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CURRENT TOPIC • АКТУЕЛНА ТЕМА

# Platinum and ruthenium complexes as promising molecules in cancer therapy

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**SUMMARY**
Cancer is one of the most common fatal diseases in humans nowadays. About 20 million new cancer cases are expected in the next two decades worldwide. The development of new chemotherapeutic agents with improved properties is presently the main challenge in the medicinal chemistry.
Cisplatin was introduced to oncology in 1978 as first chemotherapeutic agent regarding its specific interaction with DNA, leading to its damage and causing the cell death. Since the first application of cisplatin in cancer therapy, there has been a growing interest in new metal-based compounds, in particular platinum and ruthenium complexes, with better anticancer activity and less side-effects compared to cisplatin. Carboplatin and oxaliplatin have shown promising action against some types of cancer, which are resistant to cisplatin. With the aim to overcome cross-resistance to these Pt(II) drugs, bioavailable platinum complexes (satraplatin and picoplatin) firstly found application as orally administered drugs, as well as some combined therapies of Pt(II) drugs (cisplatin, picoplatin) with specific resistant modulators. In recent years, novel polymer and liposomal formulations of platinum drugs (prolindac, lipoplatin, lipoxal, aroplatin) have been designed with strategy to improve drug delivery to target cancer cells and reduce toxicity. Complexes based on ruthenium have great potential to become leading candidates for the medical use in anticancer therapy. Some of these compounds have shown good anticancer activity, both *in vitro* and *in vivo* and two of them (KP1019 and NAMI-A) have passed clinical trials and given promising results.
**Keywords**: cancer therapy; platinum; ruthenium; metal complexes; anticancer activity

## INTRODUCTION

For thousands of years, many metal-based compounds have had application as therapeutic agents. Application of zinc and silver in healing of wounds and infection prevention dates back to ancient times [1]. Nowadays, cisplatin and auranofin, two important drugs based on platinum and gold metals, are widely used for the treatment of cancer and rheumatoid arthritis, respectively [2, 3]. Although platinum and ruthenium are non-biogenic elements, many of their complexes have shown potential application in cancer therapy [4, 5].

Due to their diversity, various metal complexes have shown therapeutic effect in treatment of many diseases [2–8]. Currently, complexes of Cu(II), Zn(II), Ni(II) and Co(II) have found application as antimicrobial and antiviral agents [6, 7]. Some polyoxometalate complexes of early transition metals (W, V, Mo) have also shown promising medical application due to their antimicrobial, antiacetylcholinesterase and anticancer effects [8, 9].

Immediately after cardiovascular diseases, cancer is the leading cause of death in humans worldwide [4]. In recent years, the focus of interest in medicinal chemistry has been application of metal complexes in treatment of malignant diseases [2–5]. Cancer therapy includes the surgical removal of tumor, radiation therapy and chemotherapy. Currently, diverse platinum complexes have found application in cancer therapy as chemotherapeutic agents, while many new synthesized complexes of gallium, gold, titanium, and ruthenium are intensively studied. Some ruthenium complexes attract special attention due to their promising results in clinical trials [5]. The main goal of this paper is to consider current knowledge of the platinum and ruthenium complexes related to anticancer therapy. Some of platinum complexes are clinically approved, while some of them including the ruthenium complexes have entered or may enter clinical trials soon.

## PLATINUM ANTICANCER COMPLEXES

Despite thousands of novel platinum complexes, only three of them are presently in clinical use in anticancer therapy: cisplatin, carboplatin, and oxaliplatin [2, 4, 5]. These drugs are administrated intravenously, and beside their good anticancer activity, they show some side-effects such as toxicity and acquired resistance which significantly limits their clinical application [2, 4, 5].

