Chapter 1

Nanoformulation as a Tool for Improve the Pharmacological Profile of Platinum and Ruthenium Anticancer Drugs

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Additional information is available at the end of the chapter

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Abstract

Cisplatin and analogs are used for the treatment of some type of cancers in combination with organic cytostatics. Also, two ruthenium (III) complexes are in clinical trials as anticancer drugs. In order to overcome toxicity and resistance associated with this therapy and/or enhance stability, a large variety of formulations based on organic, inorganic, or hybrid matrix were developed and tested both *in vivo* and *in vitro*. The best results were obtained for systems properly functionalized in order to enhance the metal content and/or to specific target the tumor tissue through overexpressed receptors.

Keywords: platinum, ruthenium, anticancer metal-based drugs, nanoformulations, conjugation

1. Introduction

Despite the use of metal compounds in empirical medicines since the ancient civilization time of Mesopotamia, Egypt, India, and China, the pharmacological bases of their therapeutic action were just began to be understood in the last 50 years [1].

A milestone in the development of inorganic medicinal chemistry was represented by the serendipitously discovery of the anticancer agent cisplatin (Platinol) [2], which opened the gate of extensive and rigorous research for anticancer metal-based drugs. Cisplatin quickly became a successful antitumor agent, but over time, its severe side effects and installation of resistance led to the orientation of research toward finding new cisplatin analogs. Thus, "the

second-generation platinum drugs" (e.g., carboplatin) with improved toxicological profiles and "the third-generation drugs" (e.g., oxaliplatin) overcoming cisplatin resistance have been developed [3].

Having in view the systemic administration, the patients experienced severe symptoms since cisplatin and its analogs, carboplatin and oxaliplatin, were introduced in cancer therapy. Moreover, the intrinsic or acquired resistance and the fact that many cancers are insensitive to platinum-based drug therapy started an assiduous search for formulations that are able to deliver these drugs with reduced toxicity but with a similar or even enhanced cytotoxic profile [4–9].

A promising strategy able to overcome most of the above limitations consists in embedding either the original drug or a precursor in a proper matrix that is able to release a high amount of active species at target site. As result, several formulations based on organic, inorganic, or hybrid materials were designed. Among organic-based materials, a large variety of lipids, polymers, or mixed species were developed as platinum- and ruthenium-based drug carriers while magnetite, gold, graphene, and silica were studied as inorganic-based materials for the same purpose. Moreover, hybrid materials based on functionalized graphene, gold, iron oxides, silica, or polinuclear complexes and polysilsesquioxanes were studied in order to facilitate the delivery of these drugs [6–9].

Beyond improving solubility and reducing toxicity, a main challenge of these formulations was to increase their selectivity for tumor cells in order to achieve an optimum pharmacological profile. The first formulation developed by platinum-based drugs embedding through noncovalent interactions generated systems with a low loading capacity. A proper functionalization of the embedding matrix with Pt(II) drugs or Pt(IV)/Ru(III) prodrugs and/or with a responsive stimulus or a targeting moiety provided species with an increased cytotoxicity [6–9].

A large variety of encapsulation matrices and conjugations were developed, and formulations exhibit a promising cytotoxicity against either multidrug resistant or platinum insensitive cancer cells.

2. Anticancer metallodrugs

Apart from extensive research undertaken in the field of platinum complexes, other metals or other therapeutic strategies have attracted attention in order to reduce the side effects, to mitigate the resistance, and to achieve the oral administration.

The anticancer metallodrugs known at this time belong to three main classes:

- anticancer therapeutics
- therapeutic radiopharmaceuticals
- photochemotherapeutic metallodrugs [10].

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Numerous *chemotherapeutic metallodrugs* developed in the last 4 decades are based on a large variety of metals: Pt, Ru, Au, Sn, Al, Ga, In, Ti [11–16]. Among the metal-based compounds, complexes of platinum (Pt(II) and Pt(IV)), ruthenium (Ru(II) and Ru(III)), gold (Au(I) and Au(III)), and titanium (Ti(IV)) are the most studied [13].

Therapeutic radiopharmaceuticals include a β-emitting radionuclide (^{89}Sr, ^{90}Y, ^{153}Sm, ^{213}Bi) or a α-emitting radionuclide (^{223}Ra). In general, α- and β-(electrons) emitters are used in radiotherapy, while β+ (positrons) and γ-emitters are used in radiodiagnosis [14].

Utilization of *photochemotherapeutic metallodrugs* is based on the photodynamic therapy (PDT). In PDT, a photosensitizing agent is delivered in tumor cells, which are activated with light, generating cytotoxic singlet oxygen. Starting to observation that Photofrin, a haematoporphyrin derivative is a strong chelator, forming a complex with Zn^{II} *in vivo*, some photochemotherapeutic metallodrugs have been developed [15].

The main platinum-based anticancer drugs currently used in clinic are presented in **Table 1**, while the emerging platinum- and ruthenium-based anticancer agents are listed in **Table 2**.

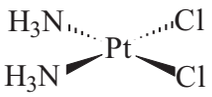
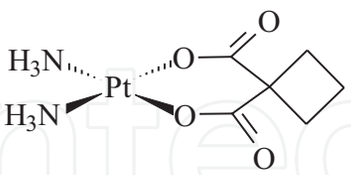
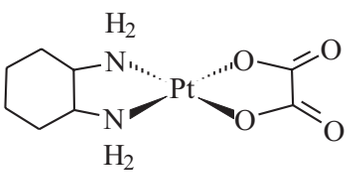
Metal	Compound	Indications	Commercial names
Chemotherapeutic metallodrugs			
Pt	**Cisplatin** (*cis*-diamminedichloroplatinum (II)) 	Testicular, ovarian and colorectal cancer	Cisplatin Platosin Sinplatin Platinol
	Carboplatin (*cis*-diammine (1,1-cyclobutanedicarboxylatoplatinum (II)) 		Carboplatin Paraplatin
	Oxaliplatin ((1*R*, 2*R*)-(N, N'-1,2 diamminecyclohexan)-(O-O')-etandioatoplatinum (II) 		Oxaliplatin Eloxatin

Table 1. Platinum-based anticancer drugs currently used in clinic.

