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PERSPECTIVES TOWARDS DEVELOPMENT OF NOVEL NON-CLASSICAL ANTICANCER PLATINUM (II) COMPLEXES (REVIEW)

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ABSTRACT

Cisplatin is one of the most widely used antitumor drug to treat a number of human solid tumors. Over the last few decades more than 3000 platinum complexes structure analogous of Cisplatin and those quite differe from it were synthesized, but only few found application in clinical trials. Only two agents besides Cisplatin have been used clinically as antineoplastic drugs – Carboplatin and more recently Oxaliplatin. This review covers the classical and non-classical platinum complexes which find application as antitumor drugs. These complexes are classified and summarized according to the charge of the complex ion, cis-trans configuration of the platinum coordination compounds and number of metal ions in the platinum complexes.

Keywords: Pt(II) complexes, antitumor activity, organic ligands, polynuclear platinum complexes.

INTRODUCTION

Cisplatin, cis-dichlorodiammineplatinum (II), is the first widely used anticancer drug against testicular, ovarian cancers and the other human solid tumors [1-3]. Despite its wide cytotoxic activity, the clinical application is limited by severe side toxic effects such as nephrotoxicity, neurotoxicity, etc.[4-7]. *Cisplatin* is not very soluble in water. Therefore, for the last three decades all the studies have been carried out to find new platinum complexes with equal and/or greater antitumor effect than *Cisplatin,* broader spectrum of cytotoxic activity and better soluble in water. So, the following drugs were prepared: *Carboplatin* is the "second generation" antitumor platinum compound, which is the *Cisplatin* analogous [8]. It is more soluble in water than *Cisplatin* and produces an equally strong antitumor effect; *Oxaliplatin* is the "third generation" platinum drug with lower myelo- and nephrotoxicity compared to *Cisplatin* and *Carboplatin,* but is very neurotoxic [9,10]. All these facts, as well as the discovery of the major "structure-activity" relationships and the platinum complexes mode of action give an opportunity for carrying out a rational synthesis of new platinum complexes [3].

In this review new directions in the development of platinum complexes with a view to their application in the contemporary cancer chemotherapy were generalized. The newly Pt(II) complexes with different organic and inorganic ligands, have been synthesized, characterized by contemporary chemical and physical quantitative and qualitative analysis methods as elemental analysis, IR, ^{1}H-, ^{13}C-NMR- spectroscopy and etc. The

obtained complex compounds were pharmacologically investigated by the author for nearly twenty years.

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After Rosenberg at al. had discovered the antitumor activity of *Cisplatin* (□) in 1969, the investigations were directed to determine the "structure-activity" relationships [12].

Initially the idea, that if one complex possessed antitumor active it must be with neutral and cis-configuration, planar structure, etc. was promoted [13]. Therefore a number of new neutral complexes with general formulae cis- $[PtA_2X_2]$ [14-17] and cis-$[PtA_2X_4]$ [18-20], where A is amino ligand and X is anionic leaving group were synthesized.

It has been established, that antitumor activity of classical platinum complexes is proportionally to the number of DNA cross-links [1]. Replacement of the chloride anions in the *Cisplatin* molecule by carboxylic groups significantly diminished the Pt(II) complexes toxicity and increased its water solubility [21].

By way of illustration for that is the clinical use of cytostatic *Carboplatin* or cis-$[Pt(NH_3)_2$(1,1'-cyclobutanedicarboxylato)] (□) and *Oxaliplatin* or [Pt(1,2-diaminecyclohexane)(oxalate)] (□) in which replacement of the chloride anions by carboxylic leaving groups such as aliphatic or alicyclic dicarboxylic acids anions as bidentate ligands [22]. In comparison with the halogen ligands these leaving groups are more stable. It has been proved that in more active platinum complexes, the leaving groups are halogenic or carboxylatic anions and the strong bound ligands (analogous to amine molecules in *Cisplatin*) are called carrier ligands [1-2].

Several Pt(II) complexes with general formula cis-$[Pt(NH_3)LCl_2]$, where L is thiazole, imidazole and derivatives have been prepared [23]. Some of these complexes exhibited significant cytotoxic activity. A few Pt(II) complexes with 2-substituted benzimidazoles have been studied, which showed lower cytotoxicity *in vitro* than *Cisplatin* [24].

