Current Status of Platinum-Based Antitumor Drugs

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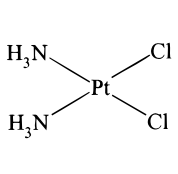
Contents

1. Introduction

The interest in platinum-based antitumor drugs has its origin in the 1960s, with the serendipitous discovery by Rosenberg of the inhibition of cell division by Pt complexes.[1] *cis*-Diamminedichloroplatinum(II) (*cis*-$[PtCl_2(NH_3)_2]$ (**1**)) and *cis*-diamminetetrachloroplatinum(IV) (*cis*-$[PtCl_4(NH_3)_2]$ (**2**)) were identified as the Pt compounds responsible for the phenomenon.[2−3] Deducing that Pt compounds would



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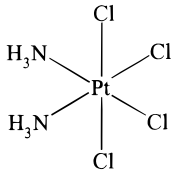

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have uses in cancer treatment, Rosenberg and coworkers performed experiments with Sarcoma 180 and Leukemia L1210 bearing mice.[2,4−7] This eventually led to *cis*-diamminedichloroplatinum(II) (cisplatin (**1**)) entering phase I clinical trials in 1971.[8] Approval of cisplatin for the treatment of testicular and ovarian cancer was given in 1978. Today, cisplatin is one of the three most widely utilized antitumor drugs in the world and has annual sales of approximately $500 million (U.S.).[9−10] It is highly effective in treating testicular and ovarian cancers, and it contributes to the treatment of oropharyngeal carcinoma, bronchogenic carcinoma, cervical carcinoma, lymphoma, osteosarcoma, melanoma, bladder carcinoma, and neuroblastoma.[9]

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Ernest Wong was born in Hong Kong in 1967. He received his B.Sc. in Chemistry and Nuclear Science from Simon Fraser University in 1991. He received his Ph.D. degree from the University of British Columbia in 1996. He then joined Resolution Pharmaceuticals, Inc., as a NSERC Industrial Research Fellow, investigating the coordination of technetium and rhenium to peptides and the synthesis of low molecular weight radiopharmaceuticals. His research interests centered on the applications of technetium and rhenium radiopharmaceuticals to oncology and neurology. In 1998, he joined the platinum development team at AnorMed, Inc., as a Senior Developmental Scientist. His current research interests include the design and synthesis of new Pt antitumor agents and the design of efficient processes for large-scale manufacture of Pt compounds.

Christen Giandomenico received his Ph.D. degree in Chemistry from Columbia University and has held Post-doctoral positions at the University of Chicago and the Stanford Research Institute. In 1985 he joined Johnson-Matthey where he was a co-inventor of JM216, the first orally active platinum anticancer drug. He is a named inventor on six patents and is the author of 19 scientific articles. In 1996 he helped found AnorMED, a company dedicated to the discovery and development of metal-based therapeutics. He is currently Director of Chemical Development at AnorMED.

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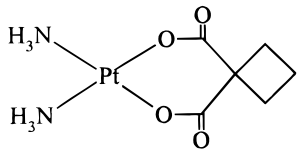
Despite its success, cisplatin has several disadvantages that include severe toxicity such as nephrotoxicity, neurotoxicity, and emetogensis. The toxic side effects of cisplatin limit the dose that can be given to patients; typical doses are 100 mg/day for up to five consecutive days.[11] To help alleviate nephrotoxicity, intravenous hydration and diuresis have been employed,[9] though they pose an inconvenience to treatment on an outpatient basis. The use of serotonin receptor antagonists have helped reduce nausea and vomiting in some patients.[12−15] A number of protecting or rescue agents such as mesna, WR-2721, diethyldithiocarbamate, and thiosulfate have also been used to control cisplatin toxicity; however, the exact role of these agents is not well understood, and they are as of yet not routinely used in Pt chemotherapy.[16−18]

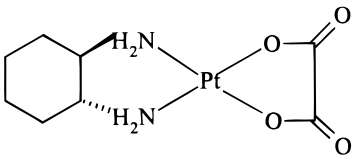
Cisplatin is used in the treatment of a number of cancers, but its applicability is still limited to a relatively narrow range of tumors. Some tumors have natural resistance to cisplatin, while others develop resistance after the initial treatment. Cisplatin also has limited solubility in aqueous solution and is administered intravenously, another inconvenience to outpatient treatment. These drawbacks coupled with cisplatin toxicity have been the impetus for the development of an improved Pt antitumor drug.

Since the introduction of cisplatin, thousands of Pt compounds have been synthesized and evaluated as potential antitumor agents. Over 28 have entered human clinical trials,[9,19] but only diammine[1,1-cyclobutanedicarboxylato(2−)]-*O*,*O*′-platinum(II) (carboplatin (**3**)) received worldwide approval and achieved routine clinical use. Carboplatin is less toxic than



(3)

cisplatin and can be given at a much higher dose than cisplatin (up to 2000 mg/dose).[11] The lower toxicity of carboplatin in comparison to cisplatin has been the advantage that enabled it to achieve worldwide approval and use. Unfortunately, carboplatin is still only active in the same range of tumors as cisplatin and is still administered intravenously. In recent years, two other Pt compounds have received limited approval for use in some countries. (*trans*-L-Diaminocyclohexane)oxalatoplatinum(II) (oxaliplatin or L-OHP (**4**)) has been approved for the secondary treatment of metastatic colorectal cancer in France and other European countries.[19] *cis*-Diammine−glycoloato-*O*,*O*′-platinum(II) (nedaplatin or 254-S (**5**)) has received approval for use in Japan.[19] As of yet,



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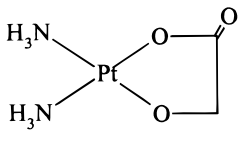

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oxaliplatin and nedaplatin have not demonstrated any clear advantages over cisplatin or carboplatin, though oxaliplatin has shown potential for use in cisplatin-resistant tumors during preclinical evaluations. Therefore, the search continues for an improved Pt antitumor agent, motivated by the desire to design a less toxic, orally active compound that is non-cross-resistant with cisplatin and carboplatin.

In the years following the introduction of cisplatin, the design of new Pt antitumor drugs concentrated mainly on direct cisplatin analogues, which adhered to the set of structure−activity relationships summarized by Cleare and Hoeschele in 1973.[20,21] More recently, there have been efforts to rationally design new Pt complexes based on an improved understanding of the mechanisms of Pt drug resistance. Specific chemical and structural features can be incorporated into new Pt compounds such that they are able to circumvent a specific drug resistance mechanism. There have also been efforts directed at the design of unconventional complexes that violate the original structure−activity relationships, such as trans Pt compounds and binuclear Pt complexes. As the in vivo behavior and mechanism of actions for these complexes are expected to be different from those of cisplatin or carboplatin, it is hoped that they will overcome Pt drug resistance in tumors and be applicable to a broader range of cancers. There has also been interest in Pt(IV) complexes for their potential as orally active agents.

Since the original discovery by Rosenberg, the volume of research into Pt antitumor drugs has been staggering. Thousands of Pt compounds have been synthesized and evaluated. Review articles have appeared regularly over the years dealing with the synthesis, preclinical screening, mechanism of actions,[11,18,22−32] and clinical trials of Pt drugs.[9,19,25,29,33] The primary purpose of this review is to give an update of the Pt drugs currently in human clinical trials and to give an overview of the design of new compounds within the last 10 years.

2. Design of New Pt Antitumor Drugs

Of the thousands of Pt compounds evaluated for antitumor activity, the majority of them adhered to the set of structure−activity relationships summarized by Cleare and Hoeschele.[20,21] These relationships state that for a Pt complex to show antitumor activity, the Pt(II) or Pt(IV) complex should have a cis geometry with the general formulas of *cis*-[$PtX_2(Am)_2$] or *cis*-[$PtX_2Y_2(Am)_2$], where X is the leaving group and Am is an inert amine with at least one N−H moiety. The leaving group, X, should be an anion with intermediate binding strength to platinum and have a weak trans effect to avoid labilizing the amine. Complexes with labile leaving groups such as ClO_4^- or NO_3^- are highly toxic, while complexes with inert leaving groups are generally inactive.

