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SEARCH FOR NEW DRUGS

DESIGN AND ANTITUMOR ACTIVITY OF PLATINUM COMPLEXES

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This review presents the main advances in the design of antitumor platinum complexes over the last five years. Particular attention is paid to unconventional antitumor platinum compounds (complexes in the *trans* configuration, Pt(IV) complexes with S and P donor ligands, multinuclear complexes).

Keywords: platinum complexes, antitumor activity.

The current arsenal of drugs for the treatment of oncological diseases includes a whole series of platinum complexes, including *cis*-diamminedichloroplatinum (II) (cisplatin), *cis*-dihydroxydiaminedichloroplatinum (platin), (cyclobutane-1,1-dicarboxylato)diammineplatinum (II) (carboplatin), and [(1*R*,2*R*)-1,2-cyclohexanediamine-*N*,*N*′]-[oxalato(2)-O,O′]platinum (II) (oxaliplatin). Serious limitations in the treatment of malignant tumors using platinum compounds arise from their neurotoxicity, nephrotoxicity, and ototoxicity.

Cisplatin is historically the first and best studied of the platinum-based drugs used in clinical practice. There are many analogs of cisplatin which also contain the amine ligand responsible for the structure of the adduct formed with DNA and the leaving halogenide ligand, which influences the intratissue and intracellular distribution of platinum complexes. The amine ligand in this complex is tightly bound with the metal center and the leaving ligands have labile bonds with platinum. The relatively high chloride ion concentration in the cytoplasm prevents substitution of the chloride in cisplatin by water. However, in the cell nucleus, where the chloride ion concentration is significantly lower, chloride in cisplatin is replaced by water, resulting in the formation of charged water complexes. This is followed by insertion of the platinum complex into DNA by coordination of the platinum through the N atoms of the nitrogenous bases. The distances between platinum-linked N7-adjacent groups or between guanine and adenine moieties in the same DNA chain are in good agreement with the geometry of the *cis*-isomer, this distance being about 3.3 Å in both cases. Other approaches to the design of antitumor platinum complexes consist of creating Pt(IV) complexes using ligands with donor atoms other than N (for example, O, S, P). The "platinum" chemotherapy of tumor diseases is developing some new directions: photoreduction of nontoxic Pt(IV) complexes to the corresponding cytotoxic Pt(II) complexes by direct application of UV or visible light to tumors, as well as electrochemotherapy, which is based on increases in the permeability to cells to Pt(II) complexes using pulsed high-tension electrical fields [1]. The advantages of these methods are their simplicity, the short duration of treatment sessions, low drug doses, and significant reductions in unwanted effects [2].

Many studies of cisplatin and its analogs have shown them to be very similar not only in terms of their antitumor efficacies, but also in terms of the resistance of tumor cells to these compounds. Cisplatin and its analogs form essentially identical adducts with DNA. Data on the structure of cisplatin and its antitumor activity have led investigators to produce new *cis* complexes of Pt(II) with higher antitumor activity than *trans* complexes. However, factors determining cytotoxicity do not always correspond to the structure-activity relationship (SAR), which assumes: (*i*) the *cis* configuration of N ligands; (*ii*) the presence of a hydrogen atom at the coordinating N atom, and (*iii*) the presence of easily leaving

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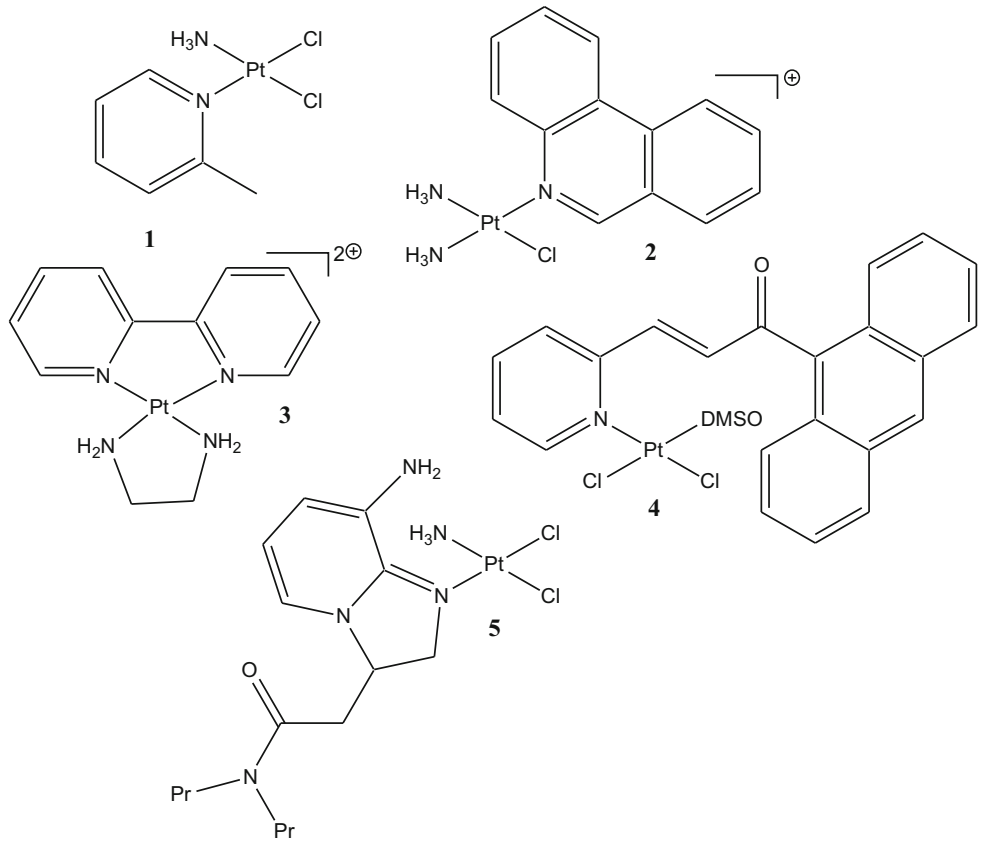