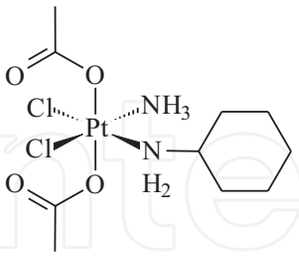
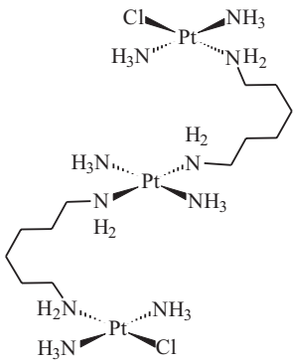
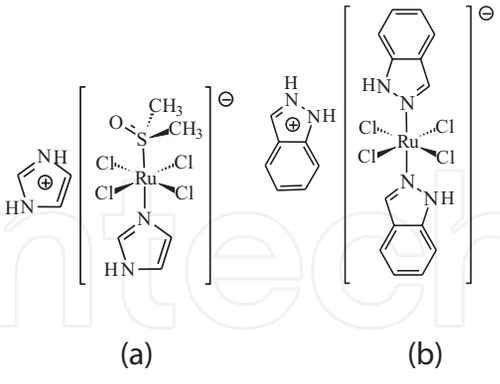
Metal	Compound	Uses/Comments
Chemotherapeutic metallodrugs		
Pt	**Pt^{IV}: Satraplatin (JM 216)** 	Satraplatin: first orally bioavailable platinum drug; extended activity spectrum; reduced resistance. Investigated in phase III clinical trials for hormone-refractory prostate cancer [14]. This compound are not only multinuclear but also polycationic, breaking the traditional design rules of platinum complexes. Has undergone phase II clinical trials for metastatic small cell lung cancer [15].
	Pt^{II}: BBR3464 	
Ru	**Ru^{III}**: [H_2im][***trans***-$RuCl_4$(DMSO-S)(Him)] **NAMI-A** Imidazolium *trans*-[tetrachloro (dimethylsulfoxide) (imidazole) ruthenate(III)] (a); **Ru^{III}**: [H_2ind][***trans***-$RuCl_4(Hind)_2$] **KP1019** Indazolium *trans*-[tetrachlorobis(1Hindazole) ruthenate(III)] (b) 	NAMI-A (Ru) in combination with gemcitabine as antimetastatic agent accomplished phase I/II [16] KP1019 antimetastatic agent; completed phase I clinical trials [16]

Table 2. Platinum and ruthenium-based anticancer drugs subjected to clinical trials.

3. Platinum-based drugs nanoformulations

The clinical use of cisplatin and its analogs evidenced pharmacological deficiencies such as poor water solubility, low bioavailability, and short circulating time, besides toxicity and resistance. Moreover, a few types of cancers are sensitive to platinum-based drugs treatment.

Therefore, in the last decades, the researches were focused in designing drug delivery systems that are able to overcome these issues, but with preserving or even enhancing the drug efficacy. A brief overview concerning nanoscale drug delivery systems based on worldwide approved platinum-based cytostatic drugs cisplatin, carboplatin, and oxaliplatin is presented with focus on systems that advanced in clinical trials or exhibited promising pharmacological profile *in vitro* or *in vivo* preclinical assays.

3.1. Cisplatin-based nanoformulations

Cisplatin was the pioneering metallodrug introduced for the cancer treatment with the best result obtained in testicular cancer cure, for which a rate of 90% survival was achieved.

An impressive work was directed in the last time to overcome the severe side effects and intrinsic or acquired resistance by its inclusion in a proper matrix. This approach provided a way to extend its curative effect to other types of cancer proved so far to be insensitive to platinum-based drugs alone or in combination with other organic antineoplastic drugs. Its encapsulation into liposomes or polymeric species seems to provide the most promising formulations so far, since some of these formulations are currently in clinical trials.

Many formulations were developed by cisplatin encapsulation in the aqueous core of liposomes, with differences that consist in the composition of lipid bilayer, platinum content, and release profile. These attempts to incorporate cisplatin into liposomes were limited by its low both hydrophilicity and lipophilicity that resulted in a very low drug-lipid ratio and unstable systems, especially when injected into the blood stream [6–9].

In order to increase the liposomes stability, these systems were coated with a biocompatible hydrophilic polymer such as polyethylene glycol (PEG). Among these, lipoplatin was developed by cisplatin incorporation in a mixture of lipids from vegetable and animal sources, some being PEGylated [17]. An optimum pharmacological profile was observed in phase I clinical trial and significant improvements in patients with acquired resistance in phase II, in combination with gemcitabine, advanced this formulation in phase III clinical trials for both nonsmall-cell lung and pancreatic carcinoma [18]. Moreover, a preclinical study evidenced the potential of lipoplatin for cisplatin-resistant cervical cancer treatment [19].

A modest pharmacological profile was evidenced in clinical trials for a similar formulation SPI-77 as a result of low amount of cisplatin released [20, 21], while for LiPlaCis, a significant renal nephrotoxicity and infusion reactions were observed during phase I clinical trial [22].

As a result, the studies were directed to increase the amount of platinum species embedded either by using negatively charged phospholipids to entrap electrostatic $[Pt(NH_3)_2(H_2O)_2]^{2+}$ species or by lipid bilayer functionalization and conjugation with platinum(II) or platinum(IV) species [7]. In this respect, some formulations with a high loading capacity were developed by *cis*-$Pt(NH_3)_2$and *cis*-$Pt(NH_3)_2Cl$ moieties coordinated to carboxylate groups of lipids, and some exhibited a significant antitumor activity both *in vitro* and *in vivo* assays [23, 24].

Moreover, systems with a pendant group having selectivity for an overexpressed receptor in the cancer cells have been exploited to enhance the platinum species accumulation through receptor-mediated endocytosis. Such liposomal system targeting epidermal growth factor

receptor (EGFR)-expressing tumors was developed by conjugation with sodium alginate and indeed exhibited enhanced delivery ability into ovarian tumor tissues and a reduced nephrotoxicity in mice [25].

A variety of polymeric formulations designed as micelle, hydrogels, nanoparticles, and nanocapsules were also studied as cisplatin carrier. The noncovalent encapsulation provided systems with similar or even lower efficacy in comparison with free cisplatin and as a result polymer conjugates were developed by Pt(II) or Pt(IV) species in reversible coordination to a functional group from the polymer backbone or its branches [6–9, 26].

Among these, nanoplatin (NC-6004) was obtained as micellar formulation by cisplatin entrapping in the core of polyethylene glycol-poly(glutamic acid) copolymer. The *in vitro* and *in vivo* preclinical assays evidenced a complete tumor regression as well as a low nephrotoxicity and neurotoxicity in C26 murine colon carcinoma cell [27]. The phase I trial evidenced a better tolerability and reduced side effects in comparison with cisplatin [28] and thus advanced nanoplatin in phase II trials for nonsmall-cell lung cancer, bladder cancer, and bile duct cancer, respectively [8].