The structure−activity relationships dominated Pt drug design for over 20 years and remained valid until relatively recently. This is reflected in the fact that all Pt compounds that have entered clinical trials so far adhere to this set of guidelines. However, it has become quite evident that mere analogues of

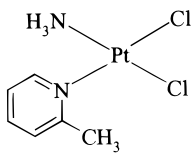
cisplatin or carboplatin will probably not offer any substantial clinical advantages over the existing drugs. A number of researchers have taken a completely different approach to Pt drug design and have prepared compounds that violate the structure−activity relationships but yet show antitumor activities. Efforts have also been directed toward the rational design of compounds with specific characteristics that could allow them to be administered orally or to circumvent known mechanisms of Pt drug resistance. The following sections present some complexes that illustrate the recent strategy used in the development of new Pt antitumor agents.

2.1. Sterically Hindered Pt Complexes

To date, there has been little success in developing a Pt drug capable of overcoming either innate or acquired Pt drug resistance and expanding Pt-based chemotherapy to a broader range of cancer. A few compounds currently in clinical trials show promise but are still several years away from approval. In recent years, much has been elucidated concerning the mechanisms underlying tumor resistance to cisplatin.[34−40] Studies have revealed that a combination of reduced platinum transport, increased cytoplasmic detoxification via elevated glutathione and/or metallothionein levels, enhanced DNA repair, and increased cellular tolerance to Pt−DNA adducts are the major mechanisms underlying resistance. A number of cisplatin resistance cell lines with known resistance mechanisms have been used for the evaluation of new complexes. Examples include 41McisR,[41] HX/155cisR[42] (resistance due to reduced platinum accumulation), GCT27cisR[43] and CH1cisR[44] (resistance due to enhanced removal of and/or increased tolerance to Pt−DNA adducts), and A2780cisR[45] and SKOV-3[46] (resistance due to detoxification via elevated glutathione levels, decreased uptake, and increased DNA repair).

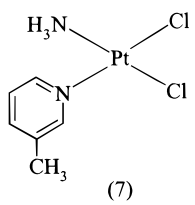
Glutathione has been implicated in resistance by reducing drug accumulation via the multidrug resistance associated protein (MRP),[47] by reacting with drugs to form inactive species,[48,49] and by enchancing DNA repair.[50] Clinical studies have shown an inverse correlation between immunohistochemical staining for glutathione S-transferase in head and neck cancer and failure to respond to Pt-based chemotherapy.[51] A correlation was also reported between glutathione levels and resistance to cisplatin and carboplatin in eight human ovarian carcinoma cell lines.[46] An inactive platinum thiol complex was detected as a metabolite in the urine of patients undergoing cisplatin treatment.[52,53]

cis-Amminedichloro(2-methylpyridine)platinum-(II), ZD0473 (**6**), was rationally designed to circumvent resistance by sterically hindering cellular detoxification by glutathione and other cellular thiols while



(6)

still retaining the ability to form cytotoxic lesions with DNA. The crystal structure of ZD0473 and its analogue, *cis*-amminedichloro(3-methylpyridine)platinum (II) (**7**) were reported.[54] In ZD0473, the pyridine ring is tilted by 102.7° with respect to the PtN_2Cl_2 square plane. In contrast, the pyridine ring was tilted



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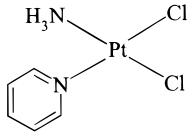


(8)

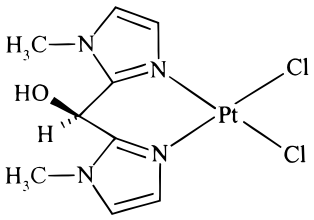
by only 48.9° in the 3-methylpyridine complex (**7**). The 102.7° tilt of the 2-methylpyridine ring placed the 2-methyl group directly over the Pt square plane and introduced steric hindrance to an axial approach of the Pt metal from above. It is well-known that axial steric hindrance decreases the rate of substitution reactions in square planar complexes.[55−56] Indeed, slower rates of hydrolysis for ZD0473 (**6**) compared to cisplatin and the 3-methylpyridine analogue (**7**) were reported.[54] The reactivity of ZD0473 toward thiourea, pyridine, methionine, and GMP were also less than that of cisplatin and *cis*-amminedichloro(pyridine)platinum(II) (**8**).[57] In reaction with naked DNA, ZD0473 also had a slower rate of reaction than cisplatin, though it did eventually platinate DNA to the same level as cisplatin.[58] The time course for the formation of DNA cross-links in SKOV-3 cells was also slower for ZD0473 compared to cisplatin.[57] The slower rate of cross-link formation may have implications in terms of DNA repair.

Preclinical evaluation of ZD0473 was performed in a variety of murine and human ovarian carcinoma cell lines, including several possessing acquired resistance to cisplatin and carboplatin.[57−59] ZD0473 produced marked in vitro activity against both murine and human ovarian carcinoma cell lines. Of particular interest was the lower resistance to ZD0473 compared to cisplatin observed in A2780cisR resistant cell lines, where detoxification by elevated glutathione levels was known to be one of the resistance mechanisms.[59] Across a panel of cisplatin-sensitive and resistant human ovarian carcinoma xenografts, ZD0473 exhibited improved or comparable activity to that observed for an equitoxic dose and schedule of cisplatin. In a direct comparative study using CH1cisR xenografts and equitoxic doses, ZD0473 demonstrated significantly greater growth delays compared to cisplatin, carboplatin, JM216 (orally active Pt(IV) complex), and JM335 (trans mixed-amine Pt(IV) complex).[58] The compound was also found to be orally active. It is interesting to note that ZD0473 was also able to circumvent acquired cisplatin resistance in cell lines (41McisR and CH1cisR) where detoxification due to elevated glutathione levels was not known to be involved in Pt drug resistance.[59]

The antitumor activity of *cis*-$[PtCl_2(NH_3)$(quinoline)] and *cis*-$[PtCl_2(R'R''SO)$(quinoline)] was reported by Farrell and co-workers.[60,61] These complexes showed moderate activity in a L1210/L1210cisR pair of cell

lines. It is uncertain whether steric effects have any role in the activities of these complexes or what activities they may show in other resistant cell lines. However, a steric effect was suggested to have played a role in the activity of the trans isomers of these complexes, which were more cytotoxic than their cis isomers.[61]

Another example of a cytotoxic Pt complex with a sterically crowded Pt center was reported by Reedijk and Krebs.[62] *cis*-[Pt(bmic)Cl_2] (**9**) was reported to have significant cytotoxicity in L1210 leukemia bearing mice, while *cis*-[Pt(bmi)Cl_2] (**10**), which has less steric bulk around the metal, was found to be inactive. The X-ray crystal structure of *cis*-[Pt(bmic)-



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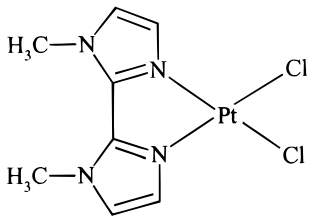
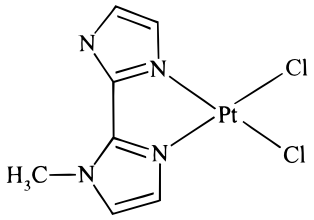


(10)

