Status of Non-Classical Mononuclear Platinum Anticancer Drug Development

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Abstract: Cisplatin has become one of the most commonly used compounds for the treatment of a wide spectrum of human malignancies. Unfortunately, cisplatin has several major drawbacks. Driven by the impressive impact of cisplatin on cancer chemotherapy, great efforts have been made to develop new derivatives with improved pharmacological properties. Among the over 30 platinum agents which have entered clinical trials after the onset of clinical studies with cisplatin in the early 1970s, only carboplatin and oxaliplatin have received worldwide approval so far, nedaplatin, lobaplatin and heptaplatin have gained regionally limited approval. It has become quite evident that mere analogues of cisplatin or carboplatin will not probably offer any substantial clinical advantages over the existing drugs. Consequently, attention turned to the synthesis of non-classical platinum anticancer drugs which were capable of forming a different range of DNA adducts which could display a different spectrum of anticancer activity compared to cisplatin. The status of non-classical bi- and multi-nuclear platinum anticancer drug development has been reviewed. This review will summarize the structural types and structure-activity of non-classical mononuclear platinum anticancer drugs, and discuss their future potential as anticancer agents.

Key Words: Anticancer, sterically hindered platinum(II) complexes, cationic platinum(II) complexes, monofunctional platinum(II) complexes, tri-functional platinum(II) complexes, trans-platinum(II) antitumor complexes, Pt(IV) complexes, hypoxia-selective platinum complexes.

INTRODUCTION

By now, cisplatin has become one of the most commonly used compounds for the treatment of a wide spectrum of human malignancies. Unfortunately, cisplatin has several major drawbacks. Common problems include cumulative toxicities of nephrotoxicity, ototoxicity and peripheral neuropathy. In addition to the serious side effects, the therapeutic efficacy of cisplatin is also limited by inherent or treatment-induced resistant tumor cell sub-populations. Driven by the impressive impact of cisplatin on cancer chemotherapy, great efforts have been made to develop new derivatives with improved pharmacological properties. Among the over 30 platinum agents which have entered clinical trials after the onset of clinical studies with cisplatin in the early 1970s, only carboplatin and oxaliplatin have received worldwide approval so far, nedaplatin, lobaplatin and heptaplatin have gained regionally limited approval (Fig. **1**), and a few drugs continue to be evaluated in clinical studies [1-4].

Cleare and Hoeschele defined a set of structure activity rule for platinum chemotherapy drugs based on cisplatin results as follows [5]: 1) have a zero net charge; 2) have two leaving groups, or one bidentate leaving group; 3) have chloride leaving groups, or other similar ligands with a lability in the window of reactivity centred on chloride; 4) have leaving groups in the *cis*-configuration; 5) not contain hydroxy ligands, as these make the complex highly toxic; and 6) have other non-leaving ligands which are inert, preferably amine or ammine ligands. This set of structure activity rule remained valid. This is reflected in the fact that all platinum compounds that have entered clinical trials adhere to this set of guideline. Although some progress had been made in reducing the toxic side effects and overcoming resistance, it has become quite evident that mere analogues of cisplatin or carboplatin will not probably offer any substantial clinical

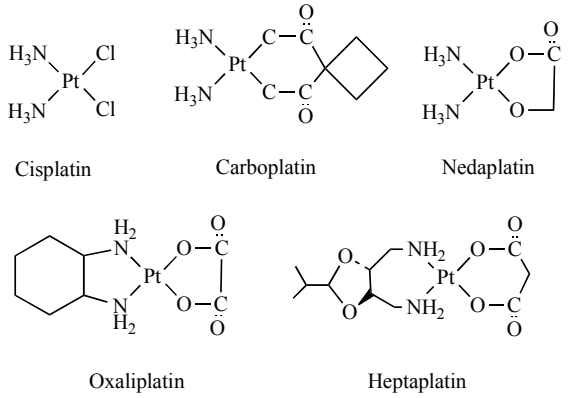

Fig. (1). Stuctures of clinically established anticancer platinum compounds.

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advantages over the existing drugs. Evidence suggests that this is due to the cisplatin analogues' forming a similar array of DNA adducts as cisplatin [6]. Consequently, attention turned to the synthesis of non-classical platinum complexes which were capable of forming a different range of DNA adducts which could display a different spectrum of anti-cancer activity compared to cisplatin. The status of non-classical bi- and multi-nuclear platinum anticancer drug development has been reviewed [7, 8].

In this paper, the purpose of this review is to summarize the current status of non-classical mononuclear platinum anticancer drug development.

1. STERICALLY HINDERED PLATINUM(II) COMPLEXES

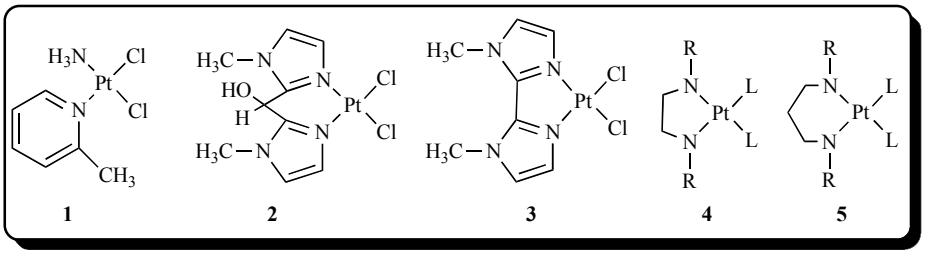
Glutathione (GSH) has been implicated in tumor resistance by reducing drug accumulation by reacting with drugs to form inactive species and by enhancing DNA repair [9-11]. Cis-amminedichloro (2-methylpyridine) platinum(II) complex (**1**) is a sterically hindered Pt complex that was rationally designed in order to circumvent resistance by blocking cellular detoxification by GSH and other cellular thiols.