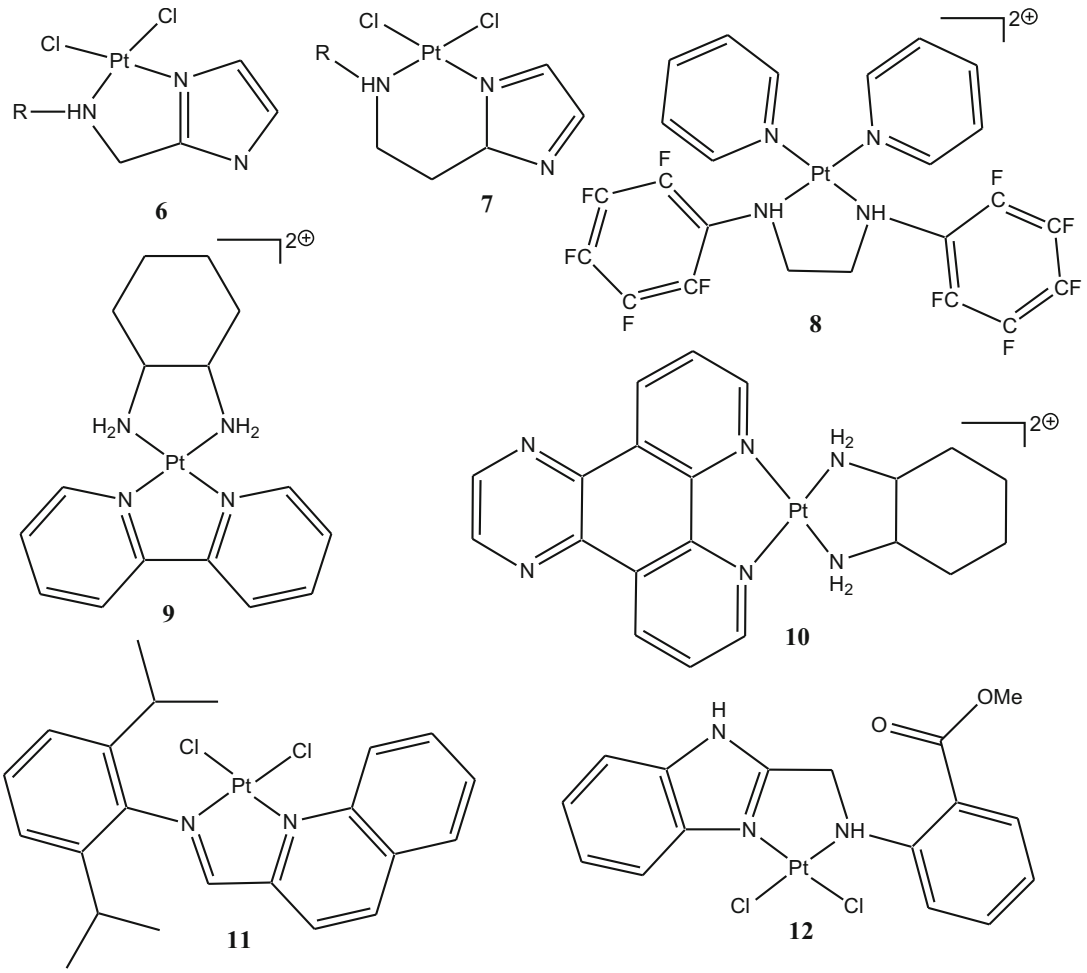
ligands, i.e., chloride or carboxylate. Thus, *trans* complexes of Pt(II) and multinuclear platinum complexes with high levels of antitumor activity have been made.

This review focuses on platinum complexes which are both conventional and unconventional from the point of view of SAR and we illustrate strategies used in the design of novel antitumor platinum compounds. Approaches to the synthesis of platinum complexes have been addressed in detail in a recent review [3].