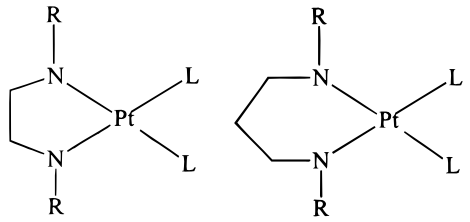
Cl_2] showed the dihedral angle between the two best least-squares planes through the two imidazole rings to be 30.6°. In contrast, the dihedral angles between the planes in *cis*-[Pt(bmi)Cl_2] and the related structure *cis*-[Pt(mimim)Cl_2] (**11**) were 3.1° and 2.6°, respectively.[63] A difference in the reactivity to 5-GMP



(11)

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 organoamide ligands (**12**, **13**) were reported by Deacon and co-workers.[64,65] The activities of these complexes were attributed to the large steric effect of the organoamide ligand. The



(12) (13)

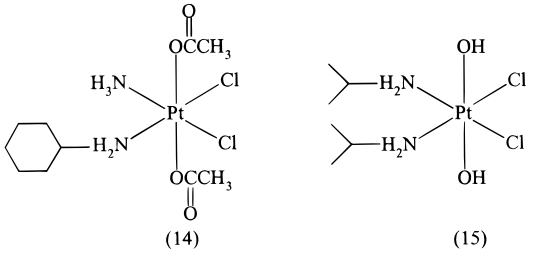
R= p-HC_6F_4, C_6F_5, p-ClC_6F_4, p-BrC_6F_4, p-IC_6F_4, 2,3,5-$F_3C_6H_2$, p-MeC_6F_4, p-$C_6F_5C_6F_4$

L= pyridine, 4-methylpyridine, 2-methylpyridine, 2,4-dimethylpyridine, 2,5-dimethylpyridine

replacement of the bulky organoamide ligand 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$][61] was less cytotoxic than *cis*-bis(pyridine) organoamide platinum(II) complexes,[64] which had comparable activity to cisplatin. A number of the complexes with different organoamide ligands, unsubstituted and methyl-substituted pyridine, were evaluated in both cisplatin-sensitive and -resistant cell lines.[64,65] There was no significant difference in activity with variation of the organoamide ligands. However, complexes with pyridine ligands having 2-methyl substitution were less active than similar complexes with pyridine or 4-methylpyridine ligands.[65] This is possibly due to the steric hindrance effect of the 2-methyl group during the formation of the Pt-DNA adduct. It is interesting to note that both the *cis*-bis(pyridine) organoamide platinum (II) complexes and *cis*-[Pt(bmic)Cl_2] violate the original structure−activity relationships as they lack a NH moiety yet exhibit cytotoxic activity.

2.2. Platinum(IV) Complexes

Since the early studies by Rosenberg and colleagues, it has been known that Pt(IV) complexes also have antitumor properties.[2,3] However, the development of Pt-based drugs in the ~20 years following the introduction of cisplatin was dominated by Pt-(II) complexes. Within the last 10 years, the desires to develop an orally active Pt drug, to improve patients' quality of life, and to expand Pt chemotherapy to outpatient treatment have reinitiated the interest in Pt(IV) compounds. The lack of cross-resistance with cisplatin reported for some Pt(IV) compounds and the excitement surrounding the clinical development of JM216 (**14**) (a Pt(IV) orally active compound) have also helped to fuel interest. Two other Pt(IV) compounds, iproplatin (**15**) and

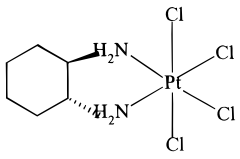


(14) (15)

ormaplatin (also known as tetraplatin (**16**)), have undergone clinical trials.[19] However, these compounds were abandoned due to severe neurotoxicity in the case of ormaplatin and the lack of superior performance in the case of iproplatin.

Pt(IV) complexes are much more inert to ligand substitution reactions than their Pt(II) counterparts.[66−69] It is generally believed that Pt(IV) complexes are reduced to Pt(II) by extracellular and intracellular agents prior to reaction with DNA. Numerous studies have provided evidence in support of this hypothesis.[70−80] Iproplatin[81] and ormaplatin[82,83] were shown to be reduced intra- and extracellularly to their reactive Pt(II) counterparts. However, the mechanism for this redox process and the effects of the coordinated ligands on the reduction are poorly understood.

The kinetic stability of the axial ligand bonds in octahedral Pt(IV) complexes is known to strongly influence the reactions and reduction of the complexes. The important influence of the axial and carrier ligand on the in vivo redox process and on the overall biological activity of the complex has been recognized.[84−92] Hambley and co-workers reported on the electrochemical reduction and DNA binding for a series of Pt(IV) ethylenediamine complexes ([Pt(en)Cl_2Y_2]) with chloro, hydroxo, and carboxylato axial ligands.[89] The tetrachloro complex was reduced more readily than those complexes with carboxylato and hydroxo axial ligands. The binding of the complexes correlated with the reduction potentials; the more readily reduced complexes bound more readily to DNA. The reduction of several Pt(IV) complexes such as [Pt(en)$(Cl)_4$], *cis*,*trans*,*cis*-[Pt(en)$(OH)_2(Cl)_2$], *cis*,*trans*,*cis*-[Pt(en)$(OCOCH_3)_2(Cl)_2$], *cis*,*trans*,*cis*-[Pt(en)$(OCOCF_3)_2(Cl)_2$], ormaplatin (**16**), iproplatin (**15**), amminediacetatodichloro(cyclohexylamine)platinium(IV) (JM216, (**14**)), and amminedibutyratodichloro(cyclohexylamine)platinium(IV) (JM221 (**17**)) by ascorbate and cathodic reduction were reported.[91] The



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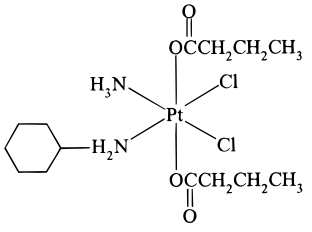


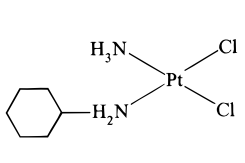
(17)

reduction rates depended on the electron-withdrawing power and steric hindrance of the axial and carrier ligands. Comparing reduction rate with cytotoxicity in cisplatin-sensitive L1210 cell lines revealed a correlation between activity and reduction rates for the four Pt(IV) complexes with ethylenediamine ligands. A comparison between the complexes with different carrier ligands but the same axial ligands revealed that a faster reduction rate coincided with a higher cytotoxic activity. These results illustrate the importance of axial and carrier ligands to the reduction and cytotoxicity of Pt(IV) complexes.

The clinical trial of the first orally active platinum drug, JM216 (**14**), has revitalized the interest in Pt(IV) complexes, which had been diminished somewhat by the disappointing results with iproplatin (**15**) and ormaplatin (**16**). JM216 belongs to a class of ammine/amine dichloro dicarboxylate platinum(IV) complexes that were designed for oral activity.[93] Synthetic routes for the preparation of these complexes[69,93] and the X-ray structures of JM216 (**14**)[94] and JM221 (**17**)[95] were reported. Within this series of Pt(IV) complexes, JM216 and JM221 were studied extensively.

