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Towards the rational design of platinum(II) and gold(III) complexes as antitumour agents

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Received 15th October 2007, Accepted 13th November 2007
First published as an Advance Article on the web 4th December 2007
DOI: 10.1039/b715903j

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Metal complexes afford an opportunity for the discovery of new antitumour drugs with truly novel mechanisms of action. Various tactics and some new concepts have been employed to improve the physico-chemical and biological properties of metal complexes. Recent advances in this area demonstrate a bright prospect for the utilization of metal complexes in cancer chemotherapy. The theme of this article focuses on the approaches towards the rational design of platinum(II) and gold(III) complexes with antitumour properties based on the updated understanding of the mechanism of action of these compounds. The complexes summarized in this work include monofunctional platinum(II) complexes, multinuclear platinum(II) complexes, hybrid and targeted platinum(II) complexes, and gold(III) complexes. Most of them violate the established structure-activity relationships and demonstrate different reactivities from cisplatin and thereby show some potential for the prevention of detoxification.

Introduction

The development of metal complexes as antitumour agents has attracted much attention in recent years.[1,2] Owing to the intrinsic nature of metal centers, characteristic coordination modes and kinetic properties, metallodrugs function through mechanisms that cannot be mimicked by organic agents, namely, they affect cellular processes such as cell division and carcinogenic reaction in different ways. To design a metal-based applicable anticancer drug, however, is quite challenging. Any candidate for an antitumour agent needs to demonstrate its positive reactions with target biomolecules and favorable physiological responses to tumours before entering clinical trials. The challenge of such design arises

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from the requirement of killing tumour cells without causing too much harm to healthy cells.

The design of platinum-based antitumour agents constitutes an indispensable part of the development of anticancer drugs. Platinum drugs have an enormous impact on the clinical cancer chemotherapy in that they have been widely used against various solid tumours including genitourinary, colorectal, and non-small cell lung cancers.[3–7] As one of the leading anticancer drugs, cisplatin (**1**) has been used for more than three decades to treat diverse malignancies.[8] However, the treatment efficacy of cisplatin has been greatly hampered by drug resistance and severe side effects.[9] Many tumours display inherent resistance to cisplatin while others develop acquired resistance after initial treatment;[10,11] and metastasis (secondary) tumours lack response to this agent.[12] High general toxicity is another disadvantage of cisplatin, especially nephrotoxicity, neurotoxicity, ototoxicity, and emetogenesis, which cause patients to suffer from severe side effects.[13] Furthermore, limited water solubility makes the use of cisplatin inconvenient in clinical practice. These defects of cisplatin give a forceful impetus to the research on novel platinum complexes.[10] Over the last 30 years, thousands of platinum compounds have been prepared and screened as potential antitumour agents.[14,15] From these endeavours four further complexes, namely, carboplatin (**2**), oxaliplatin (**3**), nedaplatin (**4**), and lobaplatin (**5**) have been approved for clinical use and around 10 other complexes are currently under clinical trials.[16] However, since most of these complexes are structural congeners of cisplatin, with two ammine or amine donor groups and two anionic leaving groups in a *cis* geometry, some drawbacks of cisplatin are consequently inherited.[17]

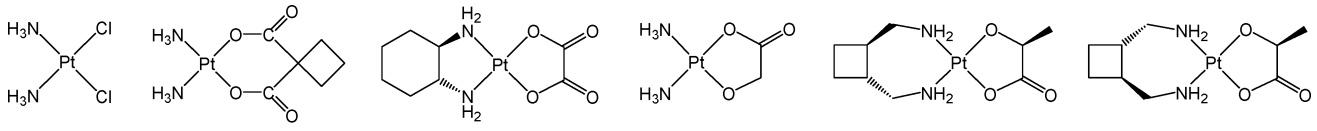
For the last few years we have been engaged in the design of novel platinum complexes that are fundamentally different from cisplatin such as monofunctional complexes and positively charged multinuclear complexes; besides, the research also stretched to the design of some gold(III) complexes. In the design of these complexes we paid considerable attention to the cellular reactions associated with platinum drugs including platinum–sulfur interactions and hydrolysis. Our objective is to obtain antitumour complexes with weak hydrolysis inclination, low reactivity towards sulfur-containing biomolecules, and strong potentiality to form unique DNA adducts. In the following parts, we will deal with some of the examples relevant to these subjects. Since many valuable reviews on this theme have appeared over the years, the material of this article is largely sourced from our own work in recent years and some related contents are only derived from the literature since 2000.

Mechanistic studies on platinum complexes

An in-depth understanding of the cellular responses to platinum compounds would benefit the design of novel platinum-based antitumour agents and inspire new strategies to improve the efficacy of existing drugs. It is known that the cytotoxicity of cisplatin originates from its binding to DNA and the formation of covalent cross-links.[13] The cellular processes that lead to the formation of Pt-DNA adducts and the early events that subsequently occur have been revealed.[18] Readers are encouraged to refer to these reviews for detailed information.[12,19] However, knowledge of the precise mechanism by which cisplatin triggers these events is still incomplete. In particular, there are gaps in understanding how platinum drugs enter cells and how Pt-DNA damage initiates various cellular signaling pathways. So far as DNA platination is concerned, binding of cisplatin to DNA causes significant distortion of the helical structure and results in inhibition of DNA replication and transcription.[20] The distorted DNA structure also serves as a recognition binding site for cellular proteins, such as repair enzymes, transcription factors, histones and HMG-domain proteins.[21] The anticancer efficacy of cisplatin is also influenced by the removal efficiency of the cisplatin-DNA adduct by the cellular repair machinery, with nucleotide excision repair being a major pathway.[22] Enhanced removal of cisplatin-DNA adducts is one of the main causes of cell resistance to cisplatin.[23,24] This particular resistance mechanism may be circumvented by platinum complexes that bind differently to DNA.[25,26] Therefore, platinum complexes with structure and mode of action different from that of cisplatin have attracted much attention in recent years, especially those that interact with specific molecular targets other than DNA; these complexes may result in new lead compounds for cancer therapy.

Sulfur-containing biomolecules such as cysteine (Cys), methionine (Met), glutathione (GSH), metallothionein (MT) and albumin are closely associated with platinum anticancer mechanisms because of their high affinity to the platinum(II) center. For example, cisplatin can react with L-methionine (L-MetH) to give different products such as $[Pt(NH_3)_2Cl(L\text{-}MetH)]^+$, $[Pt(NH_3)_2(L\text{-}Met)]^+$ (L-Met = deprotonated L-methionine), $[Pt(NH_3)Cl(L\text{-}MetH)]^+$, $[Pt(L\text{-}Met)(L\text{-}MetH)]^+$ as well as some binuclear complexes.[27] Carboplatin can also react rapidly with L-MetH to form complexes such as $[Pt(NH_3)_2(CBDCA)(L\text{-}MetH)]^+$ (CBDCA = cyclobutane-1,1-dicarboxylate), $[Pt(NH_3)(CBDCA)(L\text{-}MetH)]^+$, $[Pt(CBDCA)(L\text{-}MetH)]^+$, $[Pt(L\text{-}MetH)(L\text{-}Met)]^+$, $[Pt(NH_3)_2(L\text{-}Met)]^+$, and $[Pt(L\text{-}Met)_2]$.[28] Considering the aquation rate of carboplatin cannot account for its *in vivo* activity, Met may play a role in the activation of this drug. Such interactions may have a high impact on the cell uptake, excretion, resistance, systemic toxicity and cytotoxicity of platinum-based drugs.