Pt(II) Complexes with Monodentate N Ligands

The discovery of cisplatin was followed by the initiation of intense studies of platinum complexes in relation to their antitumor activity. The first direction in the design of antitumor platinum compounds consisted of creating cisplatin analogs; this approach retains its relevance [4]. The aim of synthesizing spatially hindered platinum complexes of this class is to produce compounds with significantly lower toxicity and higher activity in relation to cisplatin-resistant tumors. One of these complexes (compound **1**) was prepared by substitution of one of the ammonia ligands in cisplatin by a pyridine group. Complex **1** was found to have marked cytotoxic activity in relation to cisplatin-resistant leukemia cell lines. Complex **1** binds DNA monofunctionally, which result in blockade of transcription. The repair of DNA damaged by complex **1** is significantly more difficult than in the case of DNA damaged by cisplatin [5]. This direction in the design of antitumor platinum complexes has received extensive development and a number of structural analogs of cisplatin have been produced with pyridine, purine, piperidine, and other heterocyclic ligands. In particular, complexes **2** and **3**, which have high activity against cisplatin-resistant tumor cell lines and great potential, have been found [6]. The development of this approach yielded highly effective platinum complexes with pyrazinocarboxamide ligands. These compounds had high activity against Ehrlich carcinoma *in vivo* [7]. This approach also yielded complexes with N-heterocyclic carbenes and demonstrated their efficacy against ovarian tumors in in vivo experiments [8].

A further direction in the design of cisplatin analogs consists of producing complexes with ligands supporting the addressed delivery of compounds to the pharmacological target (for example, complexes **4** and **5**). Compound **4** is an example *cis* complex with a monodentate N ligand based on anthracene for addressed delivery due to the affinity of the ligand for peripheral benzodiazepine receptors (PBR) in tumor cells. This complex rapidly binds DNA and has high activity against a cisplatin-resistant human ovarian carcinoma line. Complex **5** also has high antitumor activity; addressed delivery of the complex is mediated by the ligand with high affinity for translocator protein (TspO) in PBR tumor cells [9, 10].



Complexes of Pt(II) with Bidentate N Ligands

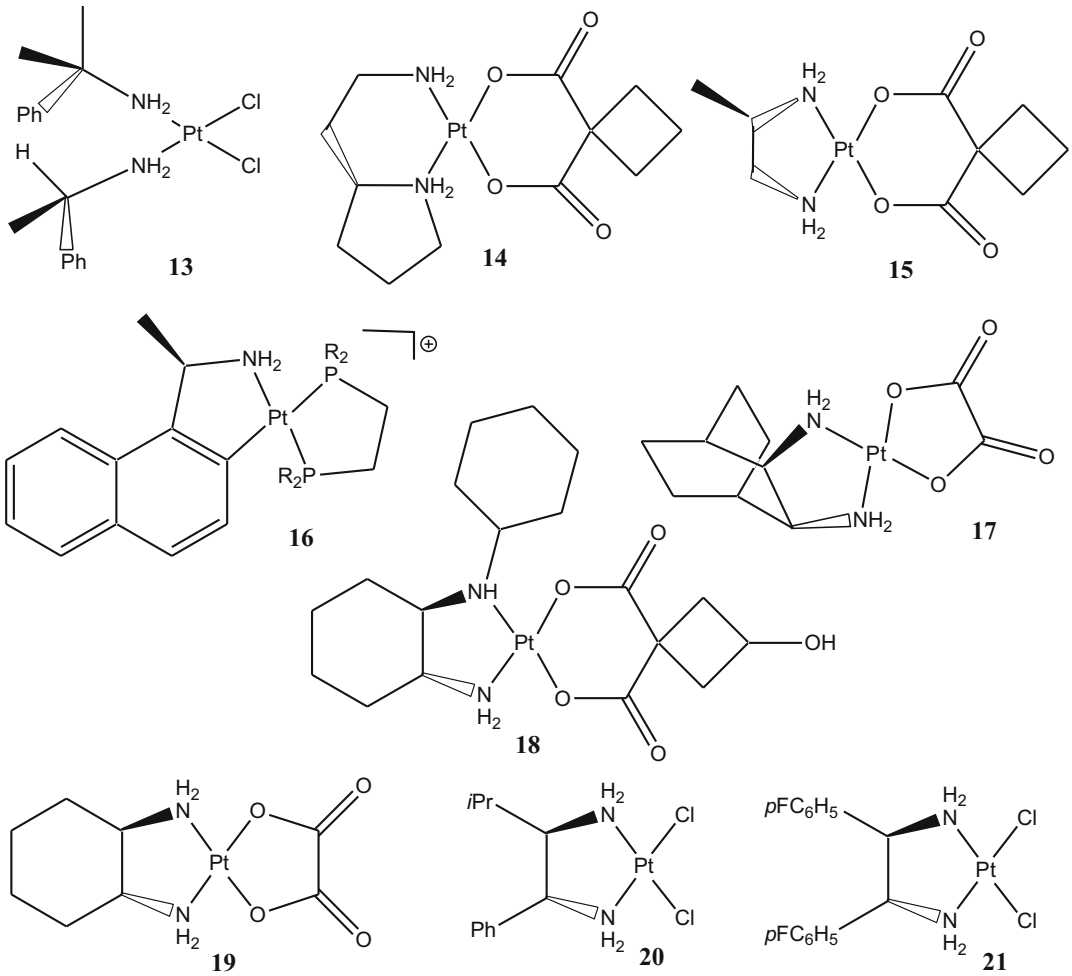
To exclude the possibility of *cis-trans* isomerism, which can occur in complexes with monodentate ligands, platinum complexes with bidentate chelating N ligands have been prepared. In particular, the synthesis of compounds **6** and **7**, which are highly active against HeLa cells, has been reported; these are in the *cis* configuration and are unable to undergo *cis-trans* isomerization because they have a bidentate N ligand [11]. Pt(II) complexes $[(Py)_2Pt\{N(C_6F_{5-n}Y_n)CH_2\}_2]$ (compound **8**, Y = H, I, $n = 0$, 1) also have in vitro and in vivo activity against HT29 and BE intestinal carcinoma cells. These compounds have high cytotoxicity and the $[Pt(Py)_2]^{2+}$ fragment binds to DNA in tumor cells in the same way as cisplatin [11].