The conjugated polymer (AP5280) was developed as nanoparticles by *N*-(2-hydroxypropyl) methacrylamide copolymer conjugation by *cis*-Pt(NH_3)$_2$ moiety to the peptidyl side chains (Gly-Phe-Leu-Gly) ended with amidomalonate group. This formulation exhibited an increased cytotoxicity in murine tumor models [29] and, moreover, evidenced reduced side effects in a phase I clinical trial conducted by intravenous infusion administration [30].

The conjugate designed by cis-Pt(NH_3)$_2$ moiety coordination to polyethylene glycol branched with citric acid exhibited an enhanced cytotoxicity in both sensitive and resistant HT1080 human fibro sarcoma cells, CT26 fibroblasts, and SKOV3 human ovarian cells [31], while another one based on poly(ethylene glycol)-poly(acrylic acid) copolymer and encapsulated in calcium phosphate evidenced its cytotoxicity against a lung cancer cisplatin-resistant cell line [32].

A good antitumor activity was also achieved by *cis*-Pt(NH_3)$_2$ moiety coordination to the carboxyl groups of poly(γ,L-glutamic acid)-based polymer [33], while by conjugation with polyamidoamines dendrimers developed nanocarriers that inhibit the subcutaneous B16F10 murine melanoma, a cisplatin insensitive tumor [34].

On the other hand, the conjugation and/or encapsulation of an organic cytostatic or a sensitive trigger together with platinum species were exploited to enhance the cytotoxicity of these formulations.

As a result, micellar carriers developed by poly(ethyleneglycol)-b-poly(L-glutamic acid)-b-poly(L-phenylalanine) tri-block copolymer conjugation with paclitaxel- and cisplatin-derived moieties exhibited an enhanced activity against A549 human lung tumor cells both *in vitro* and *in vivo* [35], while conjugates of both paclitaxel and *cis*,*cis*,*trans*-[Pt(NH_3)$_2$$Cl_2$(OH)(HSucc)] ($H_2$Succ: succinic acid) (**Figure 1a**) prodrug with poly(ethylene glycol)-b-poly(ε-caprolactone)-b-poly(l-lysine) tri-block amphiphilic biodegradable copolymer exhibited an enhanced efficacy in U14 cervical tumor line xenograft in mice as a result of the synergistic effect [36].

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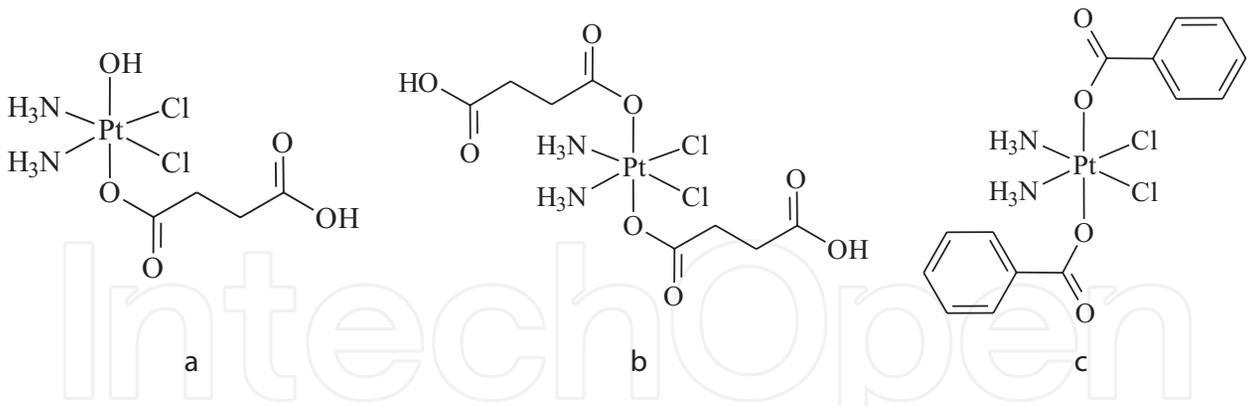

Figure 1. Platinum (IV) complexes embedded into cisplatin based formulations: cis,cis,trans-[$Pt(NH_3)_2Cl_2(OH)(HSucc)$] (a), *cis,cis,trans*-[$Pt(NH_3)_2Cl_2(HSucc)_2$] (b), and *cis,cis,trans*-[$Pt(NH_3)_2Cl_2(Bz)_2$] (c).

A combination of doxorubicin- and peptide-modified with *cis*-$Pt(NH_3)_2$ moiety loaded in positively charged mucoadhesive chitosan-polymethacrylic acid-based nanocapsules demonstrated an enhanced cytotoxicity against UMUC3 human urothelial carcinoma cell line [37]. Likewise, glutathione-sensitive micelles based on carboxymethyl chitosan crosslinked with 3,3′-dithiobis-N-hydroxysuccinimidyl propionate modified with folic acid exhibited synergistic cisplatin-doxorubicin effect against HeLa tumor cell line [38].

Another co-delivery system was developed by self-assembly of the anionic polyglutamic polymer *cis*-$Pt(NH_3)_2$ conjugated with an cationic metformin polymer. This formulation suppressed tumor growth for H460 human NSCLC xenografts in mice by a synergistic effect related to protein kinase α pathway activation and mammalian target rapamycin inhibition [39].

In order to achieve a high selectivity in targeting tumor cells, peptide and glycoside residues were inserted in the polymer backbone as groups that can be specifically recognized by the tumor tissue. This strategy resulted in thermosensitive nanoparticles obtained by cisplatin and indocyanine green loading in a complex matrix of poly(lactic-co-glycolic acid) copolymer and lipids functionalised with Gly-Cys-Gly-Ala-Ala-Asn-Leu heptapeptide. This formulation was designed to target MGC803 gastric tumor cells that overexpress the legumain and as a result exhibited a good activity *in vitro* [40].

Another formulation was developed as lyophilized system by *cis*-$Pt(NH_3)_2(OH_2)$ moiety coordination to carboxyl groups of hyaluronan, a naturally occurring glycosaminoglycan polysaccharide that targets tumor cells through specific interactions with CD44 receptor highly overexpressed in many cancers tissues. This conjugate demonstrated a suppressed cancer progression through intratracheal administration in Lewis lung carcinoma allografts in mice [41]. A platform targeting the same receptor was prepared by cisplatin incorporation in calcium phosphate and then embedded in hyaluronan-chitosan cross-linked polymer shell. These nanoparticles demonstrated target specific delivery in A549 human lung cancer cells confirmed by an eightfold increase of drug efficacy [42].

Some inorganic materials such as magnetite, graphene, gold, and silica were also studied in order to develop proper formulations for cisplatin delivery. The attempts to obtain nanoparticles based on these species have been discouraged by the low amount of cisplatin that can

be noncovalent-retained and consequently promote an early release of the active species in the plasma. This problem has been solved either by coating the inorganic species-cisplatin assembly with an organic shell or by its surface functionalization with groups that are able to coordinate platinum species [6–9].