From the crystal structure of the complex (**1**), it has been concluded that the methyl group situated in the 2-position of the pyridine ring, which is nearly perpendicular to the platinum square plane, sterically hinders an axial approach to the platinum centre and therefore partially protects from associative ligand exchange [12]. Sterichindrance results in reducing reactivity compared to cisplatin towards sulphur donors such as methionine and thiourea, and binding to DNA is less affected in the presence of glutathione. Comparison of the complex (**1**) with analogues containing either unsubstituted pyridine or dimethylpyridine revealed that the rate of cross-link formation consistently becomes slower with increasing steric hindrance by bulkier ligands. Model experiments indicate that steric hindrance by the methylpyridine group influences binding to DNA, as formation of a single stereoisomer is favoured, when the complex (**1**) binds to a double-stranded oligonucleotide containing two adjacent guanosines, whereas little stereoselectivity is found for reactions with a corresponding single-stranded oligonucleotide.

The complex (**1**) has shown intermediate cytotoxicity between cisplatin and carboplatin in two panels of cancer cell lines [13-15]. In the first panel of 11 human carcinoma cell lines, the complex (**1**) showed an average cytotoxicity of 8.1 μM, compared to 2.6 μM for cisplatin and 20.3 μM for carboplatin [14]. In the second panel of 6 HOC cell lines, the complex (**1**) had an average cytotoxicity of 14.7 μM, again less than carboplatin (23 μM), but more than cisplatin (3.5 μM) [10]. In addition, the complex (**1**) demonstrated its ability to overcome resistance, even in cell lines where the resistance was not due to increased glutathione levels [13, 14]. Now the complex (**1**) has undergone phase I and II clinical trials [7]. From phase I, the drug has demonstrated a broad spectrum of activity and a manageable toxicity profile, with no clinically significant ototoxicity, neurotoxicity or nephrotoxicity.The dose-limiting toxicity (DLT) appears to be neutropenia. Phase I trials have also confirmed the potential of the drug to be delivered orally with 40% bioavailability. Phase II trials have been completed for HRPC, SCLC, NSCLC and mesothelioma. In all, 500 patients have received treatment with the complex (**1**), and over 200 of those received treatment for at least 2 cycles.

Another example of a cytotoxic Pt complex with a sterically crowded Pt center was reported by Reedijk and Krebs [16]. *cis*-[Pt(bmic)Cl_2] (**2**) was reported to have significant cytotoxicity in L1210 leukemia bearing mice, while *cis*-[Pt(bmi)Cl_2] (**3**), which has less steric bulk around the metal, was found to be inactive. A difference in the reactivity to 5-GMP was observed between *cis*-[Pt(bmic)Cl_2] and *cis*-[Pt-(bmi)Cl_2]. The greater steric hindrance around the Pt metal in *cis*-[Pt(bmic)Cl_2] caused it to be less reactive than *cis*-[Pt(bmi)Cl_2] and rendered it less susceptible to deactivation by cellular thiols. *Cis*-[Pt(bmic)Cl_2] may have interesting activity in cisplatin resistant tumors, but as of yet, no extensive evaluation of *cis*-[Pt(bmic)Cl_2] cytotoxicity in various cisplatin-resistant cell lines has been reported.

The antitumor activities of *cis*-bis(pyridine)platinum(II) complexes with organic amine ligands (**4**, **5**) were reported by Deacon and co-workers [17]. The activities of these complexes were attributed to the large steric effect of the organic amine ligands. The replacement of the bulky organic amine ligands by chloride as in *cis*-[Pt(pyridine)$_2$$Cl_2$] reduced the cytotoxicity of the compound. In a L1210/L1210cisR pair of cell lines, *cis*-[Pt(pyridine)$_2$$Cl_2$] was less cytotoxic than *cis*-bis(pyridine) organic amine platinum(II) complexes, which had comparable activity to cisplatin. A number of the complexes with different organic amine ligands, unsubstituted and methyl-substituted pyridine, were evaluated in both cisplatin sensitive and -resistant cell lines. There was no significant difference in activity with variation of the organic amine ligands. However, complexes with pyridine ligands having 2-methyl substitution were less active than similar complexes with pyridine or 4-methylpyridine ligands. This is possibly due to the steric hindrance effect of the 2-methyl group during the formation of the Pt-DNA adduct.



1 **2** **3** **4** **5**

2. CATIONIC PLATINUM(II) COMPLEXES

2.1. Cationic Platinum(II) Complexes with Pt-S Bond

For cationic platinum complexes with Pt-S bond, the incorporation of a sulfur ligand has been generally considered to be deactivating because of the potential labilization of the amine groups in the trans position. The use of bidentate amines such as dach or damch prevents this and gives complexes non-cross-resistant with cisplatin. In addition, incorporation a Pt-S bond in a well-defined complex prior to any administration may have effects on tissue binding and metabolism [18, 19], nephrotoxic side effects, and reactivity of endogenous thiols such as glutathione.

In this series (Fig. **2**), the activity of the complexes is dependent on the nature of both the amine and the sulfoxide, and where unsymmetrical sulfoxides are used, the antitumor activity (resistance factor) also dependent on the chirality of the sulfoxide ligand. Due to the potential labilization of the amine groups in the trans position, the incorporation of a sulfur ligand has been generally considered to be deactivation. A platinum(II) complex with a thiourea ligand showed excellent cytotoxicity against a leukemia cell line. The complex exhibited activity against two ovarian cancer cell lines at micromolar concentrations, but slightly less activity than that of the free ligand [20, 21]. In summary, cationic platinum complexes with Pt-S bond represent a good example, although the final adducts are similar to cisplatin, the structure is sufficiently different [22].

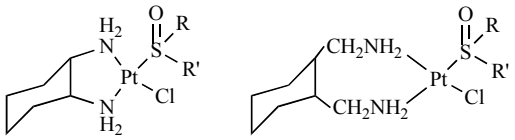
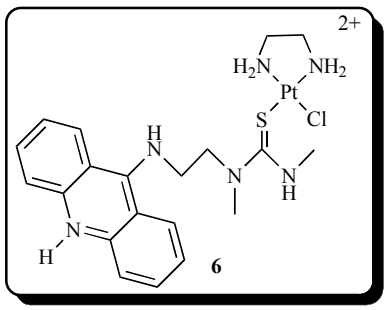


Fig. (2). Structures of antitumor-active cationic platinum(II) complexes containing a platinum-sulfur bond.