Unfortunately, most of the platinum–sulfur interactions are considered to have negative effects on the therapeutic efficacy of the drugs.[29] For instance, they have been related to drug detoxification, nephrotoxicity and resistance; and reactions of platinum drugs with sulfur donors in peptides and proteins are believed to alter the conformation of proteins and lead to changes in biological activity, especially when enzymatic reactions are affected.[30] In the nucleus, GSH can quench Pt-DNA monoadducts



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before their conversion to the cross-linking bis-adducts. The major reaction products of platinum drugs with GSH are believed to be the S-bridged dimers or oligomers. The principal binding modes in these adducts have been identified as either monocoordinated Pt–GS or bridged Pt–GS–Pt adducts. In the reactions of [Pt(MetH-*S,N*)Cl_2], a model complex of cisplatin, with GSH and L-Cys, a series of stable polymeric species such as $[Pt_2(\mu\text{-}SG\text{-}S)_2(\text{Met-}S,N)_2]^-$, $[Pt_3(\mu\text{-}SG\text{-}S)_4(\text{Met-}S,N)_2]^{2-}$, $[Pt_4(\mu\text{-}SG\text{-}S)_6(\text{Met-}S,N)_2]^{2-}$, and $[Pt_5(\mu\text{-}SG\text{-}S)_8(\text{Met-}S,N)_2]^{3-}$ were detected for GSH, while only a mononuclear complex [Pt(L-Met-*S*,*N*)(L-Cys-*S*,*N*)] was observed for L-Cys.[31] For oxidized GSH (GSSG), mononuclear complexes and S-bridged dinuclear complexes with the cleavage fragments of GSSG were the main products.[32] Even the chelated L-MetH in [Pt(L-Met)$_2$] can be readily displaced by both GSH and L-Cys, giving rise to the thiolate-bridged polynuclear Pt(II) adducts.[33]

Formation of the Pt–GS or Pt–GS–Pt complexes has a dramatic effect on the cellular metabolism of cisplatin, because it reduces the amount of intracellular platinum available for interaction with DNA and protects dividing cells from cisplatin toxicity. Thus, strong and irreversible binding of cisplatin to intracellular thiolate ligands such as GSH and Cys-rich MTs has been considered as a major inactivation step for this drug.[34] Related advances in this area have been thoroughly summarized in our recent review.[35] The knowledge gained through these studies would provide valuable insights into the mechanism of reaction between platinum complexes and sulfur-containing biomolecules. Moreover, the understanding of the interactions will be of benefit to the rational design of new platinum-based drugs. By replacing the NH_3 groups in cisplatin with a thiocarbonyl or thiol containing ligands, the reaction of platinum complexes with sulfur-containing proteins may be prevented or at least limited. Based on this hypothesis, thiourea, thiosemicarbazones, sulfur-containing amino acids and so on have been incorporated into platinum complexes to modulate the general toxicity.[36]

The hydrolysis of platinum drugs is of fundamental importance for the mechanism of action of these agents. Hydrolysis of cisplatin is believed to be the key activation step before the drug reaches intracellular DNA. Therefore, the kinetic studies of the hydrolysis of cisplatin and its analogues in solutions comprise an essential part in platinum chemistry. Besides experimental studies, the hydrolysis process of cisplatin has also been investigated by molecular dynamics simulations.[37] To obtain an accurate hydrolysis theory for square-planar platinum(II) complexes, the following typical hydrolysis reactions of cisplatin and its diethylenetriamine (dien) analogue with the solvent effect have been studied by computational methods:

$$cis\text{-}[PtCl_2(NH_3)_2] + H_2O \rightarrow cis\text{-}[PtCl(OH_2)(NH_3)_2]^+ + Cl^-$$

$$cis\text{-}[PtCl(OH_2)(NH_3)_2]^+ + H_2O \rightarrow cis\text{-}[Pt(OH_2)_2(NH_3)_2]^{2+} + Cl^-$$

$$[PtCl(dien)]^+ + H_2O \rightarrow [PtCl(OH_2)(dien)]^{2+} + Cl^-$$

Both geometrical and thermodynamic profiles of these complexes demonstrated common second-order nucleophilic substitution (S_N2) reaction character in both gas phase and aqueous solution. The true five stationary states in the S_N2 pathway for the hydrolysis process, namely, reactant (R) → intermediate 1 (I1) → transition state (TS) → intermediate 2 (I2) → product (P), were obtained and characterized theoretically for the first time. The equatorial plane of the five-coordinate trigonal-bipyramidal-like structures of I1, TS, and I2 plays a significant role in determining the hydrolysis behavior, because the most remarkable structural and atomic charge variations in the hydrolysis process occur in this plane, and the most affected structural parameters after solvation are also related to this plane.[38] This work provides a thorough and detailed theoretical interpretation of the hydrolysis mechanisms of cisplatin and its analogues, which may be helpful for understanding the reaction kinetics of cisplatin with DNA and other biomolecules and be useful in the design of novel platinum-based antitumour agents.

Monofunctional platinum(II) complexes

Platinum complexes with different mechanisms of action from that of cisplatin may exhibit favorable pharmacological properties such as a broader spectrum of antitumour activity or a distinctive cytotoxicity profile; they may also overcome the resistance pathways that have evolved to eliminate the cisplatin-like drugs. In view of these potential merits, particular attention has been given to platinum complexes that bind to DNA in a different mode to cisplatin in recent years in the hope of finding new candidates as antitumour agents. As expected, a number of this kind of compounds such as platinum(IV) complexes[39,40] and *trans*-platinum complexes[41,42] have demonstrated biological profiles different to those of cisplatin and its analogues.

Monofunctional platinum(II) complexes represent a class of antitumour agents that do not adhere to the classic structure-activity relationships of platinum complexes but still exhibit potent cytotoxicity against tumour cells.[43] In the past 5 years, we have designed and synthesized a series of monofunctional platinum(II) complexes with a general formula of [PtLCl] (**6–10**), where Cl^- acts as the only potential leaving group. These complexes have been tested against a wide range of tumour cell lines including the human liver carcinoma cell line BEL-7402, the human colon carcinoma cell line HCT-116, the human lung adenocarcinoma cell line SPC-A4, the T-cell leukemia cell line MOLT-4, the murine leukemia cell line P-388, the human acute promyelocytic leukemia cell line HL-60, the human non-small-cell lung cancer cell line A-549, the human stomach cancer cell line SGC-7901, the human gastric cancer cell line MKN-28, or the human epithelial ovarian cancer cell line HO-8910. Complexes **6–8** exhibited significant cytotoxicity against most of these cell lines. The most cytotoxic compound **6** (Fig. 1) even showed an inhibition rate of 75.1% to BEL-7402 at 6.6×10^{-7} mol L^{-1}, which is nearly 6 times higher than that of cisplatin.[44] Complexes **9** and **10** did not show significant cytotoxicity against P-388 and A-549 cell lines at low concentrations ($<10^{-5}$ mol L^{-1}), though **10** is more effective than cisplatin at high concentrations ($>10^{-5}$ mol L^{-1}). On the whole, their cytotoxicity is comparable to that of cisplatin at the tested concentration ranges (10^{-4}–10^{-7} mol L^{-1}).[45]

The variations in activity among these complexes may be attributed to their differences in lipophilicity. Higher lipophilicity can facilitate the passive uptake of drug molecules across the lipidic cell membrane and affect the activity of the drugs. Thus, the most lipophilic **6** is also the most cytotoxic complex. The interesting correlation between lipophilicity and cytotoxicity for this class of complexes deserves further investigation.