Complexes based on 2,2-dipyridyl (compound **9**) and its derivatives (**10**), which cannot undergo *cis-trans* isomerization, also have high cytotoxicity [6]. Complexes of the type of compound **11**, with iminoquinoline ligands, were highly effective in relation to human intestinal and breast tumor lines [13]. Compound **12**, with a benzimidazole ligand, also had high cytotoxicity against human liver and intestinal carcinomas [14]. Use of bidentate ligands such as bipyridine led to the production of novel Pt(II) complexes with high in vivo activity against lung cancer [15].

Complexes of Pt(II) with Asymmetrical Ligands

Most studies of the antitumor activity of chiral platinum coordination compounds have addressed complexes with chiral monodentate primary amines. This is because the antitumor activity of *cis* complexes of platinum with primary amines is generally significantly greater than the activity of complexes with secondary amines [16]. For example, complex **13**, with a chiral monodentate phenylethylamine ligand, has antitumor activity comparable with that of cisplatin [17].

The design of chiral antitumor platinum complexes has also made use of a variety of enantiomerically pure bidentate N ligands (compounds **6**, **14**, **15**). Enantiomers often have different cytotoxic properties. For example, complex **14**, containing the S enantiomer, has a cytotoxic effect, while the complex with the enantiomer in the opposite configuration has no cytotoxic activity [17]. Cyclometallic chiral ligands have also been used in the design of antitumor platinum complexes. For example, complex **16**, with a 1-(1-naphthyl)ethylamine ligand, was two orders of magnitude more effective against intestinal cancer line HCT-116 than



cisplatin [18]. Complexes with the chiral bidentate ligand *trans*-bicyclo[2.2.2]octan-7*R*,8*R*-diamine (compounds **17**), which are highly effective against the cisplatin-resistant line SGC7901/CDDP, have been obtained recently [19].

Complexes with N-monoalkyl-1*R*,2*R*-diaminocyclohexane ligands are highly active against cell lines MCF-7 and A549. One of these compounds with the greatest potential is complex **18**, which has extremely low nephrotoxicity and no cross-resistance with cisplatin [20]. Overall, platinum complexes based on diaminocyclohexane occupy the leading position in terms of the number of platinum complexes with chiral ligands with potentially highly effective antitumor activity synthesized [21, 22]. The importance of studying chiral platinum complexes is indicated by the fact that one of the most effective antitumor drugs used in clinical practice is oxaliplatin (compound **19**), which is an oxalate complex of Pt(II) with a chiral diaminocyclohexane ligand.

The recently produced complexes **20** and **21**, based on a substituted chiral ethylenediamine, demonstrated more marked antitumor activity than cisplatin in in vivo experiments [23]. Complexes based on chiral 1,2-diaminocyclopentane also have cytotoxicity against L1210 leukemia cells [24]. Further development of this theme led to a production of Pt(II) complex with the chiral ligand (1*R*,1′*R*,2*R*,2′*R*)-*N*-1,*N*-1′-(1,4-phenylenebis(methylene))dicyclohexane-1,2-diamine, which was highly effective against large intestine adenocarcinoma [25].

Trans Complexes of Pt(II)

The discovery of several *trans* complexes of platinum with marked cytotoxicity produced a number of contradictions with established SAR rules. The cytotoxicity of platinum *trans* complexes does not follow the rules typical of cisplatin and its analogs. Isomerization of *trans* compounds to the active *cis* isomer in vivo might explain the observed activity of the *trans* isomer, though in many cases *cis* isomers are significantly less active than the corresponding *trans* isomers. In addition, *trans* isomers are effective against cisplatin-resistant tumor cells: for example, complex **22**, with a 4-hydroxyethylpyridine ligand and ammonia in the *trans* configuration, forms more DNA crosslinks than the corresponding *cis* isomer [26].

A series of *trans* complexes with dimethylsulfoxide was synthesized and their antitumor activities were evaluated. The most effective against cisplatin-resistance lines was complex **23** [27]. Complexes in the *trans* configuration with

a thiazole ligand (for example, compound **24**) also had high antitumor activity [28]. A reaction providing dipolar cyclo-attachment of nitrones to nitriles in Pt(II) complexes yielded a series of *trans* complexes **25** with oxadiazoline and dihydropyrazolotriazole ligands [29 – 32], some of which were characterized by high antitumor activity, significantly greater than the activity of cisplatin. The design of *trans* complexes of Pt(II) also used N-heterocylic carbenes [33], cyclic peptides [34], and hydroxyalkylpyridine ligands [35, 36].