2.2. Triamine Cationic Platinum(II) Complexes

In this series (Fig. **3**), no displacement of pyridine occurs and complexes appear to bind to DNA in a monodentate fashion [23, 24]. Unlike the monodentate complex, [PtCl (dien)]Cl (**6**), DNA replication is inhibited effectively by the triamine complexes and sequencing studies showed little attack at multiple guanine sites. While no comparison can be made with activity in cisplatin-resistant tumor cells, the results show that formally monodentate lesions can lead to cytotoxic events. The role of the planar ligand pyridine is obviously critical in augmenting the cytotoxicity. It may transpire that pyridine ligands in this series and in active trans complexes exert similar structural roles. The steric effects in both cases will slow substitution reactions compared to the smaller, less sterically demanding NH_3. This feature could greatly affect the pharmacokinetics of the complexes. It is intriguing to consider that reducing chemical reactivity may result in enhancement of biological activity in traditionally antumor-inactive compounds.



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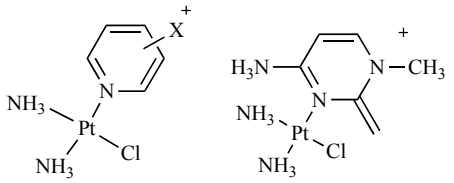
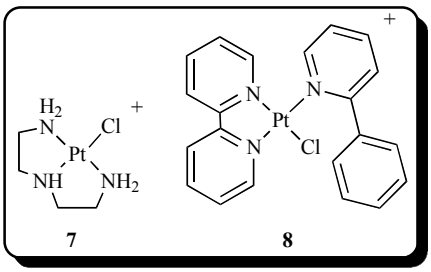


Fig. (3). Stuctures of cationic triamine platinum(II) complexes with demonstrated antitumor activity.

In the search for cis-amminedichloro(2-methylpyridine)-platinum(II) (**1**) derivatives with improved antitumor activity, an unexpected monofunctional platinum(II) complex with one normal and one cyclometalated 2-phenylpyridine ligand (**7**) was discovered, it exhibited high antitumor efficacy against cisplatin-resistant mouse sarcoma 180 (S-180cisR) cell lines [25]. Consistent with its higher activity in the resistant cells, more efficient cellular uptake of this new complex compared with cisplatin was demonstrated. As a monofunctional complex, the platinum–phenylpyrindine compound cannot form DNA cross-links, indicating a different binding mode from that of cisplatin unless a ligand is displaced intracellularly. Its high cytotoxicity in cisplatin-resistant cells may possibly be a consequence of diminished DNA repair [26].

Another example of a platinum(II) complex with a thiourea ligand (**8**) was reported that showed excellent cytotoxicity against a leukemia cell line. The complex may bind to DNA in a dual manner involving platinum coordination and acridine intercalation. The complex exhibited activity against two ovarian cancer cell lines at micromolar concentrations, but slightly less activity than that of the free ligand [20, 21].



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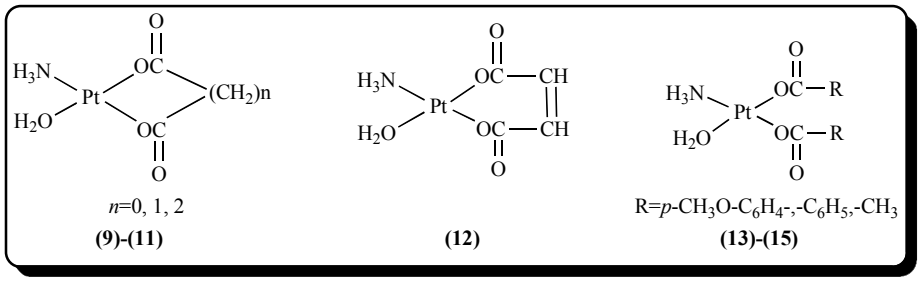
3. TRI-FUNCTIONAL PLATINUM(II) COMPLEXES

Zhang *et al*. have synthesized seven new tri-functional mononuclear platinum(II) complexes (**9-15**), which have better cytotoxicity when leaving groups are aromatic carboxylates, moreover, the substituent in benzene ring also influences cytotoxicity. In addition, when leaving groups are dicarboxylates, dicarboxylates coordinating with platinum through oxygen atoms form different chelate cycle, cycle



size also affects their cytotoxicity. In comparison to cisplatin, these compunds have weaker cytotoxicity against HCT-8 and MCF-7. The complexes (**9, 10, 11** and **12**) also exert weaker cytotoxicity against BGC-823 with respect to the IC_{50} values obtained. The complexes (**9, 10, 13** and **14**) have better cytotoxicity against EJ, but their cytotoxicity is weaker than that of cisplatin. The complexes (**11, 13** and **14**), they confer substantially greater cytotoxicity against HL-60 with an IC_{50} value of 7.68±0.23, 3.87±0.19 and 2.41±0.18 μM respectively, moreover, cytotoxicity of the complex (**14**) is equal to that of cisplatin. The complexes (**11, 13** and **14**) cause significant G2/M arrest and a concomitant decrease of cell population in G_1 and S phases.Complexes (**11, 13** and **14**)**,** the levels of total platinum bound to DNA in HL-60 are increased with increasing concentrations**,** moreover, their total DNA platination levels are higher than that of cisplatin under the same experimental conditions [27]. There is no correlation between total DNA platination levels in HL-60 and cytotoxicity of complexes. According to the characteristic of chemical structures, They deduced that the major adduct formed by tri-functional platinum complexes might be *via* tridentate coordination through bases on DNA. The mechanism of action for these complexes remains to be further studied.