During the past few years *Nedaplatin* (cis-diamino(glycolato)platinum (II)) (□) was synthesized. Considerable interest to this complex has been stimulated by its higher cytotoxicity, exceeded those of *Cisplatin* in the preclinical studies. *Nedaplatin* is low nephrotoxic against various experimental tumor test systems and developes, significantly antitumor activity at preclinical tests. *Nedaplatin* as well as *Carboplatin* is the "second generation" antitumor drug [9, 25-27]. At present *Nedaplatin* is one of the clinically approved platinum cytostatic (available in Japan only) and it is used for treatment of non-small cell lung cancer, malignant melanoma, uterus cancer, neck and head cancers, etc. [25, 27].

Lobaplatin (1,2-diaminocyclobutanelactatoplatinum (II) D-19466) contains seven membered Pt-1, 2-bis (methylamino) cyclobutane chelating ring [9]. The leaving group in the structure of this compound is a bidentatly lactate anion. *Lobaplatin* shows remarkable cytotoxicity against animal tumor test systems including resistant to *Cisplatin* leukemia P388 and human tumor heterotransplantante [9]. The clinical trials of *Lobaplatin* showed high cytotoxic activity against different malignant tumors but its cytotoxicity is highest to chronic myeloid leukemia. Nowadays *Lobaplatin* is permitted for use only in China for the treatment of chronic myeloid leukemia, mammary and lung cancers [28-29].

Heptaplatin (cis-malonato-(4R,5R)-4,5-bis(aminemethyl)-2-isopropyl-1,3-dioxolanplatinum (II) (SKI-2053R)) was developed by Korean scientists on the basis of series of compounds containing dioxalone derivatives as ligands carrier [30]. *Heptaplatin* is permitted for use only in South Korea.

The Pt(II) complexes with aminosugars: D(+)glucosamine and D(+)glucosamineoxime with general formula cis-$[Pt(NH_3)LCl_2]$ have been synthesized by the author. The compounds exhibited cytotoxic effects *in vivo* comparable to that of *Cisplatin* against several tumor test systems – leukemia L1210, leukemia P388 and Ehrlich ascites tumor [31].

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Transplatin is less cytotoxic, but recently the complexes with trans-geometry have been described with comparable antitumor activity as cis-complexes [32]. L. Kelland and co-workers have developed trans-complex JM335 (trans,trans,trans-dichlorodihydroxoammine (cyclohexylamine) platinum (IV) [3, 19, 33]. The pharmacological investigations show, that it is distinguished

by its high cytotoxic activity, with IC_{50} (concentration necessary for reducing 50 % of the vital cells) values of ca. 50-fold lower than those of *Transplatin* and exerts antineoplastic activity in different tumor test systems.

[illegible]

Cationic and anionic Pt(II) complexes are inactive [33]. The cationic complexes are very toxic, while the anionic are less toxic. The latter is due to the impossibility of anionic complexes to penetrate through the system of cell and cytoplasmatic membranes. Another explanation for the lack of antitumor activity of these compounds is their rapid and simple elimination from the system [34-35]. In 1976 the first data about the high antitumor activity of some non-classical anionic Pt(II) and Pt(IV) complexes came out. Such compound is the cyclophosphamide Pt(II) complex, displaing cytotoxicity *in vivo*. At the same year Presnov at al. determined the inhibited effect of the complex $(NH_4)_2[PtBr_4(OH)_2]$ [36].

Anionic Pt(II) complex with monochloroacetic acid – cis-$[Pt(NH_3)(CH_2ClCOO)_3]^-$ developing possess high antitumor activity *in vivo* exceeding those of *Cisplatin* in some animal tumor test systems – leukemia L1210, leukemia P388 and Ehrlich ascites tumor was synthesized and investigated by the author [24].