It was shown that the introduction of bulky planar ligands such as pyridine and substituted pyridines could maintain the cytotoxicity of platinum(II) complexes while significantly reduce

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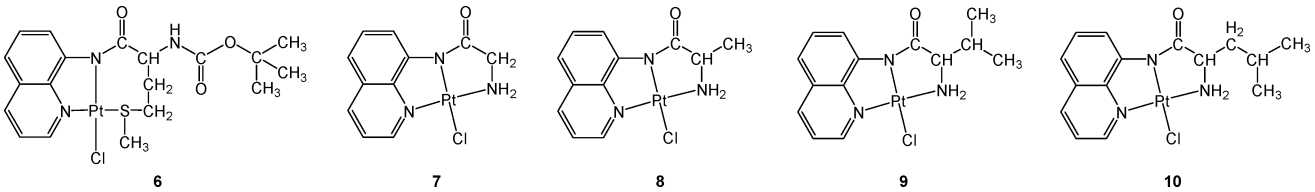

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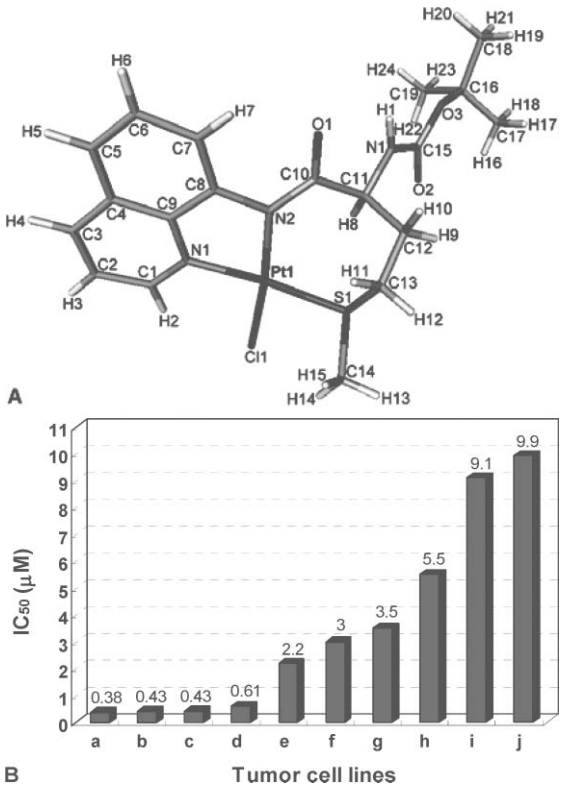


Fig. 1 The crystal structure (A) and *in vitro* cytotoxicity (B) of complex **6**. Cell lines: a, HCT-116; b, SPC-A4; c, BEL-7402; d, MOLT-4; e, HO-8910; f, P-388; g, HL-60; h, A-549; i, SGC-7901; j, MKN-28.

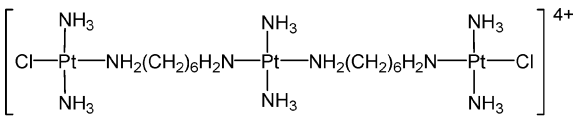
the rate of deactivation by sulfur-containing molecules.[46] For example, sterically hindered complex ZD0473 is less reactive towards sulfur-containing molecules than cisplatin. Therefore, a more pronounced decrease in reactivity towards GSH is expected when a bulky 8-aminoquinolyl was introduced into the above complexes. Indeed, both **9** and **10** hardly react with GSH; thereby the GSH associated side effects are very likely to be reduced by this class of complexes. All five complexes could react with guanosine-5′-monophosphate (5′-GMP) to give mono-adducts and the chelate rings remain unchanged during the reaction, implying they have the potential for DNA binding. However, their binding mode to DNA may be radically different from that of existing platinum drugs and the mechanism of action may be dissimilar to that of the established pattern. It has been reported that monofunctional platinum(II) complexes can also significantly destabilize DNA and affect the conformation of DNA duplex,[47] which suggests that the formation of bifunctional DNA adducts may be not a prerequisite for platinum(II) complexes to display cytotoxicity.[41]

Additional mechanisms other than DNA platination have been implicated in the cytotoxic mode of action of platinum-based drugs,[48] and they might be fit for monofunctional platinum complexes. In summary, monofunctional platinum(II) complexes merit further investigation, which may provide a new avenue to gain promising anticancer agents. The exact mechanism of action of these complexes remains to be elucidated.

Multinuclear platinum(II) complexes

Multinuclear platinum complexes comprise a novel class of compounds that have shown great potential for cancer chemotherapy.[49] These complexes contain two, three or four platinum centers with both *cis* and/or *trans* configurations and bind to DNA in a manner different from that of cisplatin. They react with DNA more rapidly than cisplatin and produce characteristic long-range inter- and intrastrand cross-linked DNA adducts.[50] The interstrand cross-links are insensitive to repair by cellular extracts, which could enhance the cytotoxicity of multinuclear complexes.[51]

One of the most outstanding examples of multinuclear platinum(II) anticancer complexes is BBR3464 (**11**), which exhibits antitumour activity against pancreatic, lung and melanoma cancers and is currently in phase II clinical evaluation.[52] The high positive charge and am(m)ine groups in **11** are believed to facilitate the specific recognition of target sites on DNA through electrostatic and hydrogen-bonding interactions.[53] In fact, the rapid binding of **11** to DNA results in various long-range inter- and intrastrand cross-links, where the interstrand adducts account for ~20% of the DNA adducts.[49] Mechanistic studies suggested that the interstrand cross-links, rather than intrastrand adducts, are crucial to the antitumour activity.[51] The preclinical evaluation in seven human tumour cell lines and tumour xenografts naturally resistant to cisplatin showed that **11** was extremely potent with IC_{50} values at least 20-fold lower than that of cisplatin.[54] Also, it was highly potent toward human tumour xenografts characterized by mutant p53, which are generally insensitive to chemotherapy, including cisplatin intervention. The hypersensitivity of human tumours with mutant p53 to **11** suggested that apoptosis induced by **11** could bypass p53-mediated pathways.[24,55,56] This important feature further suggested that multinuclear platinum agents may find utility in the over 60% of cancer cases where mutant p53 status is indicated.