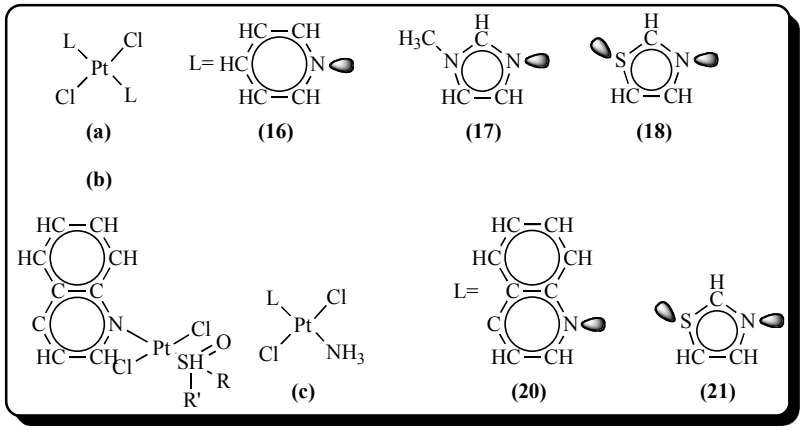
4. TRANS- PLATINUM(II) COMPLEXES

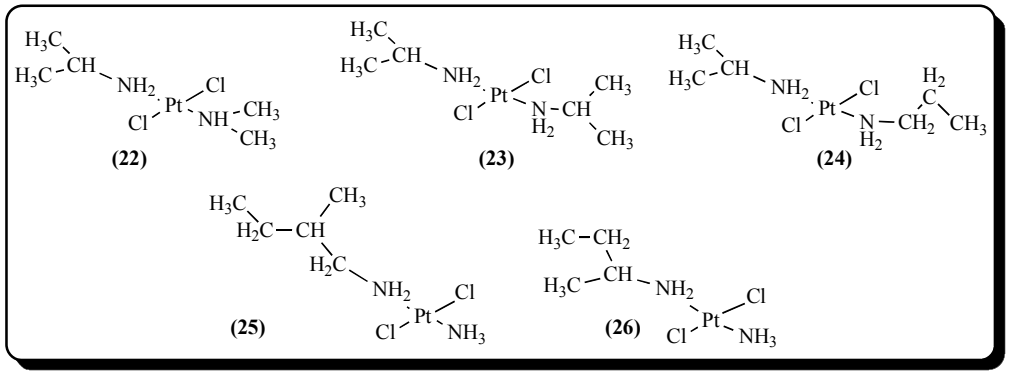
4.1. *Trans*-[$PtCl_2$ (L)(L')] (L = N-donor aromatic heterocycle; L' = ammine, sulphoxide or a second molecule of L ligand)

Three distinct series of *trans*-[$PtCl_2$(L)(L')] complexes have been proposed by Farrell *et al.* [10]: (a) L = L' =pyridine (**16**), N-methylimidazole (**17**), or thiazole (**18**), (b) L =quinoline and L' = RR'SO (R= Me, R' = Me, Bz, or Ph) (**19**), and (c) L = quinoline (**20**) or thiazole (**21**) and L' = NH_3 [28-32]. The cytotoxicities of these complexes are approximately 100-fold higher than those of transplatin and comparable to those of cisplatin against murine and human tumor cell lines [30]. A study of the cytotoxicity has shown that substitution of ammine ligands in transplatin with more bulky ligands led to compounds with higher *in vitro* tumor cell growth inhibitory potency, often active towards cisplatin resistant tumor cells, and in some cases also endowed with significant *in vivo* activity, thus they have a unique profile of activity, and are also active against cisplatin and oxaliplatin resistant cells [33]. It can be noted that the replacement of a single NH_3 ligand of transplatin by a N-donor heterocycle, such as quinoline or thiazole (**20** and **21**), will increase dramatically the cytotoxicity of the trans complexes [34]. Importantly, compound (**21**) also shows antileukaemic activity *in vivo*. In order to overcome the poor solubility, water-soluble derivatives containing acetate ligands in place of the chlorides have been recently synthesized. Interestingly, the new derivatives maintain the activity profile of the parent chloro compounds [35]. However, due to unexpected inertness of trans diacetate complexes, the activity decreased compared to the dichloro species.

4.2. *Trans*-[$PtCl_2$(L)(L')] (L = isopropylamine, L' = aliphatic-substituted amine; L =2-me-butylamine or sec-butylamine, L' = ammine)

Transplatin analogs with aliphatic amines, such as *trans*-[$PtCl_2$(isopropylamine)(L')] (L' = dimethylamine, isopropylamine,or propylamine (**22-24**) represent another class of antitumor-active platinum compounds with *trans* geometry [36-38]. Complexes (**22-24**) exhibit a cytotoxic activity in cisplatin sensitive cells comparable to that of cisplatin and considerably higher than that of cisplatin in several cisplatin