The synthesis of JM216 is notable by its unusual length compared to that other potential platinum antitumor agents. It is manufactured in four steps from potassium amminetrichloroplatinate,[69] which is itself prepared from cisplatin. Such long synthesis is practical on large scale in facilities equipped to recover waste Pt from the manufacturing process. Limited availability of the potassium trichloroplatinate has restricted the investigation of platinum compounds containing mixed-ammine ligands such as JM216 and the previously mentioned ZD0473. However, a convenient laboratory-scale synthesis with a modest yield (55%) has been reported.[69]

An advantageous feature of the ammine/amine dichloro dicarboxylate Pt(IV) complexes is that they can be chemically modified at three locations, the two axial carboxylate ligands and the equatorial amine ligand. These complexes with aliphatic or alicyclic amine ligand and aliphatic or aromatic carboxylate ligands were evaluated in L1210 leukemia cell line with and without acquired resistance to cisplatin, ormaplatin, and carboplatin.[96] All complexes overcame cisplatin, carboplatin, and ormaplatin resistance. Cytotoxicity in cisplatin-sensitive L1210 cell line increased with increasing number of carbons in the axial aliphatic carboxylate ligands. Regardless of the equatorial amine ligand, the most cytotoxic compounds had aromatic axial carboxylate ligands. For Pt complexes with axial butyrato ligands and varying alicyclic amines, cytotoxicity was maximized at cyclohexylamine (JM221) (**17**). The complexes were also evaluated in a panel of six human ovarian carcinoma cell lines with varying Pt drug sensitivity from cisplatin-sensitive 41M and CH1 cell lines to intrinsically resistant HX/62 and SKOV-3 cell lines.[44,97−98] The pattern of activity observed in the L1210 cell lines was also observed in the human ovarian carcinoma cell lines. Interestingly, the complexes not only showed substantially greater cytotoxicity than cisplatin and carboplatin but also greater activity than ammine(cyclohexylamine)dichloroplatinum(II) (JM118 (**18**)) and *cis*,*trans*,*cis*-amine(cyclohexylamine)dihydroxodichloroplatinum(IV) (JM149 (**19**)).[97] This could



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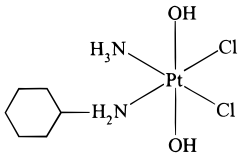
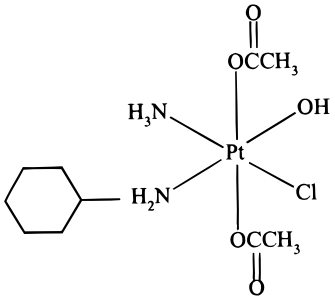


(19)

be due to the Pt(IV) complexes having less vulnerability to deactivation in the case of JM118. In the case of JM149, the differences in activity could be due

to differences in the reduction of complexes with carboxylate and hydroxo axial ligands. JM216 and JM221 were evaluated in a number of intrinsic and acquired cisplatin-resistant cell lines.[44,97−98] The two complexes showed a lack of cross resistance with cisplatin in some cell lines, particularly in those where reduced platinum accumulation played a dominant role in resistance. The results suggested that the greater lipophilic nature of the complexes enable them to circumvent resistance due to decreased Pt accumulation.

JM216 is currently evaluated clinically as an orally active Pt drug. High uptake of dose is desirable for an orally administered cytoxic agent because this increases the clinician's ability to predict platinum blood levels based on a prescribed dosage. Studies of JM221 and JM216 showed that 76% and 71%, respectively, of the administered dose were absorbed by mice when orally administered in arachis oil.[99] This compared favorably with carboplatin and cisplatin where only 22% and 37% of the administered dose was absorbed.[99] Clinical study showed that carboplatin administered orally caused severe gastrointestinal side effects and poor absorption.[100] Several papers discussing the biotransformation of JM216 following oral administration were published.[101−103] No JM216 was observed in patient's plasma ultrafiltrate samples.[103] JM118 (**18**), amminediacetatochloro(cyclohexylamine)hydroxoplatinum(IV) (JM518 (**20**)), and amminediacetato(cyclohexylamine)dihydroxoplatinum(IV) (JM383 (**21**)) were observed in the plasma ultrafiltrate samples.[102,103] A Pt glutathione



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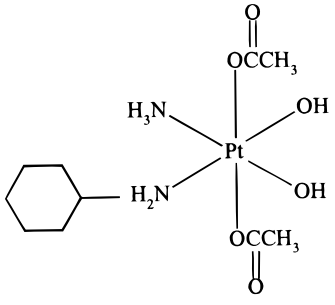


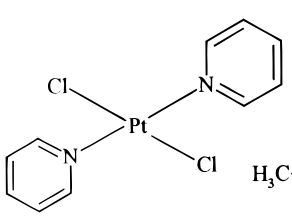
(21)

complex was also present and it probably represents a major deactivation product for JM216.[101]

2.3. Trans Platinum Complexes

The original empirical structure−activity relationships considered the trans Pt complexes to be inactive. However, several groups have shown that some trans compounds are active in vitro and in vivo.[60,61,104−111] While isomerization of the trans compound to an active cis isomer could account for some activity of trans isomers, in several cases cited below, likely cis isomers are less active than the corresponding trans isomer. A distinct difference between cisplatin and its trans analogue, transplatin, is that transplatin is kinetically more reactive than cisplatin[66,112] and more susceptible to deactivation. Careful design using a sterically hindered ligand may reduce the kinetic reactivity of trans Pt complexes. As the trans isomer forms different Pt-DNA adducts than cisplatin analogues,[109,112−122] it is hoped that trans Pt complexes could overcome cisplatin resistance in certain tumors. Several groups have pursued this concept of activating the trans geometry. The following section briefly summarizes their work.

Farrell and colleagues examined and compared the cytotoxicity of three series of trans complexes with the general formulas of $[PtCl_2(L)(L')]$: (i) L = L′ where L and L′ were pyridine (**22**), *N*-methylimidazole (**23**), and thiazole (**24**); (ii) L = quinoline and L′ = RR′SO (**25**) where R = methyl and R′ = methyl, phenyl benzyl; (iii) L = quinoline and L′ = NH_3 (**26**).[60,61,104,105] In cisplatin-sensitive and -resistant cell



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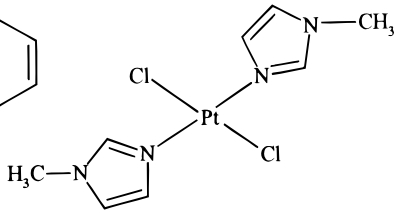

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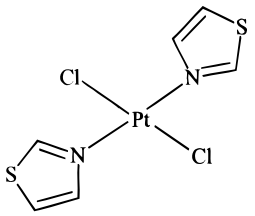

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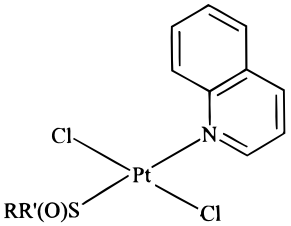

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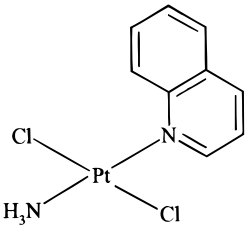
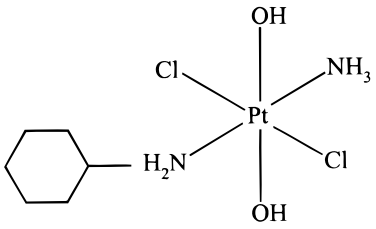


(26)

lines, the trans Pt complexes in the three series showed comparable activity to cisplatin and greater activity than transplatin. In cisplatin-sensitive and -resistant L1210 cell lines, the trans isomers exhibited greater activities than their cis counterparts.[60,61] Of particular interest were the reported activities of the trans complexes in cisplatin resistant cell lines

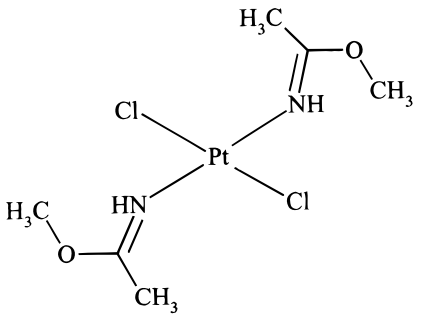
where the mechanisms of resistance were known to be due to reduced Pt accumulation and enhanced removal of and/or increased tolerance to Pt-DNA adducts.[61]

A trans Pt(IV) complex *trans*,*trans*,*trans*-ammine(cyclohexylamine)dichlorodihydroxoplatinium(IV) (JM335 (**27**)) was reported to have greater activity than transplatin and its cis analogue, JM149 (**19**), in a panel of human ovarian carcinoma cell lines.[106] It also



(27)

exhibited good in vivo activity in several ovarian xenograft models.[106] Lack of cross-resistance was observed in cell lines where resistance was mediated through reduced platinum accumulation. This was consistent with the results obtained with similar compounds such as JM216 (**14**) and JM221 (**17**). However, in contrast to the cis Pt(IV) ammine/amine complexes, lack of cross-resistance was also reported for JM335 in cell lines where resistance was attributed to enhanced repair and/or increased tolerance to Pt-DNA adducts. This supports the notion that the unconventional Pt-DNA adducts formed by trans complex may allow it to overcome cisplatin resistance in tumors. In A2780cisR cell line, where elevated glutathione level is known to play a role in cisplatin resistance, JM149 was more effective than JM335. Differences in reduction potential between the cis and trans isomers may have played a role.