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In multinuclear platinum complexes, the active platinum centers are commonly linked by flexible aliphatic polyamines.[57,58] For example, the two platinum centers in dinuclear *trans*-platinum complexes **12–17** are linked by an aliphatic diamine with each platinum

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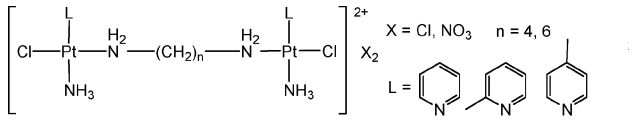
core bearing one planar ligand. The cytotoxicity of these compounds was determined in L1210 murine leukemia and a cisplatin-resistant derivative L1210/2 cell lines. In general, they are less cytotoxic than their NH_3 counterparts (L = NH_3; $n = 4, 6$), which could overcome cisplatin resistance.[59] Complexes **18** and **19** contain the biogenic polyamines spermidine [$H_2N(CH_2)_3NH(CH_2)_4NH_2$] and spermine [$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$] as bridging linkers. They display a rather high antiproliferative and cytotoxic activity toward the human cervical cancer cell line HeLa and HSC-3 epithelial-type cells and their effect on healthy cells is reversible upon drug removal.[26]



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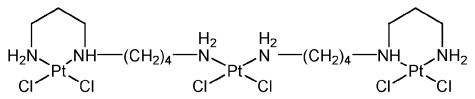

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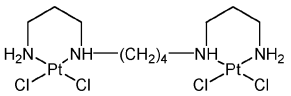


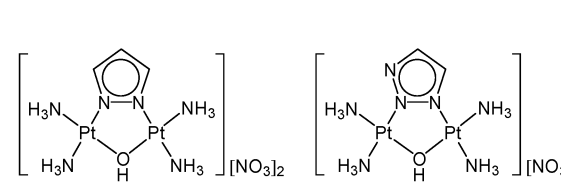
19

However, rigid ligands can also be used as linkers between platinum centers in multinuclear platinum complexes.[6] For instance, a series of azole-bridged dinuclear platinum(II) complexes **20–23** have been prepared. **20** and **21** show much higher cytotoxicity than cisplatin on several human tumour cell lines, including MCF7 and EVSA-T (breast cancer), WIDR (colon cancer), IGROV (ovarian cancer), M19 (melanoma), A498 (renal cancer), and H226 (non-small cell lung cancer);[60] **21** and **23** exhibit higher cytotoxicity than cisplatin on both L1210 murine leukemia cell lines sensitive and resistant to cisplatin; **22** is effective against the cisplatin-resistant L1210 cell line and equally good as cisplatin on the parent cell line.[61] Similar rigid linkers also appear in dinuclear platinum(II) complexes **24–27**. In general, these azine-bridged complexes display lower cytotoxicity than cisplatin for the above human tumour cell line except for the IGROV cell line, yet **26** and **27** exhibit remarkable cytotoxicity in the cisplatin-resistant L1210 murine leukemia cell line.[62,63] In spite of these examples, multinuclear platinum complexes containing an aromatic linker have not been fully explored.

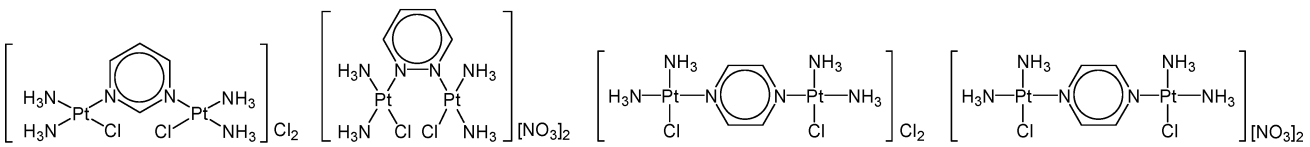
In our attempt to find novel multinuclear platinum(II) antitumour complexes, mesitylene was used to bridge three 2,2′-dipyridylamine units, forming a ligand with some flexibility. This ligand is more rigid than aliphatic polyamines but more flexible than pure aromatic rings, which may confer a favorable condition for DNA cross-linking. Thus, trinuclear platinum(II) complexes **28** and **29** were prepared but only **29** can bind to calf thymus DNA (CT-DNA) and the CBDCA group can be replaced by thiourea.[64] In contrast with this, their mononuclear counterparts **30** and **31** can interact with CT-DNA, but the *in vitro* cytotoxicity against melanoma B16-BL6 cells and human Jurkat T-cells only appears at high concentrations ($>10^{-4}$ mol L^{-1}).[65] Based on the reactivity of **28** and **29** to DNA and the *in vitro* cytotoxicity of **30** and **31**, these complexes do not warrant further investigation.

The properties of the above trinuclear complexes are significantly improved when three more flexible 2,2′-bis(pyridylmethyl)amine units are linked by the mesitylene moiety. The 3N-chelated trinuclear monofunctional platinum complex **32** binds strongly to DNA and exhibits more potent cytotoxicity against P-388 and A-549 cell lines than cisplatin. The rigidity as well as the flexibility of the linker in **32** together with the distances between metal centres (Fig. 2) offers the possibility of forming both intra- and inter-strand DNA cross-linking adducts. Gel mobility shift assay showed that **32** affects the tertiary structure of DNA more significantly than cisplatin does.[66]

The remarkable differences between **32** and **28** or **29** suggest that the reactivity and cytotoxicity of multinuclear platinum complexes can be finely tuned by selecting the bridging spacer and chelators. Some favorable properties that could ameliorate the biostability and bioavailabilty of complexes may result from the thoughtful modification. For example, **32** reacts with GSH to form mono- and disubstituted products such as $[Pt_3L(GS)Cl(OH)_2]^{2+}$ and $[Pt_3L(GS)_2(OH)_2]^{2+}$ (GS = deprotonated GSH) but keeps the trinuclear skeleton stable for 24 h. This is an improvement over BBR3464 (**11**), where an excess of GSH would cause it to fragment into smaller species because of the *trans* labilization of the linker upon binding of the sulfur atom of GSH.[67] So far as we know, **32** appears to be the first trinuclear platinum(II) anticancer complex in which three 3N-chelated monofunctional Pt(II) units are linked by a rigid ligand. It should be noted that early structure-activity relationships have defined the necessity of at least one NH moiety in ligand, which is believed to be important for H-bonding