Following these strategies, an enhanced therapeutic effect in A549 human lung cancer xenograft model was obtained by magnetite-cisplatin assembly encapsulated in poly(vinyl alcohol) and poly(acrylic acid) [43]. Another formulation designed by *cis*-$Pt(NH_3)_2$ conjugation and magnetite embedded in (methacrylic acid)-*g*-poly(ethylene glycol methacrylate) polymer exhibited an enhanced anticancer efficacy in cisplatin-resistant HT-29 human colon adenocarcinoma model, particularly when a magnetic field gradient was applied at the tumor site [44].

An improved antitumor effect was also obtained either for gold nanoparticles PEGylated and *cis*,*cis*,*trans*-$[Pt(NH_3)_2Cl_2(HSucc)_2]$ (**Figure 1b**) conjugated [45] or for that functionalized with oligonucleotide and *cis*,*cis*,*trans*-$[Pt(NH_3)_2Cl_2(OH)(HSucc))]$ conjugated [46]. It is to be pointed the higher cytotoxicity against cisplatin-resistant line exhibited by such formulations.

Nanoparticles developed by *cis*-$Pt(NH_3)_2(OH)$ moiety coordination to functionalized mesoporous silica exhibited also an enhanced cytotoxicity on HT-29 colon cancer cell line [47].

Concerning graphene-based materials, a cisplatin nanotube conjugate modified with epidermal growth factor (EGF) proved an enhanced activity against EGF overexpressing head and neck squamous carcinoma cells [48], while functionalized multi-walled carbon nanotubes (MWCNTs) conjugated with *cis*,*cis*,*trans*-$[Pt(NH_3)_2Cl_2(Bz)_2]$ (HBz: benzoyc acid) (**Figure 1c**) exhibited a selective accumulation in mice lungs [49].

Some hybrid materials based on coordination polymers were also developed as cisplatin carriers. Such supramolecular assembly was developed by $[Tb_2\{Pt(NH_3)_2Cl_2(Succ)_2\}_3]_n$ encapsulation in amorphous silica (**Figure 2**) as cytotoxic agent against HT-29 human colon carcinoma cell line [50].

Another platform was designed by hetero-metallic coordination polymer $[Zn_2\{Pt(NH_3)_2Cl_2(Ncp)_2\}]_n$ (Ncp: N-carbamoyl phosphate) embedding in an asymmetric lipid layer modified with polyethylene glycol. This assembly, with a high amount of cisplatin incorporated, exhibited an

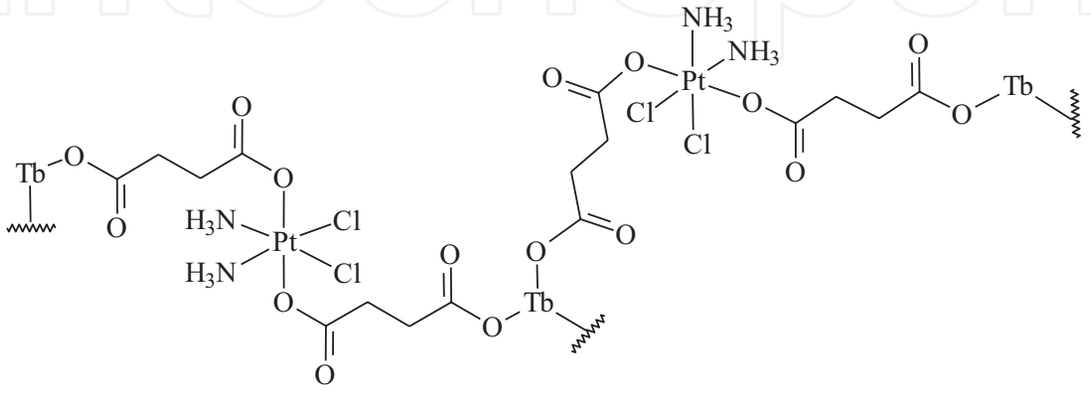

Figure 2. Hybrid nanoformulation developed by $[Tb_2\{Pt(NH_3)_2Cl_2(Succ)_2\}_3]$ encapsulation.

enhanced efficacy in comparison with free cisplatin in H460 human nonsmall cell lung cancer and AsPC-1 human pancreatic cancer xenograft in mice [51].

A carrier system based on the same hetero-metallic coordination polymer and pyrolipid as photosensitizer exhibited a synergistic effect in cisplatin-resistant human head and neck cancer SQ20B xenograft in mice [52], while another formulation with small interfering RNA (siRNA) in addition and coated with a cationic lipid layer exhibited cytotoxicity both *in vitro* and *in vivo* against SKOV-3cisplatin-resistant ovarian cancer [53].

On the other hand, polysilsesquioxane-based hybrid nanomaterials developed by *cis*,*cis*,*trans*-$[Pt(NH_3)_2Cl_2(HptsSucc)_2]$ (H_2ptsSucc: propyltriethoxysilane succinic acid) polymerization (**Figure 3**) and coated with polyethylene glycol demonstrated an enhanced efficacy in combination with radiotherapy against A549 and H460 human lung cancer cells xenograft in mice [54].

These formulations can be internalized into the cancer tissues through passive or active transport. The passive transport is based on the ability of nanosystems to accumulate better in tumor tissue as a result of its increased permeability and poor lymphatic clearance, phenomenon known as enhanced permeability and retention (EPR) effect [55]. Moreover, the intratumoral nanoparticles content can be enhanced through an active transport facilitated by an overexpressed receptor.

Upon endo- or phagocytosis, the platinum species release is triggered in cytosol or other cellular compartments by several processes that can be acid, redox, and/or enzymatic assisted. For conjugated formulations, the cisplatin structure is restored either by reaction of Pt(II) species with chloride anions or by Pt(IV) species reduction with glutathione or ascorbic acid [6–9].