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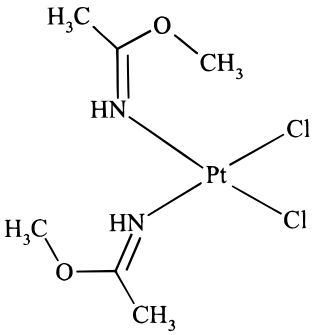

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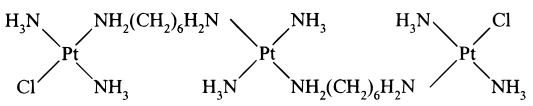


(30)

The antitumor activity of trans Pt complexes have also been demonstrated by Natile and co-workers with a series of Pt(II) complexes with iminoether ligands.[107,108] Both the cis and trans isomers reacted slower with DNA than cisplatin and transplatin.[108] This was attributed to the greater steric hindrance introduced by the iminoether ligands. In P388 leukemia-bearing mice, the *trans*-EE isomer (**28**) showed greater antitumor activity than the *cis*-EE (**29**) compound.[108] Against an acquired cisplatin-resistant P388 cell line, *trans*-EE exhibited in vivo activity whereas *cis*-EE was inactive.[108]

2.4. Multinuclear Platinum Complexes

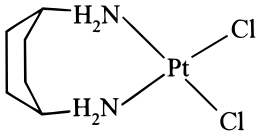
An approach to the design of Pt drugs that can circumvent Pt resistance in tumor is to develop compounds that form radically different Pt-DNA adducts than the current Pt drugs. Activation of trans isomers with bulky ligands is an example of this approach. Another example of this strategy is multinuclear platinum complexes with bridging linkers.[123−146] Farrell and colleagues have been the most active in this area and have extensively investigated binuclear Pt complexes, particularly ones with the general formulas $[\{PtCl_m(NH_3)_{3-m}\}\mu\text{-}H_2N{-}R{-}NH_2{-}\{PtCl_n(NH_3)_{3-n}\}]^{[(2-m)+(2-n)]+}$ (m or $n = 0-3$ and R is a linear or substituted aliphatic linkers).[123−129] A host of complexes have been generated, and some have shown activity in both cisplatin-sensitive and -resistant cell lines. In complexes with two $[PtCl_2(NH_3)(NH_2R-)]$ centers, a relationship between chain length and activity was observed. For dicationic complexes with two $[PtCl(NH_3)_2(NH_2R-)]$ centers, the cis or trans position of the leaving Cl group had an effect on activity. The binding of the binuclear Pt complexes to DNA were reported to be faster than for cisplatin, and a completely different array of Pt-DNA adducts that were totally inaccessible to mononuclear platinum complexes were observed.[126−132] More recently, other binuclear Pt complexes with bifunctional thiourea,[136,137] spermine,[134,145] spermidine,[134,145] and modified tetraamine[134] linkers have been reported. Trinuclear[138−141,144] and tetranuclear[142,146] complexes have also appeared. The most important of these complexes is the trinuclear Pt compound BBR 3464 (**30**). In preclinical evaluation, this compound has exhibited a complete lack of cross-resistance to cisplatin-resistant cell lines.[139,141,237,238] It is also significantly more potent than cisplatin in vitro in an osteosarcoma cell line.[238] The increased potency was attributed to increased cellular Pt uptake of BBR 3464 relative to cisplatin and the extent of DNA binding. There is good hope that these multinuclear Pt complexes may represent a new class of Pt antitumor drugs and help to expand the realm of Pt chemotherapy treatment.

2.5. Diaminocyclohexane (DACH) Platinum Complexes

One of the earliest leads in the development of Pt complexes with activity in resistant tumor cells was a series of complexes with 1,2-diaminocyclohexane (DACH) carrier ligand.[147,148] Many DACH complexes were evaluated,[28,149,150] and a total of 12 compounds have entered human trials. Three compounds are still currently in human trials (oxaliplatin, L-NDDP, and TRK-710).[9,19,151] More recently, Pt compounds prepared from another isomer of DACH, *cis*-1,4-diaminocyclohexane, have also been reported.[211−212]

Following the initial report by Burchenal et al. on the activity of Pt−DACH complexes in cisplatin-resistant L1210 cell line,[147] other groups have demonstrated the cytotoxic activity of DACH complexes in other cisplatin-resistant tumor cells.[152−163] However, it has become clear that Pt−DACH complexes are not effective in all cisplatin-resistant tumors. For example, Pt-DACH complexes were shown to be cross-resistant with cisplatin in small cell lung[161,164] and cervical squamous cell lines.[165] In a series of human ovarian carcinoma cell lines, Pt-DACH compounds were effective in only some of the cell lines.[157,159,162] A better understanding of the manner in which these complexes overcome cisplatin resistance is needed. In recent years, synthesis of new Pt-DACH complexes included the synthesis of Pt(IV) complexes with various axial and equatorial carboxylate ligands.[84,85,166−169] There were also efforts directed at Pt(IV) analogues of oxaliplatin with axial carboxylato ligands.[170] Pt(II) DACH complexes with diphosphine ligand[171−173] and thiourea ligand[136,137] have also been reported.

A complex of the 1,4-isomer of DACH, Pt(*cis*-1,4,-dach)Cl_2 (**31**), exhibited significant in vitro activity in Pt (1,2-dach) resistant cell lines.[213] This may be

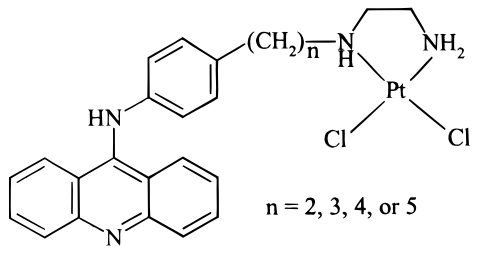


(31)

because the structure of the Pt complexes of *cis*-1,4-diaminocyclohexane are quite different from those of the 1,2-isomer. However, this compound exhibited only slightly better in vivo activity than cisplatin in Pt-resistant sublines of L1210 and P388.