It should be noted that the ligand does not have to have a complex structure for compounds to have antitumor activity. For example, structurally very simple *trans* complexes were prepared – $[PtCl_2(3\text{-hydroxymethylpyridine})_2]$, which were five times as active against ovarian cancer in *in vivo* studies as cisplatin [37].

Thus, the design strategy for cytotoxic platinum compounds based on the synthesis of *trans* complexes has in recent years undergone extensive development and has become the leading direction in the synthesis of unconventional antitumor platinum complexes, leading to some reevaluation of SAR rules [26].

Water-soluble Pt(IV) complexes

Low solubility and low bioavailability prevent cisplatin from being used via the oral route. A number of water-soluble Pt(IV) compounds with antitumor activity have now been synthesized. These substances have important clinical advantages linked with the ability to be used in out-patient conditions, significantly decreasing hospitalization costs.

Pt(IV) complexes are chemically more inert in ligand substitution reactions than the corresponding Pt(II) complexes. Activation of the antitumor activity of Pt(IV) complexes requires them to be reduced to the corresponding Pt(II) complexes [38]. The rational design of novel Pt(IV) complexes therefore needs knowledge of the interaction between the structure of the complexes and their ability to be reduced. In the case of Pt(IV) complexes based on ethylenediamine, studies have shown that their ability to undergo reduction to Pt(II) complexes depends on the nature of the axial ligand. The rate of reduction of Pt(IV) complexes correlates with the electron-acceptor influences of the axial ligand and increases in the sequence $OH < OCOCH_3 < Cl < OCOCF_3$ [39].

One important direction in the design of antitumor Pt(IV) complexes consists of creating and studying complexes containing carboxylate and amine ligands. For example, complex **26**, with a malonate leaving group and a 1,4-diaminobutane ligand, forming a mixed chelate ring with a metal center, has high activity against HL-60, HCT 116, HCT 15, SK-BR-3, MCF7, MDA-MB231, and L1210 cancer cell lines. This complex has good solubility in water and its antitumor effect is 2 – 4 times greater than that of cisplatin [40]. Introduction into the coordinate sphere of the malonate ligand, ammine ligands, and two monodentate carboxyl ligands led to the creation of novel active compounds. For example, complex 27 was highly effective against CH1 ovarian cancer, A549 lung cancer, and SW480 intestinal carcinoma [41].

Despite the fact that dicarboxylate Pt(IV) complexes of general formula *cis*, *trans*, *cis*-$[(OCOR^1)(NH_3)(RNH_2)PtCl_2]$ were significantly more active in vitro against HeLa cells than cisplatin, they were less active than cisplatin in experiments on Balb/c mice *in vivo* [42]. Reduction of these Pt(IV) complexes with loss of axial ligands occurs too quickly *in vivo* and is followed by loss of lipophilicity.

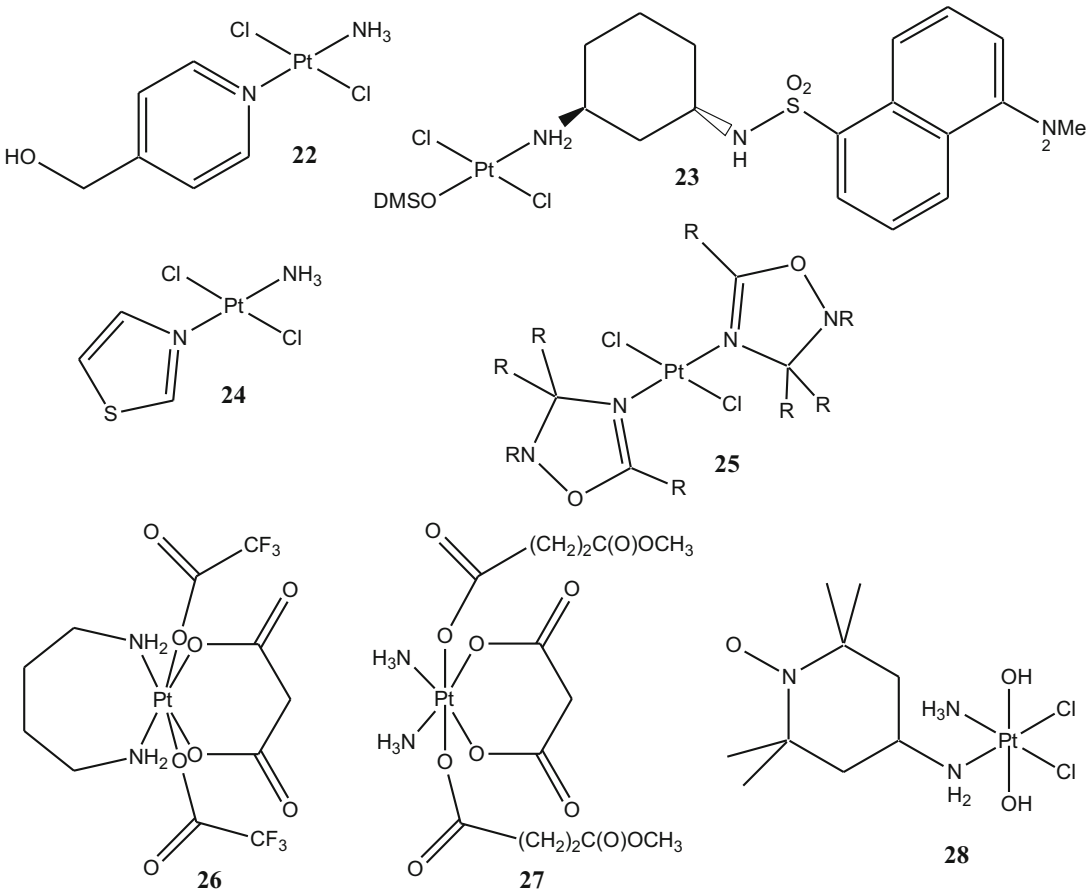
Recent studies have developed the design of Pt(IV) complexes which can undergo photoreduction on irradiation with visible light to form cytotoxic Pt(II) complexes within tumors. Such complexes with high *in vivo* activity include *cis*, *trans*, *cis*-$[Pt(N_3)_2(OH)_2(NH_3)_2]$, *cis*, *trans*-$[Pt(en)(N_3)_2(OH)_2]$, *trans*, *trans*, *trans*-$[Pt(N_3)_2(OH)_2(NH_3)(Py)]$, and their related diazo complexes containing methylamine, ethylamine, picoline, and thiazole, which are reduced by irradiation with light to form the corresponding Pt(II) complexes with loss of two azide ligands, after which they then bind with DNA [43].

