Review

Anticancer cyclometalated complexes of platinum group metals and gold

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Abstract
The clinical success of cisplatin and its derivatives has had an enormous impact on the discovery of novel metal-based drugs. Extensive studies have focused on the interaction of metal complexes with their potential targets. The array of organometallic compounds with useful anticancer activity has been significantly extended with respect to metals and structures. This review highlights recent exciting results of cyclometalated C–N complexes and C–N–C, C–N–N and C–N–S pincer complexes of platinum, palladium, gold, ruthenium, rhodium, and iridium with potential anticancer properties.
Keywords: Medicinal; Cyclometalated; Organometallic; Anticancer; Platinum; Palladium; Gold; Ruthenium; Iridium; Rhodium; Cancer; Cytotoxicity.

1. Introduction

The breakthrough synthesis of cisplatin in 1965 revolutionized cancer chemotherapy and many cisplatin analogs have been biologically evaluated. However, few of them possess pharmacological

advantages relative to the original compound. Only three platinum-based anticancer drugs (cisplatin, carboplatin and oxaliplatin) have been approved worldwide (Fig. 1) and they are still used in more than 50% of the treatment regimens for cancer patients. The global market for platinum-based drugs represent several billion euros even though they are untargeted, their use is often accompanied by side effects such as nephrotoxicity and they are often sensitive to resistance mechanisms [1–3]. A main limitation of traditional platinum-based molecules is their inactivation by small cellular molecules (in particular glutathione) and efflux out of the cell [4]. Overcoming these limitations of cisplatin is a real challenge in pharmaceutical research [5–7]. It is thus not surprising that a wide range of transition-metal drug candidates are currently under consideration for future development [8–16].

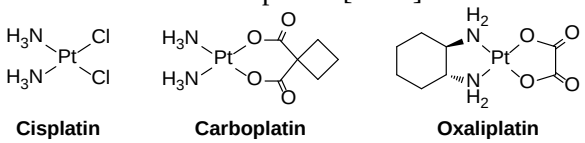


Fig. 1. Current platinum-based anticancer drugs used globally.

In this context, organometallic compounds with properties somewhat intermediate between classical inorganic and organic drugs have recently been considered as promising alternatives in medicinal chemistry for several reasons [17–27]. First, these hybrids combine the features of both the metallic centre and one or more organic scaffolds. Moreover, they are endowed with versatile stereochemistry (geometries ranging from linear to octahedral and even beyond, and up to 30 stereoisomers in the case of an octahedral complex) and the redox properties of the metal cation, together with its ability to bind to biological targets [28]. In addition, organometallic species are relatively lipophilic and can be endowed with a huge variety of functionalized organic ligands with very specific reactivities.

To improve the stability of transition metal complexes against biological reduction and ligand exchange reactions, a number of research teams have generated cyclometalated complexes in which a chelating ring contains a strong C–M σ bond (Fig. 2) [29,30]. Cyclometalated compound properties can be easily tuned by modification of either the anionic cyclometalated or the ancillary ligands, possibly enhancing their cytotoxicity and pharmacokinetics. The sequence and regiospecific interactions, resulting from the ligand type and specificity, also play an important role in the mechanism of action of these compounds. It should be noted that these compounds behave as prodrugs and require activation in several instances. Moreover, they are generally rather stable and are thus easy to characterize. Many cyclometalated compounds have been thoroughly investigated because of a wide range of potential applications in many areas, such as organic and organometallic synthesis and the design of advanced materials [31–33]. Thus, many research papers on these compounds have been published in the last 40 years [30].

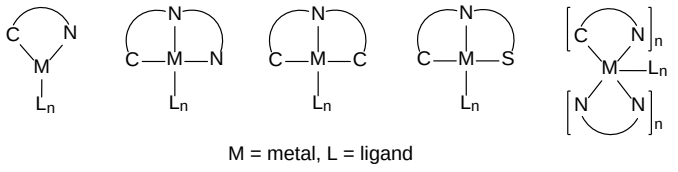


Fig. 2. General representation of cyclometalated complexes.

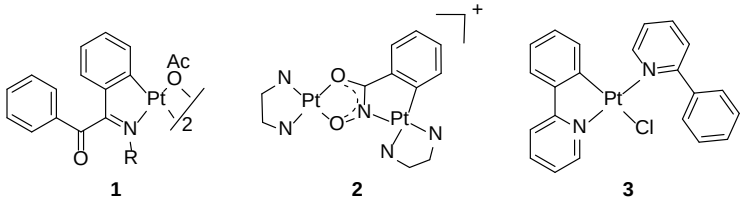
This review includes recent significant results on cyclometalated C–N and C–N–N, C–C–N and C–N–S pincer complexes of platinum(II), palladium(II), gold(III), ruthenium(II), rhodium(III) and iridium(III) with potential anticancer properties. The mechanisms of action identified for cyclometalated compounds are discussed, as well as structure–activity relationships as far as possible.

2. Platinum(II)

Although cisplatin analogs have overcome the side effects of cisplatin to some extent, some side effects are inherited owing to structural similarities to cisplatin, albeit to a lesser extent [34–39]. Efforts to provide broad-spectrum antitumor agents with distinctive cytotoxic profiles have led to structurally different organoplatinum complexes with many opportunities for revealing antitumor drugs with different mechanisms of action. A variety of organoplatinum compounds have been designed, synthesized and studied, with an emphasis being placed on the interplay between chemical structure using diverse ligands, the mechanism of DNA interaction and favorable cytotoxicity against cancer cells.