2.6. Complexes with Biologically Active Carrier Ligands

Another approach to the design of novel Pt drugs is to target the Pt coordination moiety to DNA by attaching it to a suitable carrier ligand. Several groups have attempted to design new Pt compounds by attaching DNA intercalators to a Pt moiety with the expectation that the compounds would localize in the vicinity of the DNA. Denny and colleagues have prepared a series of complexes by attaching (1,2-diaminoethane)dichloroplatinum(II) and (1,3-diaminopropane)dichloroplatinum(II) to anilinoacridine (**32**, **33**) and acridinecarboxamide (**34**, **35**).[214−219] These



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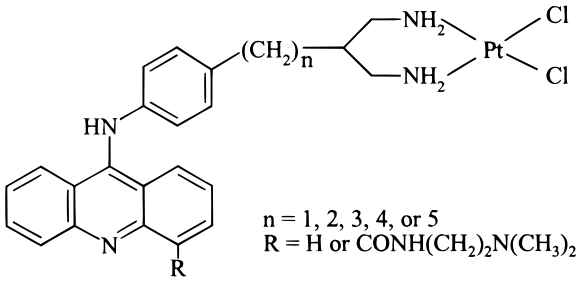

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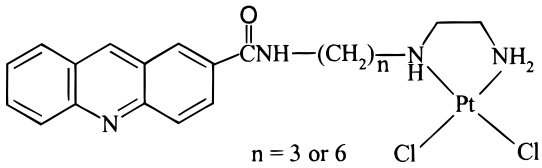

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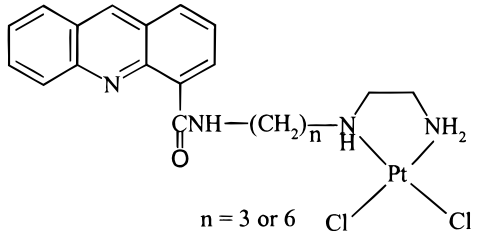
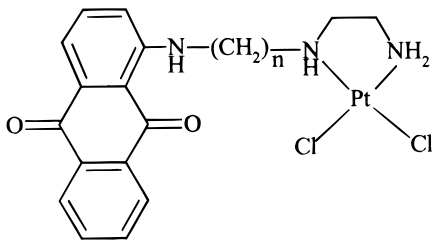


(35)

complexes exhibited improved activity in cisplatin-resistant cell lines compared to the parent Pt compounds, but there was no improvement relative to the carrier ligands. An interesting structure−activity relationship, which arose from this work, was that higher activity was observed when the Pt moiety was attached at the 4-position (**35**) versus at the 2-position (**34**). This relationship was also observed by Gibson and colleagues in a series of complexes with anthraquinone, where the attachment of the Pt moiety at the 1-position (**36**) resulted in the complex having greater activity than the analogue where the attachment was at the 2-position (**37**).[220]

Other examples of Pt complexes with bioactive carrier groups include the attachment of a Pt moiety to doxorubicin[221,222] and to oestrogen analogues that bind to oestrogen receptors.[223−225] Lippard and colleagues reported Pt complexes with 9-aminoacridine and chloroquine,[226] ethidium bromide,[227] and acridine orange.[228] The attachment of a Pt moiety to amino acids, sugars, and antitrypanosomatid drugs have also been reported.[229−230] Overall, studies of Pt compounds with biologically active carrier groups have



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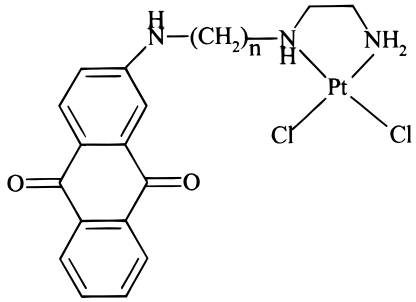


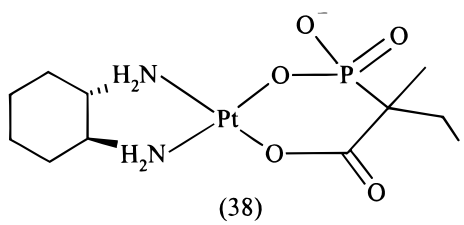
(37)

yielded interesting results, and there is potential for varying the biological activity of these compounds by altering the structure of the carrier group. However, to date, there have been no clinically significant advances that have developed from this design approach.

2.7. Water-Soluble Complexes

Increasing the water solubility of platinum antitumor compounds has been an important practical objective of many analoguing programs. The solubility of cisplatin (~1 mg/mL) approaches the practical limit of solubility for a cytotoxic agent of its potency that is administered parenterally. Orally administered compounds can be less soluble, but they must be soluble enough to be absorbed. Unfortunately, most Pt(II) dichlorides are substantially less soluble than cisplatin. The most common method of increasing water solubility has been to replace the chloride ligands with chelating carboxylates (such as cyclobutane dicarboxylate), oxalate and glycolate. Oxidation of Pt(II) to its Pt(IV) dihydroxo complex often increases water solubility. These classes of compounds are discussed elsewhere in this review.

Several novel approaches have also been described. A series of anionic phosphono carboxylate complexes (**38**) with high solubility and stability have been reported.[231] These compounds exhibited pronounced



(38)

activity in S180a, L1210, and M5076 murine models. Another approach has been to prepare a stable colloidal solution (hydrosol) of an otherwise insoluble platinum compound. For example, the insoluble complex [(+1)-1,2-bis(4-fluorophenyl)ethylenediamine]-dichloroplatinum was solubilized as a hydrosol and demonstrated to be active in a hormone-sensitive murine breast cancer.[232] An unusual water-soluble platinum compound can be prepared in a chelate-opened zwitterionic form under acidic conditions. At physiological pH, the diamine chelate closes, forming a conventional platinum compound that has in vivo activity.[233]

3. Clinical Update

Though 28+ platinum antitumor compounds have been clinically tested, only a subset continues to be investigated. Only a few of those compounds have ever achieved clinical acceptance. The most recent compounds tested, as well as the successful compounds with their typical or dose-limiting toxicity and current clinical status are listed in Table 1. New compounds continue to reach the clinic when preclinical evidence demonstrates a potentially significant mechanistic mode of action or an advantage over previously tested compounds. Recent examples of this are the development of JM216 (**14**), an orally active platinum agent under development by Bristol-Myers Squibb, and ZD0473 (**6**), an agent under development by AstraZeneca with the potential to circumvent thiol-mediated deactivation and preclinical data supporting circumvention of resistance in certain animal tumors. This continued development activity is further evidence that while nontoxic cytostatic agents that control cancer are desirable, effective well-tolerated cytotoxic agents that kill cancer continue to be extremely important in cancer chemotherapy.

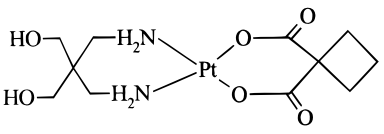
The putative mechanism of in vitro cytotoxicity of the standard platinum antitumor compounds, which is also attributed to its antitumor activity, involves (i) intracellular loss of the labile ligands attached to platinum and (ii) the formation of an intrastrand DNA cross-link between adjacent guanines and the PtAA′ core where A and A′ are the nonlabile amine ligand(s). Platinum(IV) compounds require an additional in-vivo reduction to the more labile platinum-(II) for activity. Cisplatin is not only the first platinum compound discovered with demonstrable antitumor activity, but is also the simplest structure that can satisfy these criteria. To date, the only clinically successful strategy for identifying next-generation platinum antitumor compounds has been to retain the *cis*-PtAA′LL′ core (where A and A′ are amine carrier ligands which may be unidentate or linked to form a bidentate group and L and L′ are leaving groups which may be unidentate or linked to form a bidentate group). On the basis of the accepted mechanism of antitumor activity, it is reasonable to predict that modification of the initial oxidation state and the labile ligands would primarily affect pharmacokinetics. This should modulate activity based on tissue distribution and those biological properties associated with chemical reactivity, such as catabolism and the tendency to react at irrelevant and toxic sites and resistance to cytoplasmic-based detoxification mechanisms. Modification of the nonlabile amine carrier ligands would affect all of these biological

Table 1. Clinical Status of Selected Platinum Antitumor Compounds[a]

drug	structure	dose (mg/m^2)	limiting toxicity	clinical status
cisplatin	**1**	60−120	nephrotoxicity	approved worldwide
carboplatin	**3**	∼900 based on GFR[175−176]	myelosuppression (thrombocytopenia)	approved worldwide
oxaliplatin	**4**	200	neuropathy	approved in France
nedaplatin	**5**	80	myelosuppresion	approved in Japan
lobaplatin	**45**	50−70	thrombocytopenia	approved in China phase II
JM-216	**14**	100−120 (dx5)	myelosuppression	phase II
L-NDDP	**46**	400	neutropenia, thrombocytopenia	phase II
cycloplatam	**42**	80−100	myelosuppresion	phase II
SKI 2053R	**43**	360	liver toxicity, myelosuppression, renal toxicity	phase II
ZD0473	**6**	TBA	TBD	phase I
BBR3464	**30**	>1.1	neutropenia and nausea and vomiting	phase I
SPI-77		320	TBD	phase I
TRK-710	**47**	TBA	TBD	phase I
ormaplatin	**16**	90	unpredictable peripheral neurotoxicity	abandoned
zeniplatin	**39**	120−145	myelosuppression, nephrotoxicity	abandoned
enloplatin	**40**	700	nephrotoxicity	abandoned
miboplatin	**44**	800−1000	myelosuppression	abandoned
CI-973	**41**	190−300 30 dx5	myelosuppression	abandoned

[a] TBD = to be determined.