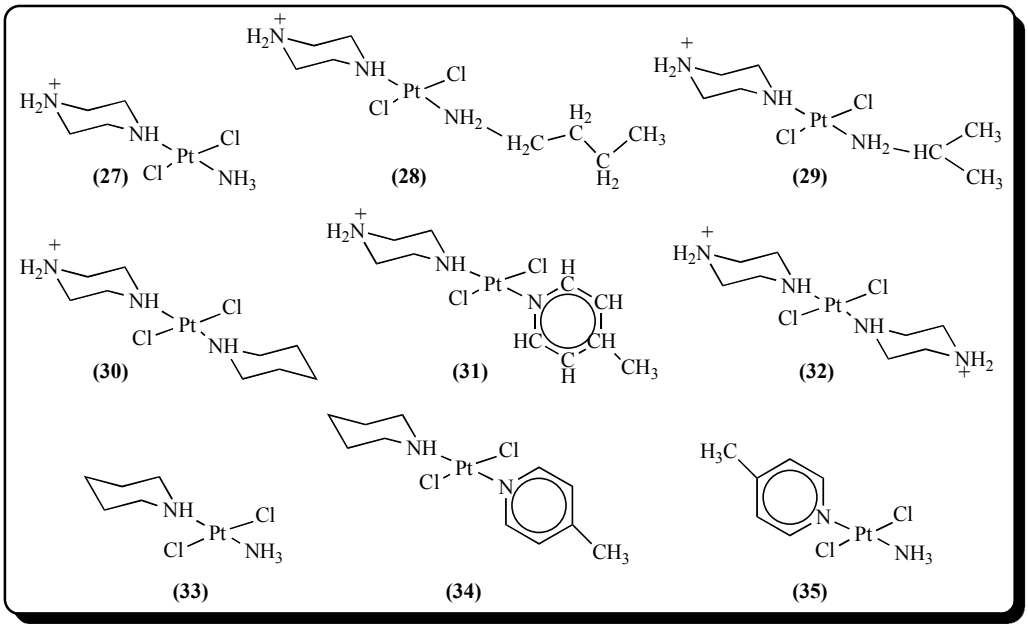
resistant tumor cells. Unfortunately, extensive data on the *in vivo* activity of compounds (**22-24**) are not available, only (**22**) has been investigated in CH1 human ovarian xenografts, the complex had no inhibitory activity upon tumor progression. In contrast, the recently developed platinum(IV) counterpart of *trans*-[$PtCl_2(OH)_2$(isopropylamine)(dimethylamine)], had activity in the CH1 xenograft system *in vivo*, and overcome completely cisplatin resistance in A2780cisR, CH1cisR, and 41McisR ovarian cancer cells (RF= 1.5, 0.8, and 0.05, respectively) [39]. In addition, compounds containing only one branched aliphatic amine, such as *trans*-[$PtCl_2(NH_3)$(L)] (L = 2-methylbutylamine or *sec*-butylamine, **25** and **26**), have been synthesized with the aim of enhancing the water solubility of the parent bis-amine compounds [40]. Compounds (**25** and **26**) exhibit cytotoxic activities similar to those of cisplatin towards human ovarian cancer cells (A2780 and CH1) and partially circumvent cisplatin resistance of A2780cisR cells [34].

4.3. *Trans*-[$PtCl_2$(L)(L')] (L = piperazine, L'= ammine, n-butylamine, isopropylamine, 4-me-pyridine, piperidine, or piperazine; L = piperidine, L'= ammine or 4-me-pyridine; L = 4-me-pyridine, L' = ammine)

Trans-Pt complexes with the bulky aliphatic amines were synthesized by Navarro-Ranninger [39]. *Trans*-[$PtCl_2$(piperazine)(L')] complexes (L'= NH_3, *n*-butylamine, isopropylamine, piperidine, 4-me-pyridine, or piperazine) (**27-32**) circumvent, either partially or completely, the cisplatin resistance dependent upon multifactorial mechanisms. Apart from *trans*-platinum compounds containing a piperazine ligand, *trans*-[$PtCl_2$(piperidine)(L')] (L'=ammine or 4-me-pyridine) and *trans*-[$PtCl_2(NH_3)$(4-me-pyridine)] (**33**, **34**, and **35**) were found to have promising growth inhibitory activities towards human ovarian carcinoma (OV-1063) and colon carcinoma (C-26) tumor cells [41]. Interestingly, both (**33**) and (**35**) circumvent, at least partially, cisplatin resistance of A2780 cisR cells, but are highly cross resistant to cisplatin in the case of CH1cisR and 41McisR cells [42].

4.4. *Trans*-[$PtCl_2$ (L)(L')] (L = imino ligand; L' = NH_3 or a second molecule of L)

Trans-platinum compounds with iminoether ligands have been reported by Coluccia and Natile. They have general formula *trans*-[$PtCl_2${HN=C(OR)R'}$_2$] or *trans*-[$PtCl_2(NH_3)$ {HN=C(OR)R'}] (**35-37**). In a panel of human tumor cell lines containing examples of ovary, colon, lung, and breast cancers, compound (**36**) shows a growth inhibitory potency comparable to that of cisplatin. Interestingly, compound (**36**) is able to circumvent the cisplatin resistance of A2780/cp8 cells. Compounds (**37** and **38**), containing only one molecule



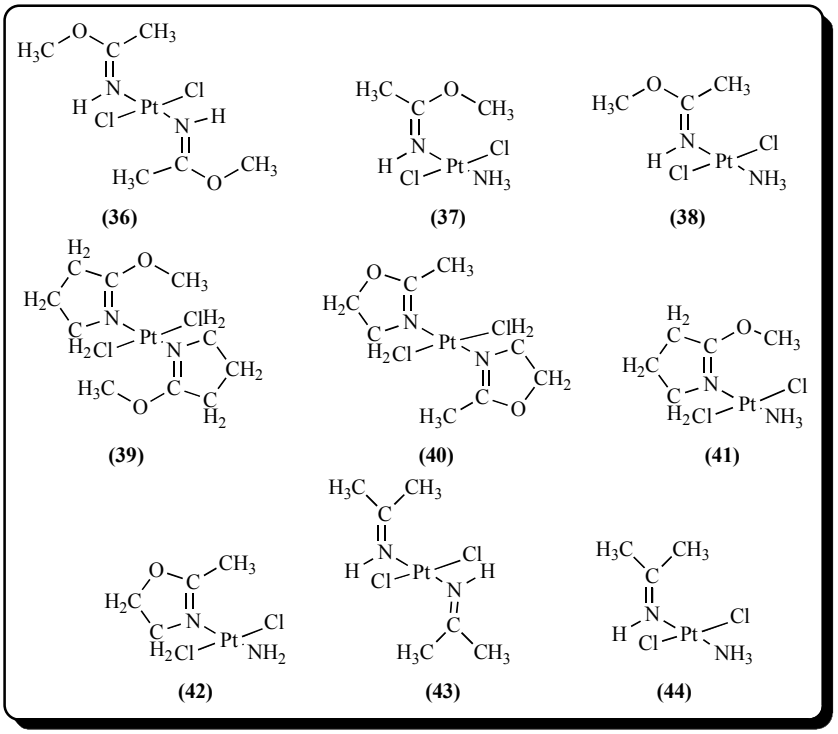
of iminoether, are less cytotoxic than (**36**), moreover the inhibitory potency is reduced for the *Z* configuration (compound **37**) as compared to the *E* configuration (compound **38**). Importantly, compounds (**37** and **38**) partially circumvent the cisplatin resistance dependent upon multifactorial mechanisms and by reduced accumulation and are characterized by an activity profile different from that of cisplatin [43]. Both *trans*-[$PtCl_2$(iminoether)$_2$] and *trans*-[$PtCl_2(NH_3)$(iminoether)] compounds are characterized by an *in vivo* antitumor activity similar to that of cisplatin towards murine leukemic and solid metastasizing tumors, as well as towards human xenografts [44-46].