For nearly 40 years, cisplatin (cis-diamminodichloro)platinum(II), cis-$[PtCl_2(NH_3)_2]$ (Figure 1) has been the most widely used chemotherapeutics in oncology, and it is being administered to ca 50% of all cancer patients [4,

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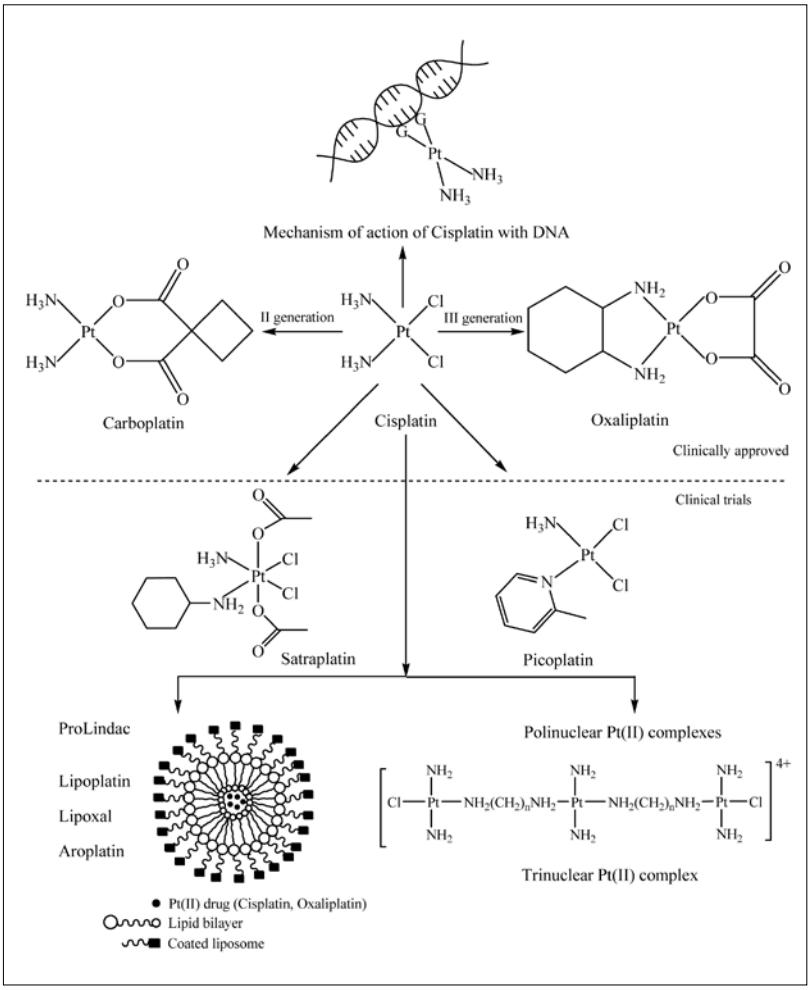


**Figure 1.** Development pathway of platinum drugs in cancer therapy

5, 10]. Cisplatin, whose trade name is Platinol, is a leading anticancer drug used in therapy of testicular, ovarian, lung, head, neck, and bladder carcinomas. It is square-planar complex whose activity is reflected by hydrolysis of chloride ligands in the cells. The complex binds to DNA across nitrogen N7 atoms of nucleobases (guanine and adenine) forming stable intrastrand links (1,2-GpG and 1,2-ApG) (Figure 1) [2, 4]. The DNA cross-linking leads to distort conformations, blocks replication, prevents transcription and triggers apoptosis. Unfortunately, cisplatin shows some disadvantages such as cumulative toxicity including nephrotoxicity, neurotoxicity, ototoxicity, nausea, hair loss, and treatment-induced resistance [2, 4, 5]. Resistance to cisplatin results from complex mechanisms at molecular and cellular levels including reduction in cellular accumulation, increased inactivation by SH-proteins, altered expression of regulatory genes, increased levels of DNA damage repair and increased adduct tolerance [11]. These drawbacks encourage the development of novel cisplatin analogues with improved properties.

Carboplatin (cis-diammine(1,1-cyclobutanedicarboxylato)platinum(II), whose trade name is Paraplatin, is the second generation of Pt(II) drugs which, compared to cisplatin, has a bidentate dicarboxylate ligand instead of two labile chloride ligands (Figure 1). Higher stability of this complex causes consequently lower toxicity leading to a long-lasting effect. To be more precise, carboplatin needs more time to reach the target biomolecules (retention half-life of 30 hours) compared to cisplatin (1.5–6 hours), forming the same type of DNA adducts [2, 4, 5, 12]. Carboplatin has showed lower toxicity than cisplatin, an insignificant nephrotoxicity in particular, being effective against some types of cancer that are not sensitive to cisplatin [2, 4, 5, 12].