20 **21** **22** **23**



24 **25** **26** **27**

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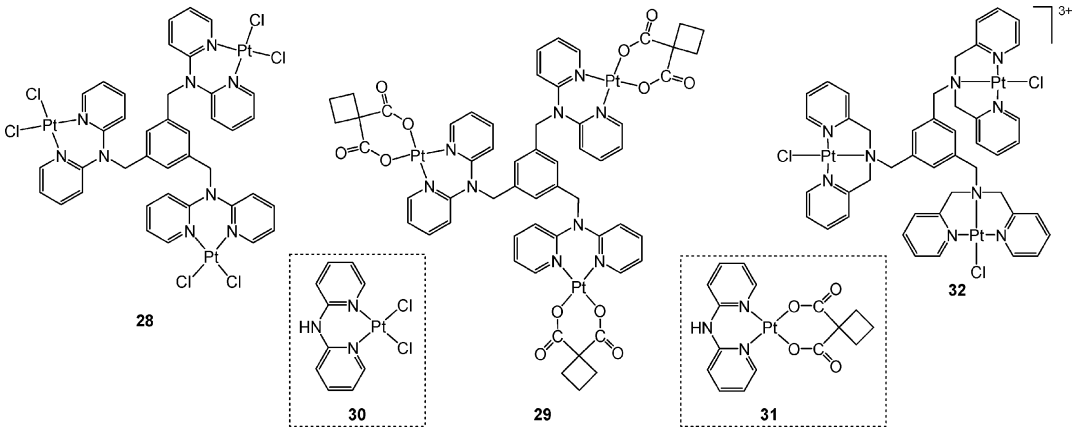


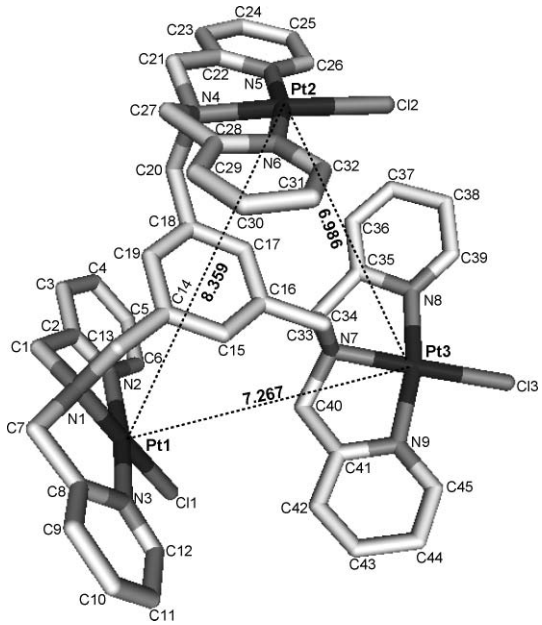
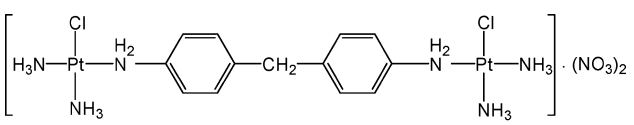


Fig. 2 Crystal structure of cation **32** with atom numbering scheme and Pt · · · Pt distances (Å). Solvent molecules and hydrogen atoms are omitted for clarity.

interactions toward DNA.[68] However, as we demonstrated in this case, an increasing number of platinum complexes contain no NH moiety but display significant antitumour activity.

Recently, we synthesized a 1,1/c,c type of dinuclear monofunctional platinum(II) complex **33**, using 4,4′-methylenedianiline as the linker. Both flexible and rigid elements as well as a steric factor are present in this complex. Complex **33** shows potent cytotoxicity against A-549 and P-388 cell lines, and is more cytotoxic than cisplatin at most concentrations tested (Fig. 3).



33

The 2D [^{1}H,^{15}N] heteronuclear single quantum coherence NMR spectra of ^{15}N-labeled **33** revealed that the cationic core of this water-soluble complex hardly hydrolyzes in aqueous solution. Hydrolysis appears not to be an essential step for the formation

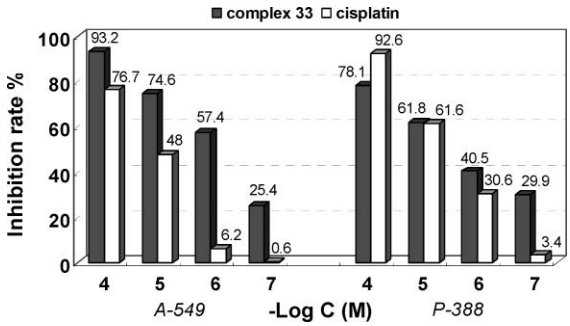


Fig. 3 Cytotoxic activity of complex **33** against the murine leukemia cell line P-388 and the human non-small-cell lung cancer cell line A-549 with cisplatin as a positive control.

of Pt-5′-GMP or Pt-DNA adducts because **33** reacts readily with 5′-GMP and partially transforms B-DNA into its *Z* form. The cytotoxicity may result from the effective interaction with DNA. The presence of phenyls in the complex largely increases the steric hindrance around platinum centers, thus the reaction of **33** with GSH proceeds very slowly and incompletely. The results suggest that the steric hindrance of the linker *cis* to the leaving group is an important factor affecting the reaction mode of a multinuclear platinum complex with GSH, and an increase in the steric hindrance and rigidity of the linker can inhibit the interaction.[69] Differing from **33**, an investigation on the reaction between GSH and a 1,1/c,c dinuclear platinum complex linked by an aliphatic diamine indicated that the generation of the platinum-GSH adducts and the disappearance of the starting complex occurred within 1 h with a stable SG-bridged macrochelate as the principal product,[70] though such complexes react more slowly with GSH and DNA than with those of their *trans* isomers. In short, high water-solubility, low aquation tendency, and inert reactivity towards GSH are distinctive characteristics of **33**; the latter particularly implies that the side effects associated with GSH *in vivo* may be reduced consequently. By contrast with the 1,1/t,t type of BBR3464 (**11**), the diamine linker in **33** remained intact throughout the reactions; therefore, the 1,1/c,c structural character may be another favorable trait for **33**. Considering the uniqueness of the chemical structure and biochemical reactivity, the mechanism of action for **33** should be different from that proposed for cisplatin.

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Hybrid and targeted platinum(II) complexes

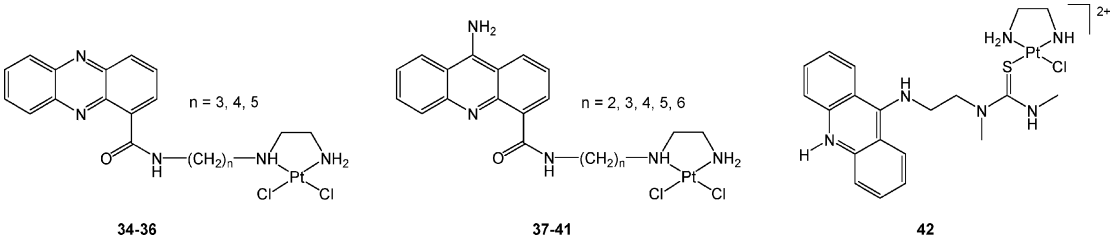
The platinum complexes to be discussed in this section are characterized by including two distinctive functional parts in the structure or composition. These dual functional complexes are rationally designed to overcome the systemic toxicity or to circumvent the drug resistance or to expand the indication of platinum-based drugs. Some approaches that are used for these purposes have been reviewed recently.[71] A common way to affect the biological activity of platinum drugs is to deliver the drug specifically to DNA by attaching the platinum moiety to a suitable carrier. Drug delivery systems that can target a tumour tissue or prevent non-DNA bindings are beneficial to reducing side effects and drug resistance of cisplatin analogues. Therefore, developing targeted platinum anticancer drugs has attracted considerable attention in recent years. To get a general appreciation, we will note some highlights in this area.