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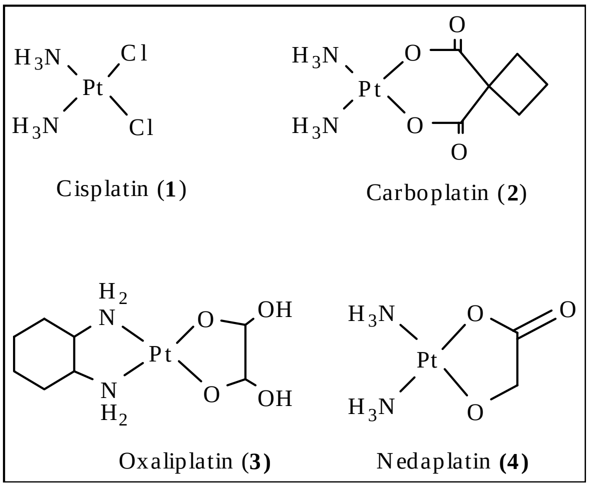
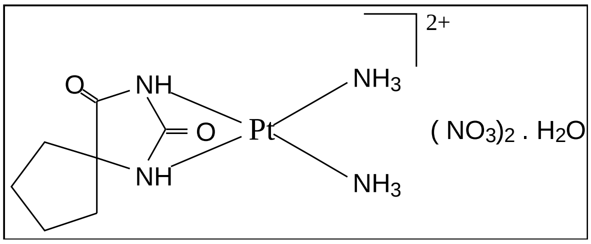
In 1989 Hollis at al., fot the first time reported a series of cationic Pt(II) complexes showing antitumor activity, thus violating some of the classical “structure-activity” relationships [36]. Cationic diammineplatinum (II) complexes having dimethylsulfoxide as a leaving group have been well known for the past two decades [37-38]. These complexes possessed cytotoxic activity against some tumor test systems [39]. Later in 1996 Shamsudin and co-workers synthesized kationic complexes of the type $[Pt(DACH)(R'R''SOClNO_3]$, where DACH was 1,2-diaminocyclohexane as a ligand and R’R”S was dialkyl or diarylsulfide as a leaving group [40]. These authors proved, that the Pt(II) complex containing dimethylsulfide was highly active *in vivo*. In addition the complexes with diphenylsulfide and thioanisole as



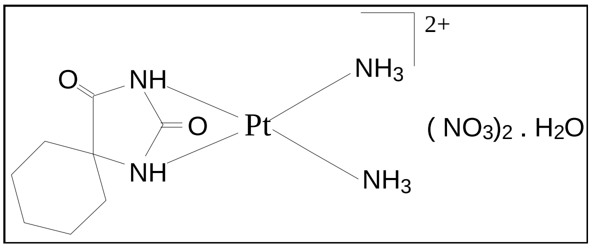
Cisplatin (**1**) Carboplatin (**2**) Oxaliplatin (**3**) Nedaplatin **(4)**

a carrier ligands demonstrated activity which was comparable to that of the reference compound *Cisplatin*. The antitumor activity of such non-classical complexes may be due to the loss of sulfide ligand, followed by the interaction with DNA [41-43].

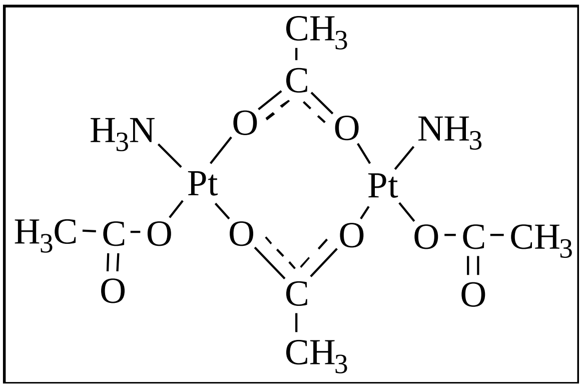
Comparative research of cytotoxic effects in *vitro* of Pt(II) complexes with cyclobutanespiro-5’-hydantoin, with formula cis-$[PtL_2(NH_3)_2]^{2+}$ and cyclopentane-PtCPH(5), cyclohexane-PtCHH(6), cycloheptanespiro-5’-hydantoins with general formula cis-$[PtL(NH_3)_2]^{2+}$ was carried out by Bakalova and cowerkers. The human leukemia cell lines HL-60 (acute myeloid leukemia-derived), SKW-3 (chronic lymphoid leukemia-derived) and BV-173 (chronic myeloid leukemia-derived) were used [44-46]. *Cisplatin* was used as a reference cytotoxic agent. The concentration-response curves were extrapolated and IC_{50} values were derived. The analysis of the data obtained showed that the increase of the cycloalkane ring in ligands of the Pt(II) complexes with cyclopentane-, cyclohexane- and cycloheptanespiro-5’-hydantoins correspondingly led to considerable decrease in cytotoxic activity. The antitumor activity of Pt(II) complex with cyclobutanespiro-5’-hydantoin is similar to those of the Pt(II) complex with cyclopentanespiro-5’-hydantoins. The monodentate binding of two hydantoin ligands in the Pt(II) complex with cyclobutanespiro-5’-hydantoins and essential difference in the molecular formulas of the Pt(II) complexes with cyclopentane-, cyclohexane- and cycloheptanespiro-5’-hydantoins could not interprete the increase in the cycloalkane ring on the biological activity. Independently that the reference