Chart 1



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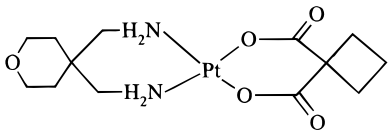

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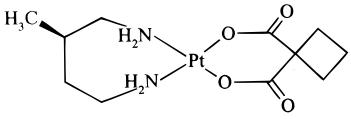

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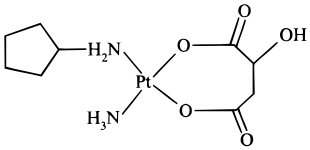

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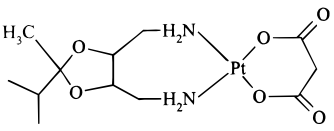

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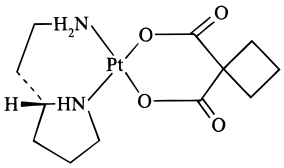

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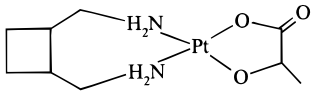

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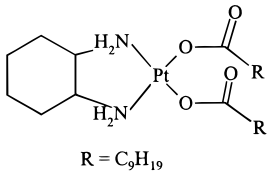
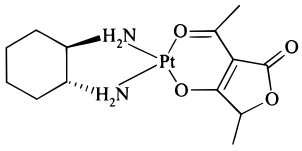


R = C_9H_{19}

(46)



(47)

properties and may affect cellular resistance based on DNA repair.

Most platinum analogues have resulted from efforts to modify one or more of these characteristics and after demonstrating an empirical advantage preclinically have sought to demonstrate a clinical advantage. The first successful effort was the development of carboplatin (**3**), which was approved in the

Table 2. Reported Circumvention of Cisplatin Resistance

compound	model	ref
Lobaplatin	murine: P388	178
Nedaplatin	in vitro	179
	murine: P388, B16, Lewis Lung	
	xenograft: MX-1, Daudi	
cycloplatam	murine: P388, MOPC, hepatoma 22a	179
	xenograft: lung (LXFS 538)	180
SKI 2053R	in vitro	179
CI-973	murine	181
oxaliplatin	in vitro	182,183
	murine: L1210, M5076, L1210/DDP	184
BBR3464	in vitro	239
JM-216	in vitro	98
ormaplatin	in vitro	185
	murine: L1210, P388	186,187
	xenograft: 2780/DDP, OVCAR-10	188
ZD0473	in vitro	57−59
	xenograft: CH1cisR	
L-NDDP	in vitro	189

United Kingdom and Canada in 1985 and shortly thereafter in the United States. Carboplatin replaces the unidentate chloride ligands of cisplatin with a chelating cyclobutanedicarboxylate ligand. The rate of aquation of carboplatin and cisplatin at 37 °C, pH 7 are 7.2×10^{-7} and 8×10^{-5} s^{-1}, respectively.[234] Carboplatin's almost 2 orders of magnitude lower rate of aquation is due to the "chelate effect", whereby a system containing ligands in a chelate ring achieves enhanced stability compared to a similar system containing no rings. In addition, the carboxylate ligand increases its water solubility. The ramifications of these modifications can be seen in Table 1, namely, carboplatin is less potent but circumvents the dose-limiting kidney toxicity of cisplatin. Clinically, carboplatin is demonstrated to be better tolerated than cisplatin while having an essentially identical spectrum of activity. For example, in ovarian cancer, cross-resistance to cisplatin is evident but because it is better tolerated, some patients who could not continue to receive cisplatin can continue treatment with carboplatin.[176] Most but not all subsequent clinical candidates incorporate a carboxylate chelate of some type which imparts enhanced stability and water solubility. Examples of other clinically tested platinum antitumor agents that contain a dicarboxylate include Oxaliplatin (**4**), Zeniplatin (**39**), Enloplatin (**40**), CI-973 (**41**), Cycloplatam (**42**), and SKI 2053R (**43**), while Nedaplatin (**5**), Miboplatin (**44**) and Lobaplatin (**45**) contain chelating glycolate ligands (Chart 1).

New compounds that can extend the spectrum of activity beyond that of cisplatin and carboplatin are of particular interest. Most recently tested compounds address this issue to varying degrees, as seen in Table 2, by demonstrating improved activity of the new agent relative to cisplatin in one or more of the following: (i) in vitro; (ii) a standard murine tumor; (iii) a xenograft tumor; (iv) a tumor model demonstrating acquired platinum resistance; or (v) in the context of circumvention of a specific repair mechanism.

Oxaliplatin (**4**) is the first clinically approved platinum compound developed as a result of demonstrated lack of cross-resistance in cisplatin-resistant L1210. The lack of cross-resistance was attributed to the 1,2-diaminocylohexane ligand (DACH).[189] The principal biochemical mechanisms of resistance which oxaliplatin has been demonstrated to circumvent are mismatch repair (MMR)[190] and replicative bypass (the ability of a cell to synthesize DNA past the site of DNA damage).[191] It is reasonable to speculate that the DACH ligand, which projects into the major groove of DNA, would have a significant impact on these mechanisms. The three possible stereoisomers of 1,2-diaminocyclohexane ligand (e.g., racemic *trans*-L(R,R); *trans*-D(S,S) and the meso form *cis*(R,S)) produce three platinum stereoisomers, each with distinct in vitro and in vivo activity.[192,193] Kidani et al. suggested that this difference is due to differences in the interaction of the PtDACH fragment with DNA.[192] Though this effect is small relative to the difference in activity between different amine ligands, the *trans*-L(R,R) isomer of oxaliplatin is the compound that is being clinically developed. These observations are all consistent with the hypothesis that the carrier ligand has a significant role influencing the spectrum of activity of platinum antitumor compounds.