Platinum-intercalator conjugates are a series of hybrid complexes that act through a dual DNA binding mode with a platinum center dominating the DNA adduct profiles. Major advances in the chemistry and biology of this type of complexes from 1984 to 2004 have been reviewed in the literature.[72] Complexes **34–42** are some representative intercalator-appended platinum(II) complexes. **34–36** show much more potent cytotoxicity against murine P388/W cell lines than either cisplatin or $[Pt(en)Cl_2]$. The presence of the intercalator leads to enhanced rates of DNA platination when compared with $[Pt(en)Cl_2]$.[73] Complexes **37–41** can overcome cross-resistance in human ovarian carcinoma cell lines *in vitro*.[74] The presence of the intercalator 9-aminoacridine-carboxamide moiety greatly increases the rate of reaction with DNA as compared with cisplatin.[75] Platinum-acridinylthiourea conjugate **42** is highly potent against the HL-60 leukemia cells and the 2008 and C13* (cisplatin-resistant) ovarian cell lines, and shows only partial cross-resistance with cisplatin.[76] Unlike cisplatin derivatives, **42** does not induce DNA cross-links but damages DNA through a unique dual binding mode involving intercalation of acridine and monofunctional platination of the DNA duplex.[77,78]

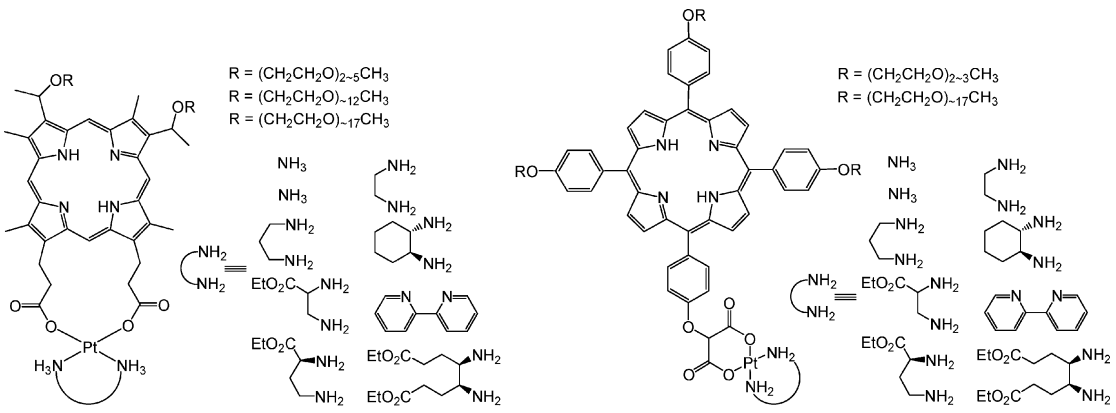
Platinum-porphyrin conjugates have been prepared to enhance tumour specificity of platinum complexes because of the preferable accumulation of porphyrin in neoplastic tissues. Besides, by linking a porphyrin moiety to a platinum complex, additional toxicity against tumour cells can be achieved upon irradiation owing to the photoactive property of porphyrins. In fact, hematoporphyrin-platinum complexes **43**[79] and tetraarylporphyrin-platinum complexes **44**[80] indeed exhibit enhanced cellular uptake and additional antitumour activity by a photo-induced mechanism.

Platinum-polymer conjugates with attached galactose residues or antennary galactose units exhibit high cell-specific cytotoxic activity against human hepatoma cells, because galactose receptors are exposed on the surface of liver parenchymal cells and the galactose unit tethered to the conjugate has an effective recognition ability toward such cells.[81,82] Other biomolecules such as bile acid[83,84] and estrogen[85] have also been incorporated into hybrid complexes as homing groups for liver and estrogen receptor positive tissues, respectively.

Coupling platinum anticancer drugs to polymers through a cleavable linker is an effective method for improving the therapeutic index of these agents. A series of platinum-polymer conjugates with *trans*-1,2-diaminocyclohexane as spectator ligands have demonstrated that the *in vitro* antiproliferative activity of the conjugates increased up to 10 times higher than that of cisplatin against the multidrug-resistant Colo 320 DM cell line.[86] Recently, platinum-*N*-(2-hydroxypropyl)methacrylamide conjugates AP5280 and AP5286 have entered phase I clinical trials, in which a diamine- or a diaminocyclohexaneplatinum(II) moiety is bound to a dicarboxylate ligand that is coupled to the polymer through the tetrapeptide spacer Gly-Phe-Leu-Gly.[87]



34-36 37-41 42



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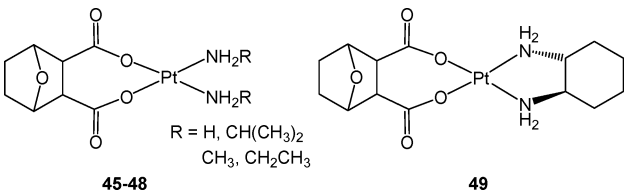
On the other hand, particulate delivery systems in which the drugs are physically incorporated into nanoparticles such as liposomes and non-covalent polymeric carriers can also be an effective way to protect platinum agents from intracellular thiols and prolong circulation time as well as to reduce lymphatic clearance of the drugs. In addition, the delivery efficiency of platinum drugs to tumour sites can be enhanced by this strategy because polymeric compounds tend to accumulate in tumour tissues. As an example, cisplatin has been efficiently encapsulated in a lipid formulation by repeated freezing and thawing of a concentrated solution of cisplatin in the presence of negatively charged phospholipids. The unique method generates small aggregates of cisplatin covered by a single lipid bilayer. These nanocapsules have an unprecedented drug-to-lipid ratio and an *in vitro* cytotoxicity up to 1000-fold higher than the free drug.[88]

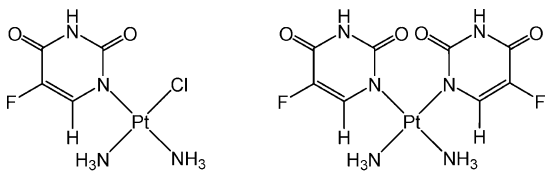
In the past few years, ligand-receptor-mediated delivery systems have received much attention because of their non-immunogenic and site-specific targeting potential to the ligand-specific biosites.[89,90] The native iron-storage protein ferritin (Ft) could be a promising vehicle for targeted drug delivery since the binding sites and endocytosis of Ft have been identified in tumour cells. Ft can be easily demineralized into apoferritin (AFt), a hollow protein cage with internal and external diameters of 8 and 12 nm, respectively. This protein cage can be employed to deliver platinum drugs, which may enhance the drug selectivity for cell surfaces that express Ft receptors. Very recently, we demonstrated that cisplatin and carboplatin can be encapsulated in the cavity of AFt and the drug-loaded protein has the potential to exert cytotoxic effect on tumour cells.[91] Two different processes were tried to generate the drug loaded AFt (Scheme 1). The shell of the protein after encapsulation remains intact as it is in AFt, thus the potential recognition nature should be retained. This character might be an advantage over other protein-based delivery systems, in which chemical modification of native proteins is usually needed for efficient drug loading[92] and hence the affinity for cellular targets would be undermined.[93] These protein coated drugs are expected to improve the toxicity profiles of the naked ones and finally lead to a novel strategy to overcome the detrimental effects of platinum-based drugs.