PtCPH (**5**)



PtCHH (**6**)



Platacetat (**7**)

cytostatic *Cisplatin* had lower IC_{50} values than the newly synthesized Pt(II) complexes in high concentrations comparable efficacy was reported.

The novel Pt(II) complexes with 1-aminocyclopentane- and 1-aminocyclohexanecarboxylic acids of the type cis-$[PtL(NH_3)_2]^{2+}$ were synthesized and characterized by Bakalova et al.. These compounds possessed pronounced cytotoxic effect *in vivo* and *in vitro* and were less toxic than *Cisplatin* [44].

Pt(II) complex with 5-methyl-5-phenylhydantoin was prepared and investigated by the author. It showed high antitumor activity *in vitro* against some human cell lines [46]. It induced programmed cell death (apoptosis) against cell line HL-60 analogical to *Cisplatin*.

One of the most successful approaches in platinum antitumor drugs design is the synthesis of polynuclear platinum complexes with bridging linkers [47]. Their success is based on the ability of such complexes to form DNA adducts, which are structurally different from those of *Cisplatin*. Some of the polynuclear (mostly dinuclear) antitumor active Pt(II) complexes described in the literature contain flexible bridging ligands [48-50], while others possess rigid linkers together with bridging leaving groups [51,52]. The complexes with flexible linkers (for instance, aliphatic diamines) are designed to form long-range cross-links to DNA [53,54], and the complexes possessing rigid bridging ligands, such as hydrazine and azoles are developed to minimize distortion of DNA double helix in a 1,2-intrastrand cross-link [55].

A new class of dinuclear Pt(II) complexes with azines as bridging ligands were described [50,56]. These compounds exhibit considerable activity *in vitro* against several human tumor cell lines.

The trinuclear platinum complex BBR3464 has been invented jointly by Novuspharma and Prof. Nicholas Farell [57]. This compound exerts profound cytotoxic effects at lower concentration compared to *Cisplatin*. It has been established that the complex constituted 1,4-intrastrand cross-links. Currently BBR3464 is under phase II clinical trial stage of development [57, 58].

Binuclear platinum complexes with acetic acid *(Platacetat)*(7) – cis-$[Pt_2(NH_3)_2(CH_3COO)_2$-]-μ-$(CH_3COO)_2]$, propionic acid–cis-$[Pt_2(C_2H_5COO)(NH_3)$-μ-$(C_2H_5COO)_2Cl_2]^-$, valeric acid–cis-$[Pt_2(C_4H_9COO)_2(NH_3)_2$-μ-$(C_4H_9COO)_2Cl]^-$ and isovaleric acid-cis-$[Pt_2(C_4H_9COO)_2(NH_3)$-μ-$(C_4H_9COO)_2Cl]^-$ were synthesized and pharmacologically investigated by the author [64]. These four complexes possessed high cytotoxic effect *in vivo* and *in vitro*, significantly exceeding those of *Cisplatin* [59]. The following tumor test systems - leukemia L1210, leukemia P388 and Ehrlich ascites tumor and a panel of human tumor cell lines were tested. *Platacetat* is very soluble

in water and possessed lower nephrotoxicity than *Cisplatin* [59, 60].

CONCLUSIONS

It is very important to note that the initially accepted view for the platinum complexes to be active they should be neutral with cis-configuration and structural analogs of cis-DDP, may undergo changes. That gives better opportunities for seeking and developing new platinum complexes with different ligands as antitumor agents.

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