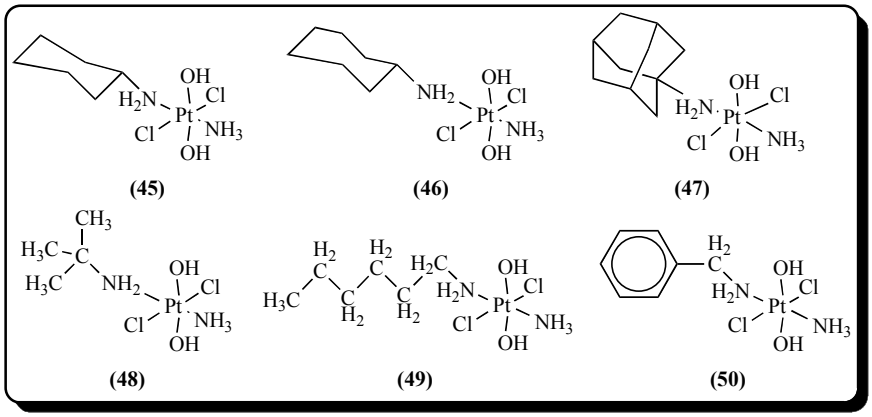
Since the antitumor activity of platinum-iminoether complexes is affected by ligand configuration, a systematic investigation of the relationships between ligand configuration and pharmacological action of the platinum complexes was undertaken. In order to avoid the complication arising from possible isomerization between *Z* and *E* configurations encountered in iminoether compounds [47], platinum complexes with cyclic ligands mimicking *Z* (**39** and **41**) or *E* iminoethers (**40** and **42**) have been synthesized. Compounds (**41** and **42**) are more cytotoxic than corresponding compounds with iminoethers (**36** and **37**), but have rather similar activity profile, effect of ligand configuration, and activity towards cisplatin resistant cells [32]. Platinum complexes with two acetonimines (*trans*-[$PtCl_2\{HN{=}C(CH_3)_2\}_2$], **43**) or with one acetonimine and one ammine (*trans*-[$PtCl_2(NH_3)\{HN{=}C(CH_3)_2\}$], **44**) have also been investigated [48]. In a panel of human tumor cell lines of different origins, both compounds (**43** and **44**) show a remarkable cytotoxic activity (mean IC_{50} = 10.6 and 26 μM, respectively) and are able to circumvent the cisplatin resistance of ovarian cell sublines, thus demonstrating that ketimines determine the activation of the *trans* geometry [34].

5. PT(IV) COMPLEXES

5.1. Cis-Ammine/Amine Pt(IV) Complexes

Seventeen alkylamine/ammine dicarboxylatodichloroplatinum(IV) complexes of general structure c,t,c-[$PtCl_2(OCOR_1)_2NH_3(RNH_2)$] (where R = aliphatic or alicyclic and R_1 = aliphatic or aromatic) have been evaluated against L1210 cell lines with acquired resistance to cisplatin (10-fold), tetraplatin (34-fold) or carboplatin (14-fold) [49]. All of these compounds overcame cisplatin, tetraplatin and carboplatin resistance. Potency increased as the number of carbon atoms in the axial aliphatic ligands (R_1) increased. The most active compounds were those possessing aromatic ligands at R_1, regardless of whether R = aliphatic or alicyclic. Using a panel of six human ovarian carcinoma cell lines varying by two orders of magnitude in terms of cisplatin cytotoxicity, Kelland *et al*. [50] have investigated the *in vitro* antitumor activity of a series of novel alkylamine/ammine dicarboxylatodichloroplatinum(IV) complexes of general structure c,t,c-[$PtCl_2(OCOR_1)_2NH_3(RNH_2)$]. A clear relationship existed between increasing the number of carbons in the R_1 substituent and increasing cytotoxicity up to R1 = C_5H_{11}. In terms of changing the R group, maximum cytotoxic effects were conferred by alicyclic substituents. Furthermore, increasing the alicyclic ring size from cyclobutane through to cycloheptane resulted in increasing cytotoxicity. The agents with longer axial chains were significantly more cytotoxic than cisplatin and, moreover, exhibited a selective cytotoxic effect against the most intrinsically cisplatin-resistant cell lines. In addition, amine/cycloalkylamine platinum(IV) homologous series was evaluated for cytotoxicity and biochemical pharmacology in murine leukemia L1210/0, L1210/DDP [51]. Within each series, which contained 4 homologs with differing alicyclic (cycloalkyl) ring size (cyclopropane, cyclobutane, cyclopentane, or cyclohex-





ane), cytotoxicity increased with increasing ring size. The results have demonstrated high dependencies on ring size of the carrier amine ligand, valence state of platinum, and the nature of the axial ligand for modulation of potency, cross-resistance property, and biochemical pharmacology of amine/cycloalkylamine complexes.