A novel direction with great potential in the design of antitumor Pt(IV) complexes consists of creating complexes containing aminonitroxyl ligands, which stand apart from classical platinum complexes with alkylamines. Aminonitroxyl complexes are active against HeLa, H1299, and MCF7 lines. In particular, the rate of development of resistance to complex **28** by P388 leukemia was 2.5 times lower than that of cisplatin [44]. In addition, increases in antitumor activity have been described on simultaneous use of low doses of cisplatin and aminonitroxyl Pt(IV) complexes, which can be explained in terms of the antioxidant properties of the nitroxyl pharmacophore and the ability of these complexes to induce p53-independent tumor cell death [44]. Highly active complexes of hexacoordinated Pt(IV) with a 2-(2-propenyl)octanoate ligand have also been synthesized recently [45], as have hybrid indomethacin-biotin Pt(IV) complexes of original structure [46].

Despite the fact that the design of antitumor compounds based on Pt(IV) has been addressed by a rather small number of studies, the development of this direction in recent years has led to the discovery of novel, highly effective, water-soluble Pt(IV) complexes and has confirmed the antitumor effects of the Pt(II) complexes to which the corresponding Pt(IV) compounds were reduced.

Pt(II) Complexes with P and S Ligands

Substitution of ligands in cisplatin by aminophosphorus ligands led to the creation of complexes effectively interacting with thymine in DNA to form strong crosslinks. Phosphorus complexes usually have good solubility in water despite the presence of phenyl groups. The main direction in the development of such unconventional antitumor platinum compounds consists of creating complexes containing both N and P ligands. For example, marked cytotoxicity against



tumor cell line K562 was seen with complex **29**, containing triphenylphosphine and N-methylthymine ligands [47], while compound **30** and a number of its structural analogs showed high levels of activity against cisplatin-resistant lines [48].

Many platinum complexes containing phosphonates show high levels of antitumor, antiviral, and antibacterial activity [49]. Complexes of the compound **31** type, with aminophosphonate esters, have good solubility in water and high activity against MG-63, SK-OV-3, HepG2, and BEL-7404 tumor cell lines [50]. Studies of platinum complexes with aminobisphosphonates have been confirmed to be active *in vivo* against bone tumors and other types of tumors associated with an anomalous balance of calcium ions and cisplatin resistance [49, 51].