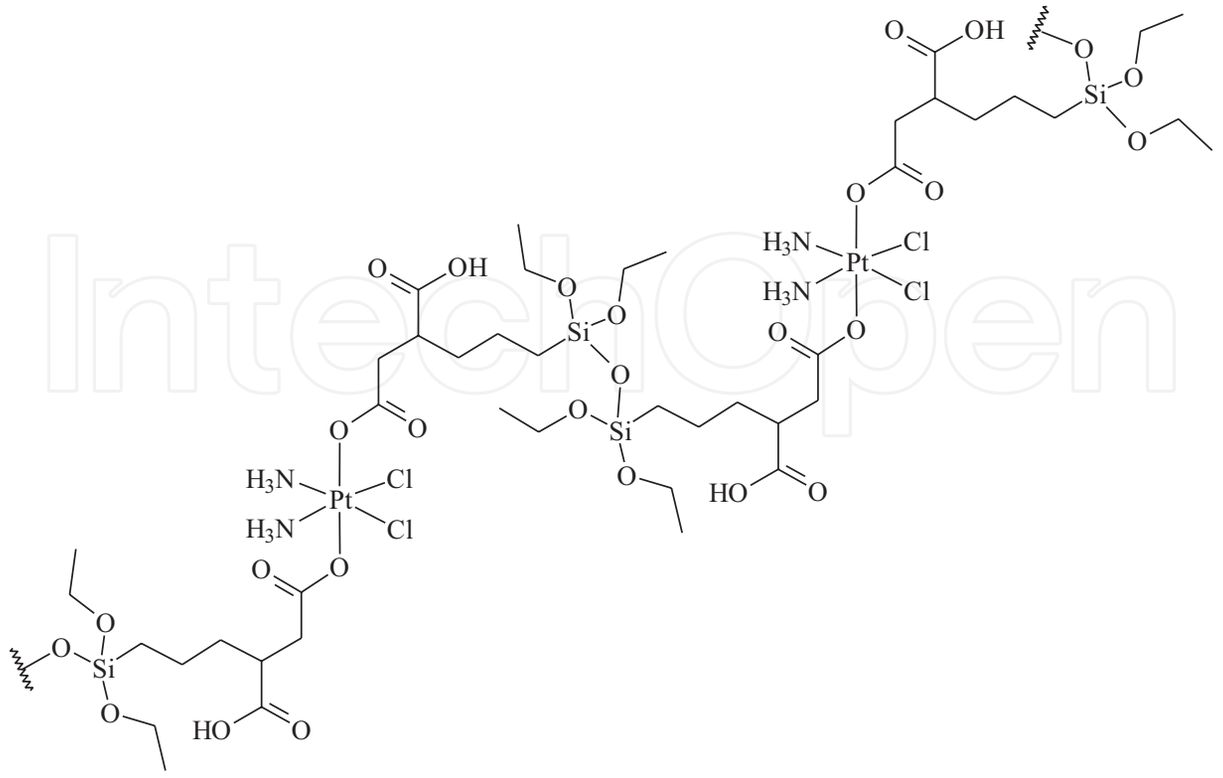

Figure 3. Hybrid nanoformulation developed by *cis*,*cis*,*trans*-$[Pt(NH_3)_2Cl_2(HptsSucc)_2]$ polymerization.

3.2. Carboplatin-based nanoformulations

The structural difference between cisplatin and carboplatin consists in replacing the chloride leaving groups by 1,1-ciclobutandicarboxylate as chelate ligand. Although carboplatin is often preferred over cisplatin in cancer therapy based on a lower nephrotoxicity, this exhibits a limited therapeutic efficacy related to its reduced uptake by the tumor cells. Moreover, the treatment induces myelosuppression and cross-resistance [14].

As a result, few studies were concerned on developing carboplatin-based formulations. Based on experience accumulated in cisplatin-based formulation development, carboplatin was embedded through noncovalent interactions especially in polymeric or hybrid materials, some proper functionalized in order to achieve either a targeted delivery or an enhanced efficacy, especially against multidrug resistant cancer cell lines.

Such a polymeric formulation was developed by loading in poly(D-L-lactide-*co*-glycolide) polymer. This nanocarrier exhibited an enhanced cellular uptake in both A549 lung and MA148 ovarian tumor cells [56], while that based on poly(ε-caprolactone) was also efficient uptakes and displayed a significant cytotoxicity in U-87 human glioma cell line, without inducing haemolysis [57]. Moreover, carboplatin-loaded apotransferrin and lactoferrin nanoparticles with high encapsulation efficacy exhibited a significantly cellular uptake and sustained intracellular drug retention in retinoblastoma cells [58], while a chitosan-based formulation demonstrated an enhanced antiproliferative effect against MCF-7 breast cancer cell line [59].

The hybrid materials were also studied in order to improve the pharmacological profile of carboplatin. Such supramolecular assembly based on multiple functionalizations of MWCNTs with amino groups resulted in a dramatic decrease of the MDA-MB-231 human mammary adenocarcinoma derived epithelial cells viability, which was related to superoxide anions production. This study also evidenced that expression of some proteins was inhibited, while the Beclin1 was overexpressed. As a result, most probably this system triggers the cell death through autophagy [60]. Another nanohybrid formulation developed by carboplatin loading in the nanographene oxide-gelatine material exhibited an enhanced efficacy in IMR-32 human neuroblastoma cell line [61].

3.3. Oxaliplatin-based nanoformulations

Oxaliplatin was introduced as first-line chemotherapeutic for the treatment of advanced colorectal cancer based on a different antineoplastic spectrum in comparison with cisplatin. However, the peripheral neuropathy and a moderate myelotoxicity in cumulative dose dependence were observed in many patients [62].

As a result, the attempts to improve its pharmacological profile and reduce the side effects resulted in several valuable formulations for this antineoplastic drug. Similar with cisplatin, a variety of organic, inorganic, and hybrid materials were studied for embedding either the original species [Pt(dach)(C_2O_4)] (dach: (1*R*,2*R*)-1,2-diaminocyclohexane) or another Pt(II) or Pt(IV) complex bearing dach as chelate ligand.

Among these, lipoxal developed as liposomal PEGylated formulation exhibited an acceptable pharmacological profile in a phase I clinical study for advanced gastrointestinal cancer [63]. By this formulation injected directly in F98 glioma implanted in rats, a reduced toxicity with preservation of the antitumor potential of oxaliplatin was achieved as well [64].

Similar with cisplatin, the efficacy of oxaliplatin-based formulation has been improved by surface of the liposomes modification with moieties that are able to assure either a specific targeting or a rapid release after the internalization of delivery system in tumor tissue.

These strategies resulted in developing a transferrin target sensitive liposomal formulation, which demonstrated increased tumor suppression in C-26 colon cancer cell line xenograft in mice as a result of transferrin receptor overexpression in this line [65]. This transferrin-targeted liposomal formulation is currently under phase II clinical investigation for the treatment of gastric cancer and gastroesophageal junction cancer [66].

By oxaliplatin encapsulation in PEGylated cationic liposomes, a formulation with a selective delivery in tumor vasculature was developed. The assays evidenced a complete suppressing tumor-induced angiogenesis and antitumor efficacy in mouse dorsal air sac as a result of dual-targeting both tumor cells and its vascular endothelial structure [67]. Moreover, the efficacy of this assembly can be improved by a sequential administration of oxaliplatin containing PEG-coated cationic liposomes [68].