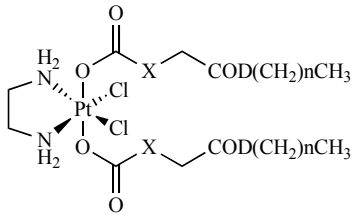
In summary, a feature of members of the ammine/amine platinum(IV) class of complex is that they may be chemically modified at a number of sites. For example, substitutions in amine, trans-axial ligands, and leaving groups are possible. The structure-activity relationships investigated have shown that the dramatic cytotoxicity effects are mediated largely through the lipophilicity of the axial ligands. However, cytotoxicity may also be mediated, but to a lesser degree, through alterations in the amine ligand. In particular, alicyclic, rather than aliphatic or aromatic, substitutions produced the greatest cytotoxic effects. Furthermore, within the alicyclic series, cyclobutane, -pentane, -hexane, and –hepane, cytotoxicity increased with each step up in the ring size. To date, the effect of varying the dichloride leaving group has not been reported [3].

5.2. *Trans* -Ammine/Amine Pt(IV) Complexes

The search for orally active platinum drugs led to the design of several platinum(IV) complexes with trans geometry of leaving ligands. A series of *trans*-ammine/amine Pt(IV) complexes were synthesized and investigated for their *in vitro* and *in vivo* antitumor activity. In a panel of human ovarian carcinoma cell lines (SKOV-3, A2780, HX/62, CH1, and 41M), many of the platinum(IV) complexes exhibit a potency comparable to that of cisplatin [34]. The *trans*-platinum(IV) complexes were able to completely overcome cisplatin resistance of 41McisR and CH1cisR, but only partially that of A2780cisR. Fourteen *trans* complexes showed significant *in vivo* antitumor activity against the subcutaneous murine ADJ/PC6 plasmacytoma model. All of them were platinum(IV) complexes possessing axial hydroxide ligands, with only one exception having axial ethylcarbamate ligands. When tested, all their dichloroplatinum(II) or tetrachloroplatinum(IV) counterparts were inactive. Three out of the fourteen complexes (**45-47**) retain some efficacy against a cisplatin resistant variant of the ADJ/PC6 plasmacytoma and five (**45**, the same as **45** but with Br axial ligands, **48**, **49**, and **50**) exhibit antitumor activity against subcutaneously grown advanced-stage human ovarian carcinoma xenografts. Importantly, complex (**45**) has been the first *trans*-platinum complex showing significant *in vivo* antitumor activity towards models of acquired cisplatin resistance [52], although as far as we know has not yet entered clinical trials, continues to have the lead in antitumor *trans*-platinum(IV) compounds.

5.3. 1, 4 or 1,2-DACH Pt(IV) Complexes

A series of platinum(IV) monoadducts of the type [Pt(IV)(DACH)trans-$(X)_2$LCl]NO_3 (where DACH=trans-1R,2R-diaminocyclohexane, L=adenine, guanine, hypoxanthine, cytosine, adenosine, guanosine, inosine, cytidine, 9-ethylguanine (9-EtGua), or 1-methylcytosine and X=hydroxo or acetato ligand) have been synthesized and characterized. Some of these synthesized models of DACH-Pt-DNA adducts have good *in vitro* cytotoxic activity against the cisplatin-sensitive human cancer ovarian A2780 cell line. Interestingly, a substituted nucleobase (9-ethylguanine) adduct was over 6-fold more potent than regular adducts. The results suggested that DNA adducts of DACH-Pt are cytotoxic with low cross-resistance. Several Pt(IV) complexes containing 1R,2R-cyclohexanediamine (1R,2R-DACH) as a carrier ligand were synthesized [53]. The cytotoxicities and the uptake of the platinum complexes by leukemia L1210 cells were compared in order to study the correlation between their structures and cytotoxicities. [Pt(IV)Cl_4(1R,2R-DACH)], trans(Cl)-[Pt(IV)Cl_2(oxalato)(1R,2R-DACH)], and trans(Cl)-[Pt(IV)Cl_2(malonato)(1R,2R-DACH)] had high cytotoxicities. In addition, trans (OH)-[Pt(IV)$(OH)_2Y_2$(1R,2R-DACH)] (Y_2: oxalato or malonato) did not exhibit cytotoxicity towards leukemia L1210 cells, whereas trans(Cl)-[Pt(IV)Cl_2Y_2(1R,2R-DACH)] (Y_2: oxalato or malonato) were highly cytotoxic. Platinum(IV) complexes, in which leaving groups are replaced by hydroxide groups, have decreased cytotoxic activity. Trans(OH),cis(Cl)-[Pt(IV)$(OH)_2$ Cl_2(1R,2R-DACH)], which has hydroxide and chloride groups, was easily incorporated into the cells and exhibited the high cytotoxic activity. This behavior indicates that the chloride group apparently overcomes the ameliorating effect of the hydroxide group. The synthesis, characterization, and antitumor activity of a series of platinum(IV) complexes of the type [DACH-Pt(IV)$(X)_2$Y](where DACH = trans-dl, or trans-l-1,2-diaminocyclohexane, X = OH or Cl, and Y = oxalato, malonato, methylmalonato, tartronato, ketomalonato, 1,1-cyclopropanedicarboxylato, or 1,1-cyclobutanedicarboxylato), were described by Khokhar *et al*. [54]. The complexes



X=CH_2, n=0-3 (**51-54**)
X=$CH_2CH(CH_3)$, n=0, 1(**55-56**)

Fig. (4). Structures of the novel bis(carboxylato)platinum(IV) complexes (**51-56**).

had good *in vitro* cytotoxic activity and were highly active *in vivo* against leukemia L1210 cells. In addition, excellent *in vivo* antitumor activities against B16 melanoma, M5076 reticulosarcoma and cisplatin-resistant L1210/DDP cell lines were also exhibited by an analog selected for further evaluation. A series of new platinum(IV) complexes of the type [Pt(IV)(DACH)trans$(L)_2Cl_2$] (where DACH = trans-1R,2R-diaminocyclohexane, and L = acetate, propionate, butyrate, valerate, hexanoate, or heptanoate) bearing the carboxylate groups in the axial positions have been synthesized and characterized [55]. These analogues were evaluated *in vitro* and demonstrated cytotoxic activity against the human ovarian tumor cell line. Structure-activity study revealed that activity was highest for the analogue where L = butyrate.