Anticancer drugs are rarely used singly to treat cancers, because only a few tumours are sensitive enough to be cured by a single drug. Therefore, effective chemotherapy usually depends on suitable combinations of several drugs with different modes of action, which often synergizes their effects. Combinations of platinum anticancer drugs with other anticancer drugs have demonstrated encouraging results in many cases, for instance, a combination of carboplatin with paclitaxel and gemcitabine is highly active in advanced urothelial carcinoma.[94] Further, such combinations may yield anticancer agents with a wider antitumour spectrum.[95,96] Although most combinations remain a physical mixture rather than a complete compound, increasing numbers of integrated chemical entity formed by different anticancer drugs have appeared recently. For example, the antitumour active demethylcantharidin (DMC), a modified component of a traditional Chinese medicine (TCM), has been combined with a platinum moiety, producing a series of TCM-based platinum complexes **45–49**. These complexes demonstrate selective cytotoxicity toward human hepato-cellular carcinoma SK-Hep-1 cell lines and can circumvent cisplatin cross-resistance. Both *in vitro* and *in vivo* antitumour efficacies of **45–49** are superior to cisplatin or carboplatin without inducing undue toxicity. The inclusion of DMC renders the complexes highly active as protein phosphatase (PP2A) inhibitors. These TCM-platinum complexes may possess a dual antitumour mechanism of action, *i.e.*, inhibition of PP2A by DMC and DNA platination. The circumvention of drug resistance may be attributed to this dual mechanism.[97–99] The pharmacokinetics and tissue distribution profiles of **45**, **47**, and **49** suggest that these complexes might afford higher clinical efficacy and reduced systemic side effects as compared with cisplatin.[100]

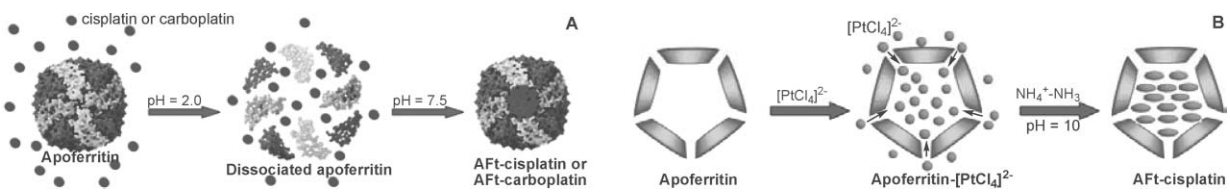


45-48 **49**

Antimetabolite 5-fluorouracil (5-FU) is a major anticancer agent used for the treatment of stomach, colorectal, head and neck cancers. A combination of an antimetabolite with a DNA-damaging agent may result in a more effective agent as compared with individual agent. We hence prepared two 5-FU-cisplatin complexes **50** and **51** from 5-FU and cisplatin. **50** reacts with 5′-GMP forming a stable mixed-ligand complex *cis*-$[Pt(NH_3)_2(HFU)(GMP)]$, whereas **51** does not undergo a similar reaction. Complexes **50** and **51** show a moderate *in vitro* antitumour activity against the melanoma B16-BL6 cell line. This work provides the basis for a potential alternative for the combinational use of 5-FU and cisplatin in cancer chemotherapy regimes.[101]



50 **51**



Scheme 1 Different ways to generate cisplatin or carboplatin loaded apoferritin: A, unfolding-refolding method; B, *in situ* generation method.

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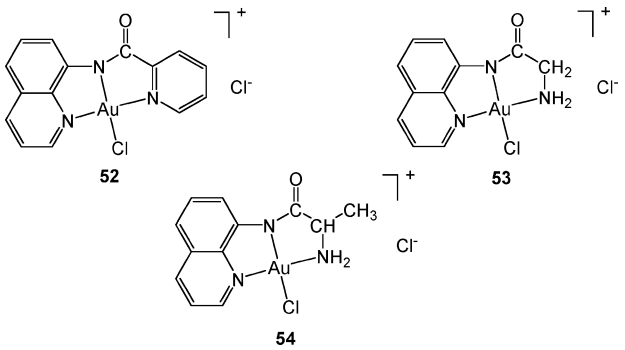
Gold complexes

A large number of gold(I) complexes, such as auranofin analogues, tetrahedral diphosphine complexes, and complexes with chiral phosphines, with bidentate thiolates, with charged thiols, with biologically active thiols and analogues, have been evaluated for cytotoxicity or antitumour activity. The results of these studies and mechanisms of cytotoxicity have been summarized elsewhere.[102–104] In brief, two distinct classes of gold(I) phosphine complexes with either linear two-coordinate or tetrahedral four-coordinate geometries display antitumour properties. Both classes appear to target mitochondria through different mechanisms.

Besides gold(I) complexes, gold(III) species have also demonstrated potential as antitumour agents.[105] Gold(III) complexes are isostructural and isoelectronic to platinum(II) complexes, therefore, they are supposed to have a similar activity profile to that of cisplatin,[106] and DNA is among the most suspected target molecules for them.[107] In fact, many gold(III) complexes are highly cytotoxic against different tumour cells[108–111] and some of them even retain efficacy against the cisplatin-resistant cell lines.[112–115] As for whether DNA is the primary target of gold(III) complexes, experiments have offered a rather puzzling picture. In some cases, there is clear evidence of direct DNA damage and apoptosis induced by cytotoxic gold(III) complexes;[116–118] while in other cases, the interactions of gold(III) complexes with DNA are significantly different and weaker than those of platinum analogues.[119] Moreover, there is no direct evidence for the formation of Au(III)-DNA adducts in living cells. The inconsistency of the data suggests that intracellular DNA might not represent the primary or exclusive biological target for gold(III) complexes. In the circumstances, mitochondria has been proposed as a major cellular target for at least some of the gold(III) complexes. The hypothesis is based on the fact that several cytotoxic gold(III) complexes have been shown to be efficient inhibitors of mitochondrial thioredoxin reductase, which would influence other functions such as membrane permeability properties.[120,121] Further, a gold(III) porphyrin complex has been shown to induce apoptosis though both caspase-dependent and caspase-independent mitochondrial pathways.[122] As alternatives, a mechanism involving inhibition of the proteasome has been suggested recently,[123] and interactions between gold(III) complexes and model proteins or target proteins have been reported as well.[124,125] In a word, the antitumour mechanism of gold(III) complexes seems substantially different from that of cisplatin.