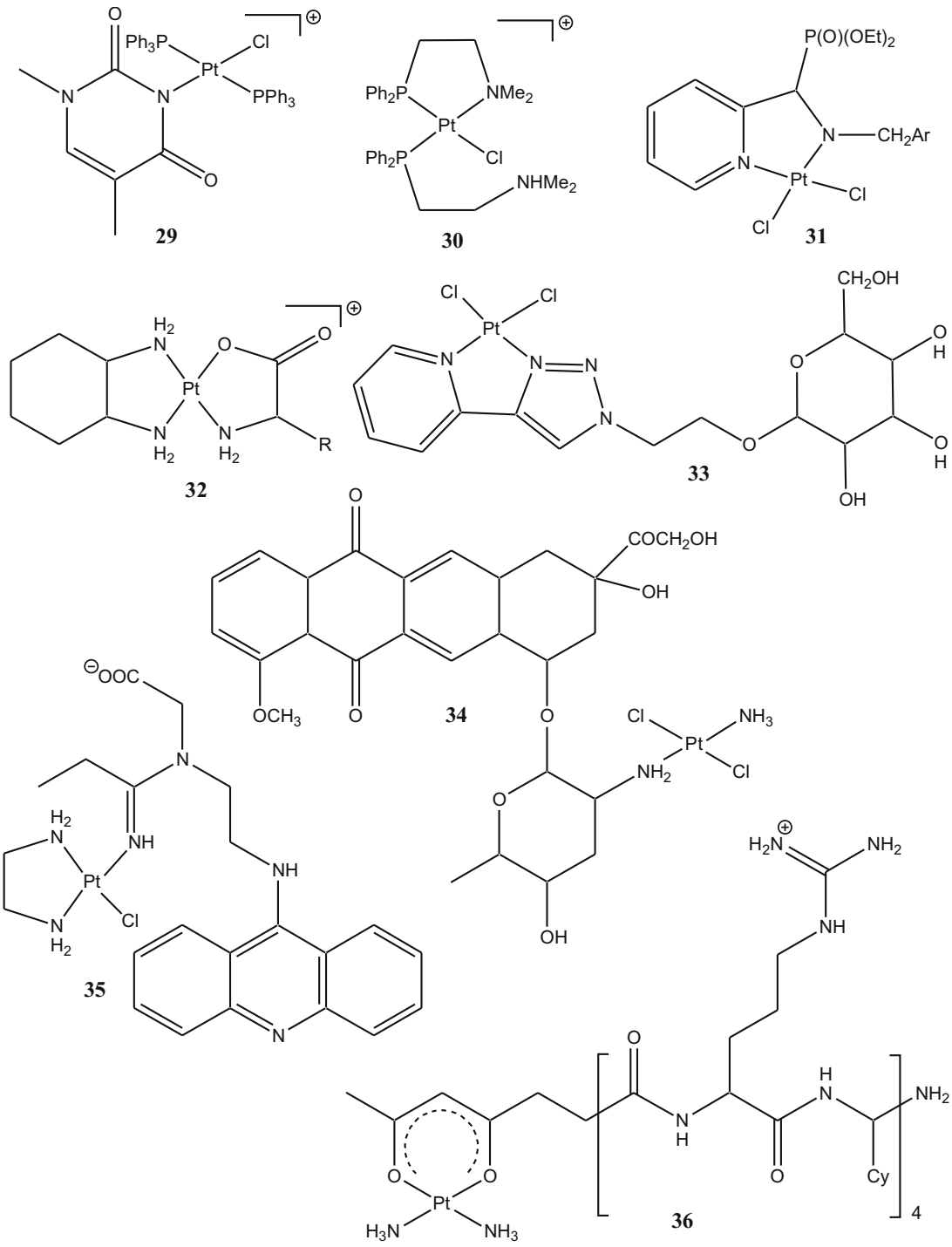
Platinum Complexes with Biologically Active Ligands

Biologically active ligands can increase the antitumor activity of complexes. For example, introduction of amino acids into the inner sphere of complexes (complexes **32**; R = H_2N-CO-CH_2, $NH_2C(=NH)$-NH-$(CH_2)_3$, HOOC-CH_2-CH_2) led to increases in cytotoxicity against many cisplatin-resistant lines [52]. Platinum complexes with sugars (for example, **33**) conjugated with tetrazoles had high activity against many cisplatin-resistant tumor lines [53].

The development of antitumor platinum complexes also makes use of a strategy based of chemical modification of ligands, for example, their conjugation with biologically active compounds or introduction into the inner sphere of the complex of biologically active compounds able to recognize defined structures on tumor cell membranes to provide addressed delivery of the complex directly to cancer cells. For example, complex **34** with doxorubicin was prepared, combining two antitumor compounds often used in combination chemotherapy. This complex was active against doxorubicin-resistant (P388) and cisplatin-resistant (L1210) lines. Addressed delivery of complex **35** to tumor cells is mediated by the ligand containing an acridine fragment [54].

Transplatin analog **36** contains a ligand conjugated with a peptide able to enter mitochondria and has good solubility in water and high antitumor activity. This compound has a different mechanism of action from cisplatin – it induces apoptosis of cancer cells without DNA damage, penetrating mitochondria in tumor cells [55].