Novel 1,4-diaminocyclohexane platinum(IV) complexes have shown activity *in vivo* against tumor models resistant to cisplatin and tetraplatin. The novel complexes include the chloro, acetate, trifluoroacetate, propionate, butyrate, pentanoate, hexanoate and heptanoate as leaving ligands and 1,4 - DACH amine ligands. The complexes showed good *in vitro* cytotoxic activity against murine leukemia L1210/0, L1210/DDP and L1210/DACH. High *in vivo* activity was shown against L1210 leukemia cells and against cisplatin resistant L1210/DDP. Excellent antitumor activity against M5076 was also exhibited by the new complexes.

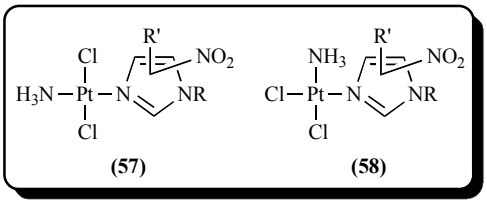
5.4. Bis(carboxylato)platinum(IV) Complexes

Reithofer *et al*. [56] have synthesized and characterized a series of novel bis(carboxylato)platinum(IV) complexes (Fig. **4**). The cytotoxic properties of compounds (**51-56**) were investigated in four human tumor cell lines (CH1, Hela, SK-OV-3 and SW480) and structure-activity relationships could be drawn. In the series of ester derivatives (**51-54**), **a** clear-cut structure–activity relationship is discernible. The methyl derivative **a** is the least active, and IC_{50} values remarkably decrease in all four cell lines with increasing chain length and lipophilicity of the alcoholate moiety, resulting in the following rank order of cytotoxicity: **51 < 52 < 53 <54**. The cytotoxicity of (**53**) and (**54**) consistently exceeds that of cisplatin by factors of 1.9–5.6 and 5.4–16, respectively, based on comparison of IC_{50} values. In the cisplatin-sensitive cancer cells CH1 and HeLa, the IC_{50} values of (**54**) are in the 10^{-8} M range, while those of cisplatin are in the 10^{-7} M range. However, the cisplatin-resistant cell lines SW480 and SK-OV-3 are also roughly an order of magnitude less sensitive to this compound, indicating that the resistance mechanisms of these cells can not be circumvented. In general, the cytotoxic properties of the tested compounds increase with increasing lipophilicity of the alcoholate moiety. Nevertheless, An influence of the carboxylation agent (succinic- versus 3-methyl-glutaric anhydride) with respect to the cytotoxic properties of the resulting bis(caboxylato)platinum(IV) complexes was found: (**55**) and (**56**) were by a factor of three more cytotoxic than their counter-parts (**51**) and (**52**).

6. HYPOXIA-SELECTIVE PLATINUM(II) COMPLEXES

Rapidly growing tumors may have regions of low oxygen levels (hypoxia) due to rapid growth (high oxygen consumption) and poor vascularization. Hypoxia-selective drugs should present the structural features of both DNA binding and redox-active portion of the molecule. These simplified principles for design of hypoxia-selective drugs are easily extended to metal complexes [57].

Hypoxia–selective platinum complexes may be obtained when one NH_3 group of the cisplatin (or transplatin) structure is replaced by a nitroimidazole in the series [$PtCl_2$ $(NH_3)(NO_2Im)$] (**57, 58**). These complexes were first developed as radiosensitizers in attempting to target radiosensitizing nitroimidazoles to DNA [58]. Their inherent cytotoxicity, independent of combination with radiation, has become of increasing interest. Unlike cisplatin, the series [$PtCl_2(NH_3)$ (NO_2Im)] shows higher cytotoxicity in hypoxic than in aerobic cells [59]. This property may be initially explained by the Pt-DNA binding resulting in aerobic toxicity with the increased hypoxic toxicity stemming from the reduction of the nitroimidazole group. Perhaps due to the presence of the planar ligand [60], there is not the same clear-cut difference in toxicity between the cis and trans isomers of [$PtCl_2(NH_3)$ (NO_2Im)] as with those of [$PtCl_2(NH_3)_2$]. The enhancement of hypoxic cytotoxicity emphasizes the fact that relatively simple changes on the parent molecule result in a significant alteration of antitumor activity [22].



7. CONCLUSIONS AND PERSPECTIVES

Recent advances in medicinal inorganic chemistry demonstrate significant prospects for the utilization of metal complexes as drugs, presenting a flourishing arena for inorganic chemistry. Significant progress in platinum based anticancer agents has been achieved, based in part on a mechanistic understanding of the DNA-binding and pharmacological effects of cisplatin. A lot of new compounds with reduced toxicity and increased specificity have been developed. Now reduction in toxicity, increased spectrum of activity, and oral administration remain the primary goals of Pt drug development.

The future development of platinum based anticancer agents requires an understanding of the physiological processing of platinum complexes, to provide a rational basis for

the design of new platinum based anticancer agents. Application of new methodologies such as combinatorial chemistry, extensively used in organic drug discovery, will be also beneficial for the development of platinum based anticancer agents. In summary, with the rapid advance in molecular biology, combined with innovation, it is possible that new Pt-based anticancer agents will be materialized in the near future.

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ABBREVIATIONS

BMI	=	Body mass index
DACH	=	1, 2-diaminocyclohexane
DAMCH	=	1-bis(aminoethyl)cyclohexane
DLT	=	Dose limiting toxicity
GSH	=	Glutathione
HRPC	=	Hormone refractory prostate cancer
IC_{50}	=	Drug concentration that produces 50% of cell killing
ICP-MS	=	Inductively coupled plasma-mass spectrometry
MTT	=	3-(4, 5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide
NSCLC	=	Non-small cell lung cancer
RF	=	Resistance factor
SCLC	=	Small cell lung cancer
SRB	=	Sulforhodamine B

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