Oxaliplatin[oxalato(2-)-O,O'] [1R,2R-cyclohexanediamine-N,N'] platinum(II), whose trade name is Eloxatin, was the first drug to successfully overcome resistance to cisplatin due to the replacement of two amine ligands in cisplatin with stable bidentate ligand, (1R,2R) -cyclohexane-1,2-diamine (R,R-DACH) (Figure 1) [2, 4, 5, 13]. Oxaliplatin is a third generation of Pt(II) compounds whose high cytotoxicity and noncross-resistance can be attributed to voluminous, hydrophobic DACH ligand that interacts significantly with major groove of DNA and prevents repair pathway. High cytotoxicity of oxaliplatin to cancer cells is caused by formation of more damaging Pt-DNA adducts, mainly intrastrand 1,2-GpG linked [13].

There are four platinum complexes that currently have importance in advance clinical trials due to either their oral bioavailability (satraplatin and picoplatin) [14] or to improved polymer and liposomal drug delivery systems with lower toxicity (prolindac and lipoplatin) [15–18].

Satraplatin (bis-(acetato-O)amminedichloro(cyclohexylamine)platinum(IV), whose trade name is Orplatna, is a Pt(IV) octahedral complex with two axial monodentate acetate ligands, which enable its bioavailability as the first platinum oral administrated therapeutic agent (Figure 1) [4, 5, 14]. Lower toxicity and lower side effects of satraplatin come from less activity of Pt(IV) compared to Pt(II) complexes (cisplatin, carboplatin, oxaliplatin), its rapid absorption through gastrointestinal mucosa and reduction to at least six different Pt(II) metabolites, out of which cis-amminedichloro-(cyclohexylamine)platinum(II) is the most abundant [14]. This metabolite is bound to DNA by 1,2-intrastrand cross-links inducing apoptosis. All metabolites of satraplatin mainly bind to plasma proteins with negligible percentage of their decomposition to free platinum. Satraplatin overcame Phase III clinical trials showing significant anticancer activity to several platinum-resistant human cancer cell lines, including lung, ovarian, and prostate cancer [14].

Picoplatin(cis-(amminedichloro-2-methylpyridine) platinum(II) is an analog of cisplatin, where an ammine ligand is substituted with bulkier 2-methylpyridine re-