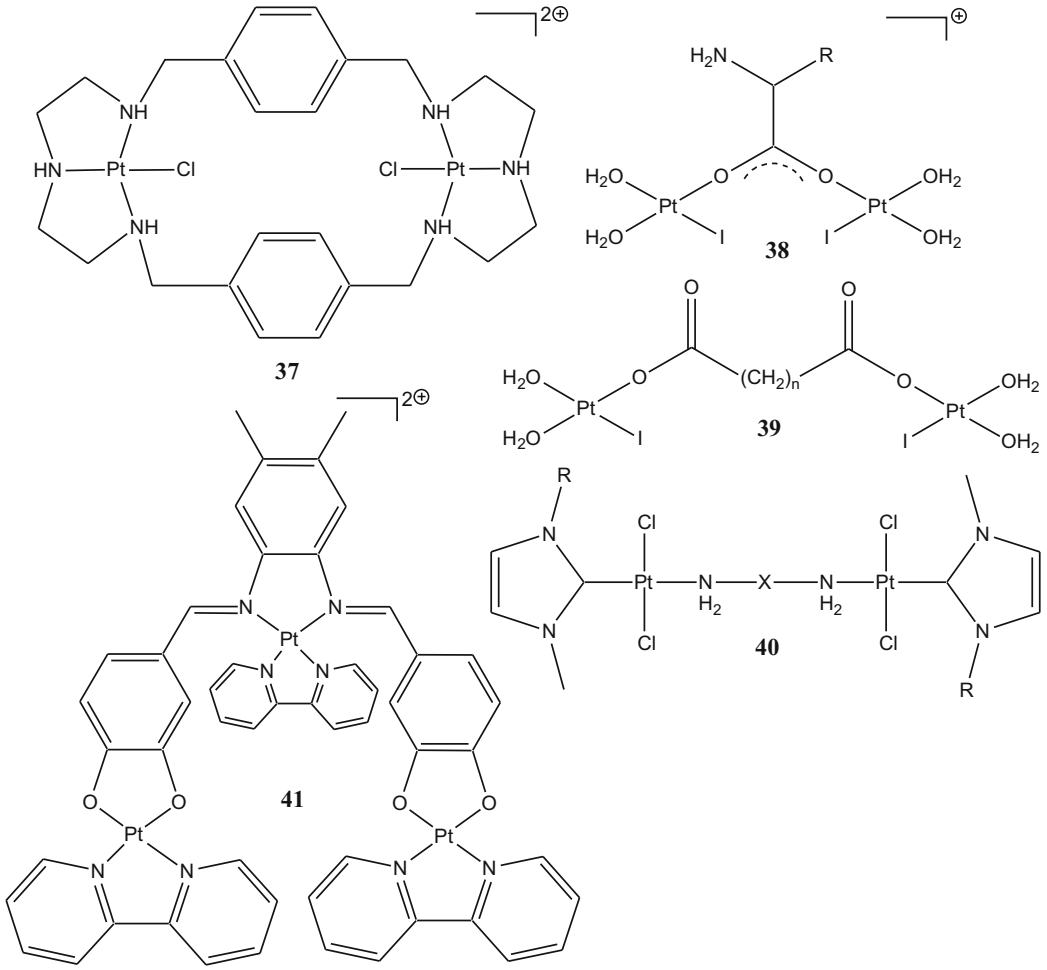
Thus, introduction of a biologically active fragment into the coordination sphere of platinum complexes is a potential direction which has recently been undergoing intense development, especially in relation to increasing interest in addressed drug delivery.



Multinuclear Platinum Complexes

Multinuclear platinum complexes occupy a special structural class of antitumor agents. These complexes are often able to overcome carboplatin and cisplatin resistance in many human cancer cell lines. Binuclear 3N-chelate complexes of platinum were obtained, in which the metal centers are linked by a 3,6,9,16,19,22-hexaazatricyclo[22.2.2.$2^{11,14}$]-triaconta-11,13,24,26(1),27,29-hexane spacer, operating as a polydentate ligand. An example of this type of complex is provided by compound 37, which has high activity against HeLa cells [56]. Binuclear complexes **38** and **39**, which have high activity against HL-60, BGC-823, Bel-7402, KB, MCF-7, HCT-8, and HeLa tumor cell lines, have metal centers linked by aminocarboxylate (**38**) and dicarboxylate (**39**) bridge ligands [51].

Binuclear complexes of platinum with diaminocarbene ligands were made, and some of these (for example, **40**) had



high cytotoxicity [29]. High activity against MCF-7 and HT29 tumor cells was typical of binuclear platinum complexes with bis(iminoquinoline) ligands [57].

Many trinuclear platinum complexes have high cytotoxicity. For example, complex **41** and its structural analogs have high activity against H460 lung carcinoma, DU145 prostate carcinoma, MCF-7 breast carcinoma, M-14 melanoma, HT-29 intestinal carcinoma, and K561 leukemia cells [58]. In addition, a series of multinuclear Pt(II) complexes with pyrazolo[1,5-*a*]pyrimidine ligands were highly effective against large intestine adenocarcinoma [59].

CONCLUSIONS

The design of cytotoxic platinum complexes has developed in two main directions: preparation of conventional *cis* platinum complexes (cisplatin analogs with N ligands) and the development of unconventional platinum complexes. In the framework of the latter approach, studies have focused on platinum *trans* complexes, Pt(IV) complexes, complexes with S and P ligands, platinum complexes with biologically active ligands, and multinuclear platinum complexes. Detailed study of unconventional platinum complexes has led to a reevaluation of existing SAR rules and the discovery of a series of coordination compounds effective against cisplatin-resistant tumors and creation of new-generation complexes.

As shown by these data, the ability of modifications of the ligand context and degree of oxidation of the metal center to open up pathways to the creation of novel platinum complexes and studies of their biological activities and mechanisms of antitumor actions will undoubtedly aid progress in medicinal chemistry, pharmacology, oncology, and related scientific fields.

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