Oxaliplatin has received clinical approval in France for advanced colorectal cancer as a single agent or in combination with 5-FU(5-fluorouracil)/FA(folinic acid).[194] Oxaliplatin in combination with 5-FU/FA has increased objective response rates to over 40% compared to response rates of 15% with 5-FU alone,[195] though increases in overall survival rates are modest. These results have been encouraging enough to inspire new clinical trails with biweekly fractionated doses, or over 4−5 days in a chronomodulated schedule, or in combination therapy with new thymidylate synthase inhibitors or topoisomerase inhibitors.[195] Oxaliplatin/cisplatin combination therapy has also shown activity comparable to high-dose cisplatin or high-dose carboplatin in patients with recurrent ovarian cancer. The efficacy of oxaliplatin in these two tumor types may be related to the observation that 15−20% of newly diagnosed colorectal cancers and 20% of newly diagnosed ovarian cancers have a defect in their MMR mechanisms. The toxicity profile of oxaliplatin[196] is significantly different from either cisplatin or carboplatin.[197] The maximum tolerated dose is 200 mg/m^2 with the recommended Phase II dose of 130 mg/m^2 every 3 weeks. Oxaliplatin does not exhibit nephrotoxicity, and myelosuppresion and hearing loss is minimal. Nausea and vomiting can be controlled by antiemetics, and moderate diarrhea is experienced by some patients. The most significant toxicity is a neurological toxicity in which the patient experiences abnormal sensation in the extremities and around the mouth. Some patients receiving high doses experience a sensation of an inability to swallow. The toxicity begins to appear at doses of 90 mg/m^2 and affects 75% of patients at 200 mg/m^2. The symptoms often appear during the infusion and persist for a few minutes to a few days. A cumulative risk of neurotoxic side effects of 10%, 50%, and 75% has been reported for patients receiving cumulative doses of 780, 1170, and 1560 mg/m^2, respectively.[196] Severe symptoms have been reported to regress in

most patients in 4−6 months. Ormaplatin (**16**), a platinum(IV) complex containing the DACH carrier ligand, has been abandoned due to neurological toxicity.[198] It remains to be seen whether oxaliplatin will carve a commercial niche for itself in the worldwide market. However, current clinical data on oxaliplatin suggest that platinum compounds that have an altered mechanism of action relative to cisplatin and carboplatin and exhibit significantly different toxicity profiles may be able to find practical application in a clinical setting.

A variety of other platinum compounds primarily designed to overcome the toxicity of cisplatin by incorporating chelating ligands have been tested clinically. Many of these compounds have been tested to varying degrees for superior activity to cisplatin in preclinical models. However, these compounds have been relatively less successful in clinical testing. Compounds that have recently been tested are described below. Nedaplatin has received approval in Japan. The dose-limiting toxicity is myelosuppression with a late recovery of 6 weeks. The recommended dose for Nedaplatin is 100 and 87.5 mg/m^2 .[199] As a single agent in phase II studies, response rates of 25% or greater were observed for head and neck, testicular, lung, esophageal, bladder, ovarian, and cervical cancer.[19] In a small randomized trial comparing cisplatin/vindensine to nedaplatin/vindensine, partial response rates and overall survival were similar with both treatments.[19] Lobaplatin has received approval in China. Trials of lobaplatin in lung cancer, head and neck, and bladder cancer have reported minimal efficacy.[19] Typical doses are between 50 and 70 mg/m^2 with the later dose administered 5 times daily. The dose-limiting toxicity is thrombocytopenia and has been correlated to patients' kidney function.[200] Cycloplatam has been reported to be superior to cisplatin in one lung cancer xenograft model.[179] Several trials have been reported with positive results in previously untreated patients.[19] However, no trials comparing the activity of cycloplatam to other platinum agents have been reported. SKI2053R exhibited antitumor activity superior to cisplatin in a variety of cell lines.[201] A phase II trial of SKI2053R as a single agent at a dose of 360 mg/m^2 in advanced gastric adenocarcinoma in Korea reported partial response rate of 17% with no unacceptable toxicities.[202] The previously determined MTD was 480 mg/m^2 with the liver toxicity being the dose-limiting toxicity.[202] Zeniplatin, Enloplatin, CI-973, and Miboplatin have all been abandoned for insufficient activity or unacceptable side effects.[19]

A new compound developed specifically to address platinum resistance is ZD0473 (**6**). The preclinical evaluation of this compound is discussed in section 2.1. ZD0473 was develeoped by AnorMED Inc. (formerly the Biomedical Research Group at Johnson-Matthey Inc., West Chester, PA) and was licensed to AstraZeneca PLC. It entered Phase I clinical trials in 1997 in the United Kingdom based on its activity in cisplatin-resistance cell lines, particularly in human ovarian carcinoma cell lines.[203]

Another approach to developing new platinum agents has been to develop compounds with radically different pharmacokinetics in the hope of dramatically decreasing toxicity or of targeting tumors by altering the distribution of the cytotoxic platinum. Two examples of this approach are liposome-encapsulated platinum compounds SPI-77 and L-NDDP. SPI-77 is a liposomal-encapsulated formulation of cisplatin. Phase I clinical trials are in progress in the United States and Europe, and doses of 320 mg/m^2 have been infused over 3.25 h without reaching an MTD or observing significant toxicities.[204] The half-life is reported to be 60−80 h compared to 1 h for cisplatin, and serum platinum levels 1000 times greater than cisplatin have been achieved.[205] L-NDDP (**46**) is a lipophilic platinum compound containing the DACH carrier ligand and lipophilic neodecanoic acid leaving groups encapsulated in a liposome. It is a mixture of 15−20 isomers.[235] In preclinical studies, L-NDDP has been reported to induce the formation of more DNA adducts than cisplatin at equimolar concentrations in whole cell systems.[206] In an in vitro repair assay, L-NDDP DNA adducts are repaired with lower efficiency than cisplatin DNA adducts.[188] In a phase II study of L-NDDP, a dose of 400 mg/m^2 was administered into the pleural space of 15 patients with malignant pleural mesothelioma. A high rate of pathological response was reported for patients receiving more than two courses of treatment.[207] Some patients experienced a fatal pneumonia that may have been related to the route of administration, though this was remedied by altering the method of administration into the pleural cavity. Otherwise, side effects were mild to moderate with no myelosuppression or kidney toxicity reported.[206]

Oral administration of a platinum cytotoxic agent offers the possibility of considerable benefit to the patient in terms of convenience and quality of life. There is also a potential significant economic advantage to shifting cancer treatment from in-patient to out-patient treatment.[208] However, there are concerns of ensuring patient compliance and proper monitoring of side effects with compounds administered near their toxic dose. The first platinum compound specifically developed to address this potential need was JM216 (**14**). Phase I trials resulted in a recommended dose of 100−120 mg/m^2 daily for 5 days with 4 weeks between courses.[209] The dose-limiting toxicity is myelosupression. Several phase II trials have been undertaken.[236] One in nonsmall cell lung cancer reported negative results. However, a good response was observed in hormone-refractory prostate cancer where 33% of evaluable patients exhibited reduction in PSA (prostate specific antigen) levels.[210] Additional phase II studies in NSCLC, ovarian cancer, cervix cancer, breast cancer, and gastrointestinal cancer and in combination studies with other orally administered anticancer agents including etoposide, UFT, and oral fluoropyrimidine are ongoing.[19]

A completely new class of platinum compound that violates the traditional structure−activity rules of platinum cytoxics has entered clinical trials. BBR 3464 (**30**) contains two reactive platinum centers, each containing a single labile chloride. Preliminary reports of the phase I trial which is still ongoing

indicate that the dose-limiting toxicity will likely be rapidly reversible neutropenia, nausea, and vomiting.[239] The MTD is expected to be >1.1 mg/m^2. One patient at 1.1 mg/m^2 has experienced a drop in the tumor marker CEA from 220 to 53.[239] If this compound proves truly efficacious, it will set off an explosion of research around this novel structure.

4. Conclusion

Of the thousands of Pt compounds evaluated as antitumor agents, only a very small fraction has shown sufficient promise during preclinical evaluation to enter human clinical trials. Reduction in toxicity, increased spectrum of activity, and oral administration remain the primary goals of Pt drug development. In contrast to the 1970s and 1980s, the design of third-generation Pt drugs in this decade has clearly shifted away from the early empirical structure−activity relationships and the synthesis of mere cisplatin analogues. Instead, efforts have been directed at the design of compounds capable of circumventing specific mechanisms of resistance and at the design of unconventional Pt compounds with radically different modes of action. As the third-generation of compounds undergo clinical trials, it is hoped that they will demonstrate significant clinical advantages over the current drugs, particularly in the area of Pt drug resistance.

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