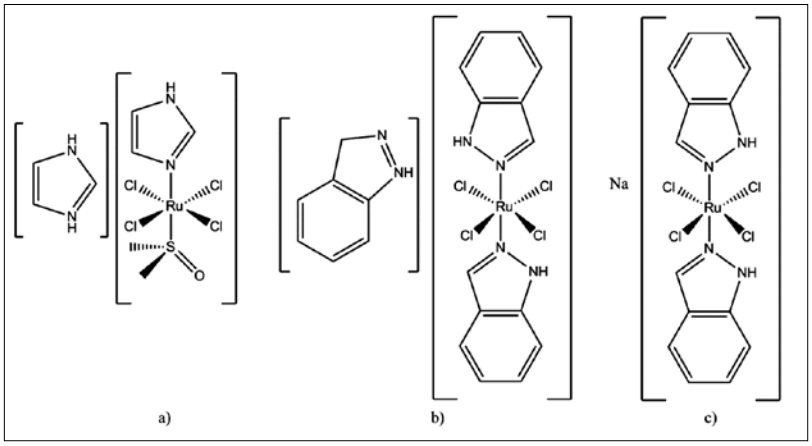


**Figure 2.** NAMI-A (a), KP1019 (b) and KP1339 (c)

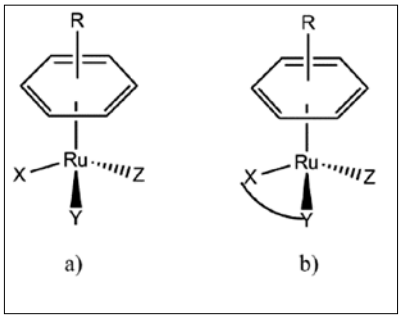


**Figure 3.** General formula of organoruthenium complexes (a) and (b)

sponsible for steric shielding around platinum(II) center (Figure 1). This ligand prevents nucleophilic attacks of SH-proteins such as glutathione, and overcomes cisplatin resistance. To be more precise, picoplatin is designed in such a way to lead slower substitution kinetics due to glutathione competition through dissociative thiol substitution, instead of an associative mechanism like in cisplatin [5, 14]. Lower toxicity of picoplatin compared to cisplatin has been confirmed, particularly regarding nephro- and neurotoxicity, showing anticancer activity in the cisplatin resistance cancer lines such as lung, colorectal, and prostate cancers. Picoplatin treatments in combination with 5-fluorouracil (FU) and leucovorin for colorectal cancer, as well as in combination with docetaxel for prostate cancer, have reached phases I and II of clinical trials [5].

In recent years, in order to improve delivery of Pt(II) drugs, reduce toxicity and get better drug tolerance profile, new liposomal and polymer based drug delivery systems have been developed [15–18]. Pt(II) drugs encapsulated in a liposome or in specially designed polymer have found various advantages over Pt(II) drugs: they have better solubility, biocompatibility, better membrane permeability, drug stability within delivery systems, and higher retention time.

Prolindac is a drug-delivery system of oxaliplatin, encapsulated in hydrophobic biocompatible polymer hydroxypropylmethaacrylamide (HPMA), which, compared to oxaliplatin, have shown higher activity and lower toxicity (neurotoxicity) in various human cancers in phase II of clinical trials (Figure 1) [4, 5, 18]. Clearly enough, HPMA polymer has the role of delivery system of oxaliplatin to the target cancer cells where it undergoes decomposition due to the low pH value within the cancer cells [4]. Prolindac has shown significant anticancer activity for treatments of breast, ovarian, lung, and prostate cancers, especially for metastatic melanoma and ovarian cancer.

Liposomal formulations of cisplatin (lipoplatin, TRX-20), oxaliplatin (lipoxal), and an oxaliplatin analogue (aroplatin) have been created recently (Figure 1) [16, 17]. Lipoplatin has overcome phases I, II, and III of clinical trials showing remarkable anticancer properties due to small sized particles (90 to 130 nm), causing easier cross through cell membranes and consequently fewer side effects, particularly negligible nephrotoxicity, ototoxicity and neurotoxicity. Lipoplatin has high anticancer activity against metastatic tumors, particularly prostate, colon, gastric, and lung cancers [16]. Cisplatin encapsulated in cationic lipid polyethylene glycol-coated liposomes (TRX-20) has shown increased delivery time to target molecules, high bioavailability, and anticancer activity in treatments of some metastatic cancers, especially refractory prostate, colon, gastric and lung cancers [5].

In recent years, polinuclear bridged platinum complexes (Figure 1) have also attracted particular attention, since they have two or three platinum centers which are able to bind at several sites along the DNA helix, causing more severe DNA damage and being more effective against cancer cells as compared to cisplatin analogues [4, 15].

## RUTHENIUM ANTICANCER COMPLEXES

Non-platinum complexes based on ruthenium, gold, palladium or titanium, have been investigated in the quest for compounds with lower toxicity and higher selectivity compared to cisplatin. Ruthenium compounds have specific physicochemical properties that make them promising as anticancer agents: (a) activation by reduction (from Ru(III) to Ru(II)), (b) different coordination geometry compared to platinum, and (c) favorable ligand-exchange kinetics [19].

In the last two decades, many papers have documented the great anticancer potential of ruthenium complexes, both *in vivo* and *in vitro*. Three of the most investigated ruthenium drugs are NAMI-A ($[H_2Im][trans\text{-}RuCl_4(DMSO)(Im)]$) (Figure 2a), KP1019 (*trans*-[tetrachloro*bis*(1*H*-indazole)ruthenate(III)]) (Figure 2b), and sodium derivative of KP1019, KP1339 (Figure 2c). All three compounds have entered Phases I and II of clinical trials.