Several oxaliplatin-based polymeric systems were also developed in order to enhance its cytotoxicity. Such oxaliplatin containing micelles (NC4016), in addition, proved the ability to overcome the oxaliplatin resistance *in vivo* are currently in clinical trials in patients with advanced solid tumors or lymphoma [69].

Another micellar formulation was developed by $[Pt_2(dach)_2(dah)_2](NO_3)_2$ (dah: 1,2-diaminohexane) complex (**Figure 4a**) embedding into methoxylpoly(ethylene glycol)-b-poly(lactide-co-2-methyl-2-carboxylpropylene carbonate) (mPEG-b-P(LA-co-MCC)) copolymer. This pH sensitive assembly exhibited a significant cytotoxicity against H22 liver cancer cell line xenograft in mice [70].

The polymeric systems were exploited not only to enhance the drug cytotoxicity through conjugation with Pt(dach) moieties, but for a combined delivery as well.

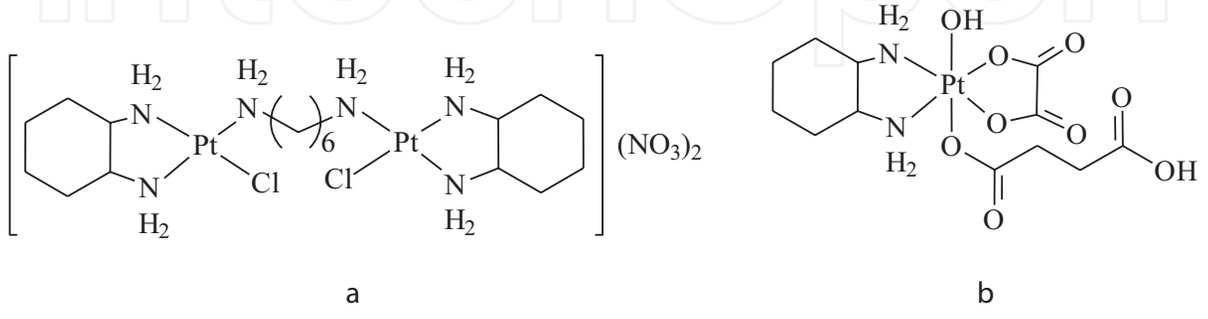

Figure 4. Platinum (IV) complexes embedded into oxaliplatin based formulations: $[Pt_2(dach)_2(dah)_2](NO_3)_2$ (a), and $[Pt(dach)(C_2O_4)(OH)(HSucc)]$ (b).

In this respect, micelles based on poly(ethylene glycol)-b-poly(glutamic acid) copolymer conjugated with Pt(dach) moiety demonstrated a potent tumor growth inhibition after an intraperitoneal injection in HeLa tumor cell xenograft in mice [71], while a similar micellar formulation inhibited the tumor growth in OCUM-2MLN scirrhous gastric cancer cell line and their lymphatic metastases in mice [72].

The polymer conjugate AP5346 was developed by Pt(dach) moiety coordination to the pH-sensitive amidomalonato chelating group from a *N*-(2-hydroxypropyl) methacrylamide-based copolymer structure. This conjugate exhibited an improved cytotoxicity in comparison with oxaliplatin in some colon tumor cell line xenograft in mice [73]. Based on pharmacological profile observed in patients with advanced solid tumors in phase I trial [69], this formulation advanced in phase II trial in recurrent ovarian cancer was initiated, but the results are so far disappointing [73].

Hybrid micelles containing mPEG-b-P(LA-co-MCC) copolymer conjugated with both Pt(dach) moiety and gemcitabine showed a low systemic toxicity and a synergic efficacy against MCF7 human breast cancer cell line xenograft in mice [74], while a similar system based on this copolymer conjugates with both [Pt(dach)(C_2O_4)(OH)(HSucc)] (**Figure 4b**) and daunorubicin showed reduced systemic toxicity and a synergistic effect in H22 hepatocarcinoma xenograft in mice [75].

In order to enhance the concentration of active species released in tumor tissue through a targeted delivery, some oxaliplatin-based polymer formulations were functionalized with glycoside residues and antibodies. Such polymeric nanoparticles were designed by carboplatin embedding in the supramolecular assembly of chitosan conjugated with hyaluronan and additionally coated with Eudragit S100. The oral administration of this formulation resulted in an enhanced activity in HT-29 cell line xenograft in mice [76].

Nanoparticles with a high amount of oxaliplatin embedded in a hybrid material consisting in a polymeric chitosan layer [77, 78] and a mixture of phospholipids conjugated with a thiolated antibody for tumour necrosis factor induced protein were developed as well [77]. Such formulations exhibited an increased cytotoxicity in comparison with oxaliplatin in HT-29 [77] and MCF7 cell lines [78].

Moreover, the functionalization allowed extending the cytotoxic effect to oxaliplatin insensitive tumors such as breast and gastric cancer. Thus, a pH-responsive nanocarrier was constructed by Pt(dach) moiety conjugation in citrate cross-linked chitosan matrix. The enhanced cytotoxicity of these nanoparticles in MCF-7 human breast cancer cell line was related to apoptosis induced in a caspase-dependent manner [67]. The nanogel system developed by embedding oxaliplatin in hydroxypropylcellulose-poly(acrylic acid) exhibited cytotoxicity against BGC823 human gastric cancer cell line [79].

Several systems based on hybrid materials were also developed for achieving an oxaliplatin enhanced delivery. Among these, superparamagnetic iron oxide nanoparticles encapsulated in pectin Ca^{2+} cross-linked exhibited 10-fold enhanced cytoxicity in comparison with free drug in MIA-PaCa-2 pancreas cancer cell line [80].

Another formulation developed by oxaliplatin incorporation into the inner cavity of PEGylated MWCNTs demonstrated a significantly improved cytotoxicity against HT-29 colorectal cell

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line [81], while similar nanocomposites additionally decorated with magnetite exhibited antitumor effect and low toxicity in HCT116 human colon cancer cell line xenograft in mice [82].

Naked gold nanoparticles functionalized with a thiolated poly(ethylene glycol) monolayer capped with a carboxylate group and conjugated with $[Pt(dach)(H_2O)_2](NO_3)_2$ yielded a supramolecular complex with about 280 Pt(dach) moieties per nanoparticle. This formulation demonstrated a similar or significant enhanced cytotoxicity in comparison with free oxaliplatin in A549 lung epithelial cancer cell line and HCT116, HCT15, HT29, and RKO colon cancer cell lines. Moreover, an unusual ability to penetrate the nucleus in the lung cancer cells was observed in these assays [83].

Mesoporous silica nanoparticles functionalised with carboxyl groups and conjugated with Pt(dach) moiety were also obtained with an improved cytotoxicity against HepG-2 human liver cell line [84].

