dithiolenes: [1, 3-dithiole- 2-one and 1,3-dithiole-2-thione]. J Enzyme Inhib Med Chem 2006;21:733-40. [PUBMED]
57. Wiseman GA, White CA, Witzig TE, Gordon LI, Emmanouilides C, Raubitschek A, et al. Radioimmunotherapy of relapsed non-Hodgkin's lymphoma with zevalin, a 90Y-labeled anti-CD20 monoclonal antibody. Clin Cancer Res 1999;5:3281s-6s. [PUBMED]
58. Witzig TE, White CA, Wiseman GA, Gordon LI, Emmanouilides C, Raubitschek A, et al. Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20(+) B-cell non-Hodgkin's lymphoma. J Clin Oncol 1999;17:3793-803. [PUBMED] [FULLTEXT]
59. Ke CY, Mathias CJ, Green MA. Targeting the tumor-associated folate receptor with an 111In-DTPA conjugate of pteroic acid. J Am Chem Soc 2005;127:7421-6. [PUBMED] [FULLTEXT]
60. Griffiths GL, Govindan SV, Sharkey RM, Fisher DR, Goldenberg DM. 90Y-DOTA -hLL2: An agent for radioimmunotherapy of non-Hodgkin's lymphoma. J Nucl Med 2003;44:77-84. [PUBMED] [FULLTEXT]
61. Richman CM, DeNardo SJ. Systemic radiotherapy in metastatic breast cancer using 90Y-linked monoclonal MUC-1 antibodies. Crit Rev Oncol Hematol 2001;38:25-35. [PUBMED] [FULLTEXT]

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