NAMI-A has significant efficacy in inhibiting tumor metastasis [20], while this compound, *in vitro,* has low potency in terms of cytotoxicity towards cancer cells. The mode of action of NAMI-A is not clear and many papers documented potency of this complex for binding to DNA and RNA [20, 21]. KP1019 synthesized by the Keppler group entered clinical trials [22], but the main problem in the

clinical investigations for KP1019 is its low solubility under physiological conditions. With better solubility, sodium salt KP1339, is currently undergoing clinical trials [23].

Arene ruthenium(II) complexes, general formula [($\eta^6$-arene)Ru(X)(Y)(Z)], where X and Y can be two monodentate or one bidentate ligand (Figure 3a and 3b), were first investigated in the field of anticancer compounds by Sadler and Dyson [24]. The presence of the chelating ligand provides the additional stability of the whole structure. Monodentate ligand Z is a good leaving group (in the most cases halogen). These complexes showed piano stool geometry, where arene is benzene (ben) or methylisopropyl benzene (cym) or biphenyl (bip) or dihydroanthracene (dha) which provide hydrophobicity of molecule and ensure the entry of the complexes in the cell [24]. It was shown for some complexes of this type that the cytotoxicity increases with the arene moiety size because of the greater ability of the arene to intercalate into DNA. Also, aromatic part stabilizes ruthenium center in oxidation state + 2. For the complexes general formula, [($\eta^6$-arene)Ru(en)Cl]$^+$, (en = etylendiamine) it has been shown that cytotoxicity increases in the series arene: benzene <p-cymene <bipheny l<dihydroanthrancene<tetrahydroantracene [25].

## CONCLUSION

Cisplatin has so far been the most used chemotherapeutic agent, regardless of its disadvantages such as cumulative toxicity and development of cancer cell resistance. With aim to overcome these side effects, many novel platinum complexes have been synthesized and studied. Regrettably enough, only about 20 out of thousands of new platinum compounds have reached clinical trials. After development of second (carboplatin) and third (oxilplatin) generation of platinum(II) drugs, by replacement of chloride and ammine ligands in cisplatin respectively, further research has led to polymer or liposome formulations of platinum(II) drugs and new dinuclear and oligonuclear platinum complexes. In recent years, ruthenium complexes have had a huge potential for application in cancer therapies, being the only non-platinum compounds that have entered clinical trials.

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# Комплекси платине и рутенијума – обећавајући молекули у терапији карцинома

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**САЖЕТАК**

Карциноми су један од водећих узрока смртности светске популације. Процењује се да ће у наредне две деценије око 20 милиона људи у свету имати постављену дијагнозу карцинома. Главни задатак медицинске хемије јесте добијање нових хемиотерапеутских агенаса са бољим антиканцерским својствима.

*Cisplatin* се примењује у онкологији од 1978. године, као први хемиотерапеутски агенс који специфично долази у интеракцију са молекулима ДНК, доводи до ДНК оштећења и узрокује ћелијску смрт. Од када је цисплатин нашао примену у терапији карцинома, расте интересовање за новим једињењима који садрже метале, а посебно за комплексима платине и рутенијума, са већом антиканцерском активношћу и мање нежељених дејстава у поређењу са цисплатином. *Carboplatin* и *oxaliplatin* су се показали ефикасним у третману неких типова карцинома резистентних на цисплатин. Са циљем превазилажења резистентности на ове *Pt*(II)-лекове, најпре су комплекси платине (*satraplatin* и *picoplatin*) нашли примену као први орални лекови, као и комбиноване терапије појединих *Pt*(II)-лекова (*cisplatin*, *picoplatin*) са специфично резистентним модулаторима. Последњих година дизајниране су нове полимерне и липозомалне формулације лекова платине (*prolindac*, *lipoplatin*, *lipoxal*, *aroplatin*) због боље циљне испоруке лека до туморских ћелија и њихове смањене токсичности. Комплекси рутенијума имају велику могућност примене у терапији карцинома. Ова једињења показују добру антиканцерску активност, како *in vitro*, тако и *in vivo*, а два комплекса рутенијума (*KP*1019 и *NAMI-A*) показала су добре резултате у клиничким испитивањима.

**Кључне речи**: терапија карцинома; платина; рутенијум; метални комплекси; антиканцерска активност