Data concerning a platform constructed by $[Zn_2\{Pt(dach)Cl_2(Ncp)_2\}]_n$ hetero-metallic coordination polymer conjugation to an asymmetric lipid bilayer modified with polyethylene glycol (**Figure 5**) were reported. This assembly with a high amount of platinum species incorporated exhibited cytotoxicity in H460 human nonsmall cell lung and AsPC-1 human pancreatic cancer cell lines xenograft in mice [53].

Hybrid nanoparticles were also obtained by $[Pt(dach)Cl_2(triethoxysilylpropylsuccinate)_2]$ base-catalyzed sol-gel polymerization similar to cisplatin derivative. Moreover, the silanol and carboxyl groups were functionalised with cyclic arginine-glycine-aspartate peptide and anisamide and then the surface was PEGylated. The cytotoxicity assay clearly indicated an increased uptake of this assembly by DLD-1 and HT-29 human adenocarcinoma cancer cells through integrin receptor and by AsPC-1 human pancreatic cancer cells through sigma receptor together with the tumor growth inhibition efficacy in pancreatic cancer xenograft in mice [85].

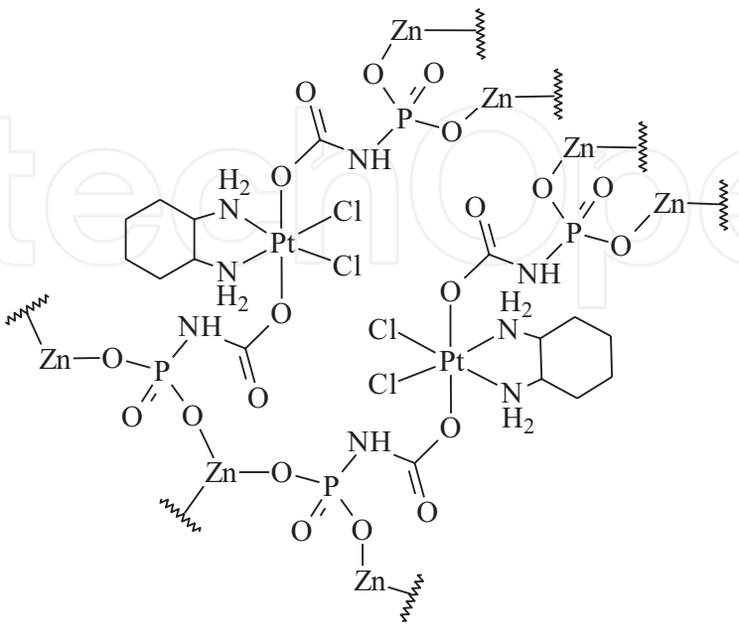

Figure 5. Hybrid nanoformulation developed by $[Zn_2\{Pt(dach)Cl_2(Ncp)_2\}]_n$ encapsulation.

4. Ruthenium (III)-based drugs nanoformulations

The studies regarding ruthenium complexes as anticancer agents were developed as an alternative of platinum complexes, especially for their reduced toxicity, large spectrum of activities (including against cisplatin-resistant tumors) and selectivity [86–88]. Among the various compounds of ruthenium investigated for their anticancer activity, two are in phase II clinical trials, namely NAMI-A (**Table 2**) as antimetastatic agent and KP1019 (**Table 2**) as antitumor for primary tumor site [89–93].

Both are pseudo-octahedral complexes having four chloride ions in the equatorial plane. The axial ligands are imidazole and DMSO molecules in NAMI-A complex, while for KP1019 are two indazole molecules. Both complexes undergo hydrolysis in aqueous solutions (chloride ions being replaced by water and/or hydroxide ions) and interact with biological reductants leading to ruthenium (II) species. These two processes seem to provide the active species in the body [94–96].

In order to improve the stability in aqueous systems, especially at physiological pH, and the delivery of drugs to the solid tumors, various drug delivery carriers have been designed and investigated. Two major ways were followed namely chemical conjugation and physical encapsulation [97].

4.1. Physical encapsulation of ruthenium-based drugs

Physical encapsulation is based on the capacity of carriers to retain the drug by physical bonds in a matrix. Different solid nanoparticles were used in order to encapsulate ruthenium complexes [97] such as poly(lactic acid) [98], mesoporous silica nanoparticles [99], or metal-organic frameworks [100]. The promising ruthenium (III) drug KP1019 was co-precipitated with poly(lactic acid) in a single oil-in-water emulsion with two different surfactants [98]. The obtained nanoparticles have an improved cytotoxicity comparing with KP1019.

4.2. Chemical conjugation of ruthenium-based drugs

4.2.1. Polymer conjugates

The main idea of this approach is to obtain a polymer, which contains a moiety that can act as ligand for ruthenium. In case of NAMI-A, this moiety can be an imidazole group. Thus, the Stenzel group [101] reports the polymerization of 4-vinil imidazole followed by addition of adequate ruthenium precursor complex. They obtained an amphiphilic co-polymer capable of self-assembly into micelles (**Figure 6**).

The tests on ovarian and pancreatic cancer cells revealed a 1.5 times increased cytotoxicity for polymeric micelles. Furthermore, these were tested for antimetastatic activity on breast cancer cells proving a higher activity comparing to NAMI-A complex.

4.2.2. Lipid base conjutates/liposomes

The Paduano group focused on developing drug carriers for NANI-A analog, named AZIRu (**Figure 7**) [102–108] and investigating their anticancer activity. Unlike NAMI-A, AZIRu contains a pyridine ligand instead of imidazole and sodium as counterion.

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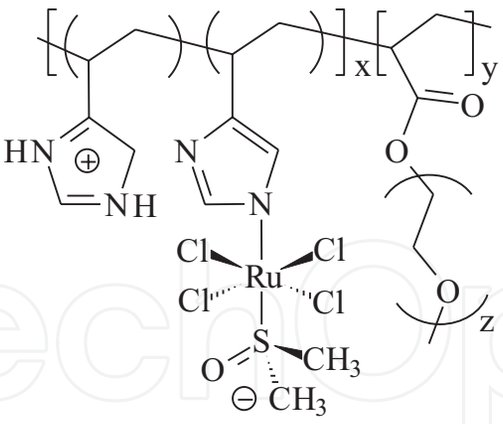

Figure 6. NAMI-A conjugated to polymer.