Generally speaking, gold(III) complexes are not very stable under physiological conditions because of their high reduction potential and fast hydrolysis rate. Therefore, selection of a suitable ligand to stabilize the complex becomes a foremost challenge in the design of gold(III)-based antitumour agents. This aim can be achieved by chelating gold(III) center with one or more multidentate ligand to enhance the stability of the complex. For example, in complexes $[Au(phen)Cl_2]Cl$ (phen = *o*-phenanthroline),[126] $[Au(bipy^c\text{-}H)(OH)](PF_6)$ ($bipy^c$-H = 6-(1,1-dimethylbenzyl)-2,2′-bipyridine),[107] and $[Au(Mephpy)Cl_2]$ (Mephpy = *N*-(4-methylphenyl)-2-pyridine-carboxamide),[127] Au(III) is coordinated by at least two chelating nitrogen donors which lower the reduction potential of the metal center and thereby stabilize the complex. Pyridine-containing molecules and macrocyclic molecules are commonly used for this purpose and many gold(III) complexes derived from them have been shown to be very stable under physiologically relevant conditions.[117,128]

In recent years, we have been endeavoured to develop new ligands that can stabilize the gold(III) center effectively. In complexes **52–54**, the derivatives of 8-aminoquinoline coordinate to Au(III) in a tridentate mode forming two five-membered chelate rings, which confer appreciable stability onto the complexes. These complexes were tested against B16-BL6, P-388, HL-60, A-549, and BEL-7402 cell lines. Complex **52** is highly cytotoxic against A-549 cells with an inhibition rate of 94.4% at 10^{-6} mol L^{-1}, which is about 3 times stronger than cisplatin; **54** is active against B16-BL6 with an inhibition rate of 67.5% at 10^{-7} mol L^{-1}. Complexes **52** and **53** can not bind to 5′-GMP while **54** limitedly forms a 5′-GMP adduct. Intercalative interactions between the complexes and CT-DNA may exist, but it is not clear whether such interaction is responsible for the cytotoxicity of the complexes.[129]



Terpyridine derivatives have been used to construct platinum(II) complexes as antitumour agents.[130] A terpyridine derived gold(III) complex $[Au(terpy)Cl]Cl_2$ also shows interesting cytotoxicity,[112] but the governing factors of activity and the biological target are unknown. Accordingly, we synthesized four gold(III) complexes **55–58** from terpyridine derivatives, incorporating factors that may change their steric and electrostatic effects. Triphenylphosphine is chosen to act as a bulky group to offer more positive charge to the cationic core of the complex, while 2-naphthol is employed only as a big spatial group, and 2-bromoethanesulfonic sodium is selected to lower the charge of the cationic core and to improve water solubility of the complex. These complexes are stable in aqueous solution for two days in the presence of biological reducing agent GSH. All of them show higher *in vitro* cytotoxicity than cisplatin against A-549, SGC-7901, HeLa, HCT-116, BEL-7402, P-388, and HL-60 cell lines, especially **57**, which exhibits the highest activity with growth inhibition rates of over 80% at 10^{-8} mol L^{-1} against A-549, HCT-116 and HeLa cell lines. The cytotoxicity of the complexes follows an order of **57** > **55** ≈ **58** > **56**. Interestingly, the ligands are also very cytotoxic against the cell lines tested. The ratio of gold(III) to nucleotide in the DNA isolated from cells treated with **55** and **57** is about 1 : 6400 and 1 : 4900, respectively, comparable to the level of DNA metallation for platinum(II) complexes. The planar complexes may interact intercalatively with DNA, where the steric and electrostatic effects of the ligand have strong influences on DNA binding affinity of the complexes. For complexes with the same positive charges (*e.g.* **55**, **66**), the stronger steric effect decreases the affinity; while for complexes with different positive charges (*e.g.* **56**, **57**), the higher positive charge enhances the affinity. As a whole, the electrostatic

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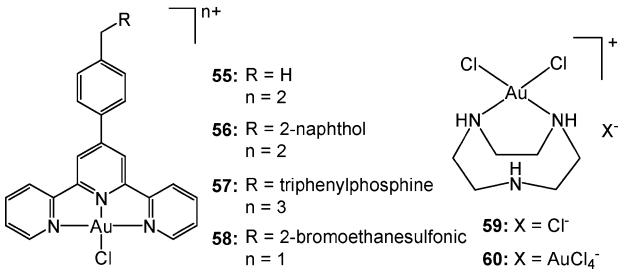
effect appears to have a greater impact on the interaction. Thus low steric hindrance and high positive charge could enhance the binding affinity of the complexes to DNA. To our surprise, a correlation between the DNA binding affinity and the cytotoxicity has been found among these complexes, suggesting the cytotoxic activity and DNA binding ability of the complexes can be finely tuned by the steric and electrostatic properties of the ligands.[131] It should be noted that complexes in this case appear to be the first examples showing that gold(III) complexes can target intracellular DNA *in vitro*. Anyway, the high stability and solubility of these complexes make them a class of excellent lead compounds for further *in vitro* and *in vivo* investigations as antitumour agents.



In gold(III) complexes **59** and **60**, 1,4,7-triazacyclononane was used as a bidentate ligand to stabilize the Au(III) center. Both complexes share the same cationic core in solution. **59** is more cytotoxic than cisplatin against A-549 and HCT-116 cell lines and can induce the distortion of DNA double helix.[132] However, estimated by the cytotoxicity of the complexes, ligand 1,4,7-triazacyclononane is not as effective as the above 8-aminoquinoline and terpyridine derivatives.

Currently, the ambiguity relating to the mechanism of action makes the design of gold complexes lack theoretical guidance. With different biological targets such as mitochondria and DNA still perplexing us, further in-depth investigation on these issues is warranted to shed light on the understanding of antitumour activity of gold complexes.

Concluding remarks

Many metal complexes with antitumour efficacy have been developed and some of them may eventually be evolved into more effective and less toxic anticancer drugs. As demonstrated by examples in this article, some desired properties can be achieved by rational design. Beyond doubt, a deep understanding of the mechanisms of existing metal anticancer agents will build the basis for the rational design. Multifunctional ligands have offered many exciting possibilities for achieving site specific targets and modulating the potential toxicity of metal complexes.[133] Structural changes may substantially alter the DNA binding mode and DNA damage and hence the mechanism of action of platinum complexes. In general, the modification of the leaving groups in cisplatin results in changes in pharmacokinetic properties, whereas modification of the carrier ligands leads to variations in efficacy and/or spectrum of activity. Therefore, rational design of new functional ligands remains the key step in realizing the desired therapeutic goals. In our cases, different factors that influence the property of a complex such as geometry, steric hindrance, flexibility, electrostatic effect, and lipophilicity are taken into consideration during the design. Consequently, most complexes have a different mechanism of action from that of cisplatin and many show potential for overcoming the GSH related toxicity and detoxification. Although gold(III) complexes are similar to platinum(II) complexes in many aspects, the alteration of metal center may cause changes in the pharmacological profiles and the development of drug resistance. A better understanding of the cellular process of gold complexes is greatly needed now for further exploration of these complexes as antitumour agents.

In conclusion, the research on metal-based antitumour agents is an area full of prospects. There is ample space for further development in this area and the rational design will lead to the discovery of more promising compounds for preclinical and clinical investigations.

Acknowledgements

We thank the financial support from the National Natural Science Foundation of China (Nos 20231010, 20631020, 90713001 and 20721002); we appreciate the important contributions made by many former group members and collaborators who have worked on the project.

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