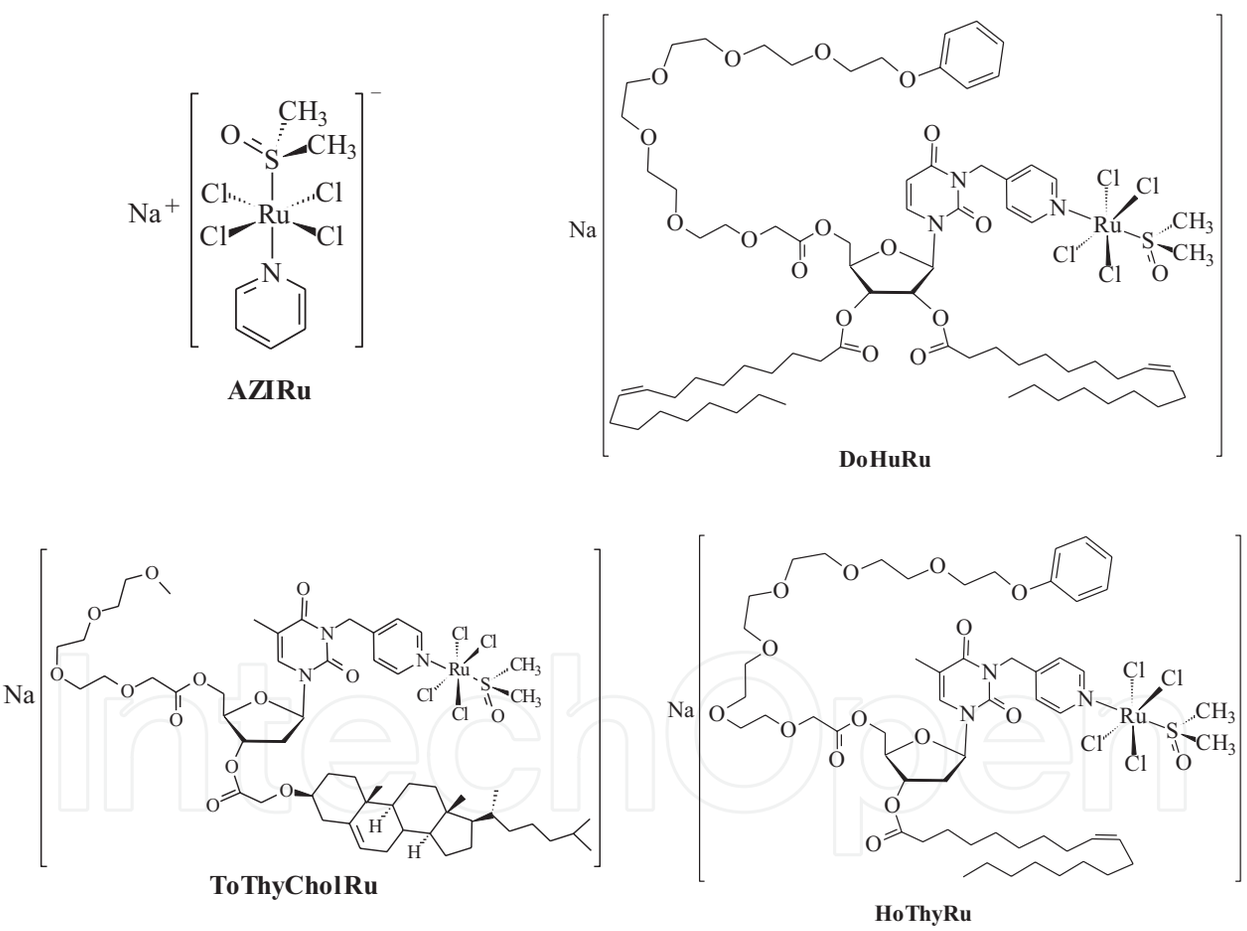

Figure 7. AZIRu and selected amphiphilic nucleolipid-based AZIRu.

New amphiphilic derivatives of nucleosides have been developed in order to act as drug carriers for AZIRu complex. In detail, a nucleobase (thymidine or uridine), which was attached with a pyrimidilmethyl group at the N-3 position (in order to act as ligand for ruthenium) was selected as starting material. The resulted compounds were further bonded to one or two lipid residues (oleoyl or cholesteroxyacetyl) and one hydrophilic oligo(ethylene glycol)

chain of variable lengths. There were thus obtained amphiphilic supramolecular aggregates, essentially liposomes [102–105].

The nucleolipidic compounds proved to have similar instability in aqueous systems as NAMI-A and AZIRu, forming insoluble precipitates in few hours. In order to reduce the hydrolysis processes, the nucleolipidic compounds were formulated with biocompatible phospholipids, POPC (1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine) [103–105] and DOTAP (1,2-dioleoyl-3-trimethylammoniumpropane) [106, 107]. The bioactivity of these Ru^{III}-containing nucleolipids was tested on human and nonhuman cancer cells proving higher anticancer activity, higher stability in aqueous systems, and lower toxicity than AZIRu [108].

4.2.3. Dendrimers

The interest in dendrimers as drug carriers comes from their characteristics namely highly branched three-dimensional molecules containing functional groups at periphery, which can react with drug molecules. So far, only one potential anticancer ruthenium (III) drug, RAPTA-C, was incorporated into dendrimer (**Figure 8**) [109], but there is no study regarding the anticancer activity.

Interactions of ruthenium (II) complexes with dendrimers and the anticancer activity of the resulted compounds, which are described in some reviews, have also attracted much interest [110, 111].

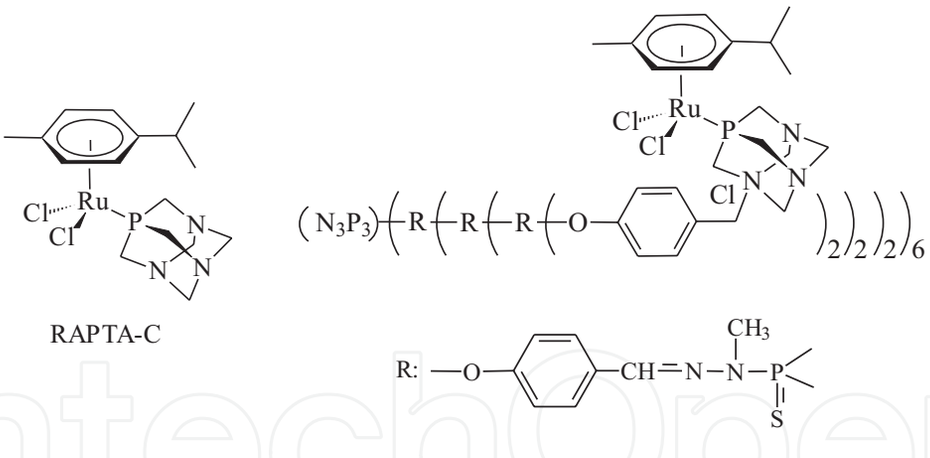

Figure 8. Ruthenium (III) drug RAPTA-C and its dendrimeric nanoformulation.

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