2.1. C–N complexes

In the early development of organometallic anticancer compounds, a variety of bidentate C–N cycloplatinated complexes with the general formula Pt(C–N)LX were synthesized and studied (Fig. 3). General guided design has emerged as a lead for future developments of C–N cycloplatinated compounds, since the C–N ligand is rather kinetically inert. By altering the structure of inert C–N ligands and/or other ancillary ligands, the kinetic, structural and electronic properties of cycloplatinated complexes can be fine-tuned to enhance their activity [35,40]. Navarro-Ranninger et al. reported the synthesis of the cycloplatinated compounds **1** (Fig. 3) using benzoylbenzylidenamine as the C–N backbone and acetato or chloride-bridged dimeric units used as labile ligands [41,42]. These compounds were more active against breast carcinoma (MDA-MB 468) and leukemic (HL-60) tumor cells than cisplatin. The antiproliferative activity of these compounds was attributed to covalent binding to DNA to form intrastrand adducts in similar way to that for cisplatin. Hambley and co-workers synthesized Pt-diamine complexes **2** with benzohydroxamate as the C–N bidentate moiety, which display promising activity profile against a panel of A2780 ovarian cancer cell lines [43]. Further studies revealed that the hydroxamate bridge possibly modifies the rate of hydration and DNA binding of these species. Kodaka's group reported a platinum(II) complex **3** with 2-phenylpyridine (ppy) that exhibits high cytotoxicity against cisplatin-resistant mouse sarcoma 180 (S-180*cis*R) cells. The high accumulation of platinum accounted for the higher activity against S-180*cis*R compared to cisplatin [44,45]. Black et al. explored cycloplatinated complexes of ppy with other ligands including halogens, dimethylsulfoxide (DMSO), phosphorus ligands and small heterocycles. The two factors revealed for the increased activity were steric hindrance about the metal centre, resulting from hindered ligands such as 2,6-dimethylpyridine, and the presence of a phosphorous donor ligand [46]. These complexes show high selectivity and binding affinity towards human serum albumin (HSA).



1 **2** **3**

Fig. 3. Early antitumor C–N cycloplatinated compounds.

In line with progress for organometallic anticancer drugs, Ruiz et al. developed highly active platinum complexes containing 2-(dimethylaminomethyl)phenyl (dmba) (e.g. **4**; Fig. 4) and some derivatives with bioligands [47−50], such as model nucleobases (e.g. **5**; Fig. 4), which introduced new directions for possible drug discoveries and an ability to host biologically important guests. These complexes exhibit greater activity than cisplatin against a panel of human cancer cell lines, including leukemia (HL-60), ovarian (A2780 and A2780*cis*R), lung (NCI-H460) and breast (T47D) cells. Atomic force microscopy images revealed that most of the complexes modify the morphology of pB*R*322 DNA in a similar mode of cisplatin. Flow cytometry results demonstrated that the majority of the cell death observed in cytotoxic assays is by apoptosis. The same research group synthesized a series of 7-azaindolate cycloplatinated complexes with high cytotoxicity (e.g., **6**; Fig. 4) [51]. Remarkably, **6** shows submicromolar activity in A2780 and T47D cell lines, as well as a very low resistance factor (RF = 1.3) against A2780*cis*R, a human ovarian cancer

cell line that has acquired resistance to cisplatin. Moreover, a family of dmba-cycloplatinated acetonimine derivatives (e.g., **7**; Fig. 4) [52] were reported as potent anticancer complexes, with higher anticancer potency than analogous platinum–acetonimine coordination complexes [53]. All derivatives are more active than cisplatin against the human tumor cell lines A2780, A2780*cis*R and T47D. In particular, complex **7** is approximately 30-fold more active than cisplatin in T47D cells. These complexes also show very low resistance factors against A2780*cis*R. The degree of superhelicity of DNA molecules was altered by interactions with these platinum complexes, as demonstrated by circular dichroism and electrophoretic mobility assays. This area of research appears to be promising for future development.

A number of research groups have synthesized platinum complexes attached to DNA intercalators [54,55]. Platinum–acridinylthiourea conjugates were reported as a new class of cytotoxic DNA-targeted agents that act through a hybrid mechanism involving monofunctional platination of nucleobase nitrogen and classical intercalation [54,56]. Ruiz et al. prepared complex **8** that is more active than cisplatin against the HL-60 tumor cell line [57]. Moreover, circular dichroism and atomic force microscopy studies demonstrated that **8** modifies the tertiary structure of pB*R*322 DNA. Using ESI-TOF MS, Palacios and co-workers recently demonstrated a low degree of interaction between **8** and proteins and the absence of covalent interaction with oligonucleotides. Fluorimetric studies confirmed a π–π interaction with dsDNA [58]. Klein and Hambley described several platinum–anthraquinone hybrids [40], since anthraquinone-containing compounds are DNA intercalators. Ruiz et al. synthesized the anthraquinone derivative **9**, which can interact with DNA through both intercalative and coordinative binding modes. This complex showed high cytotoxicity against T47D and A2780 cancer cell lines (approx. nine- and three-fold more cytotoxic than cisplatin, respectively) and a very low resistance factor in A2780*cis*R. Remarkably, **9** was less toxic than cisplatin towards normal human LLC-PK1 renal cells [59].

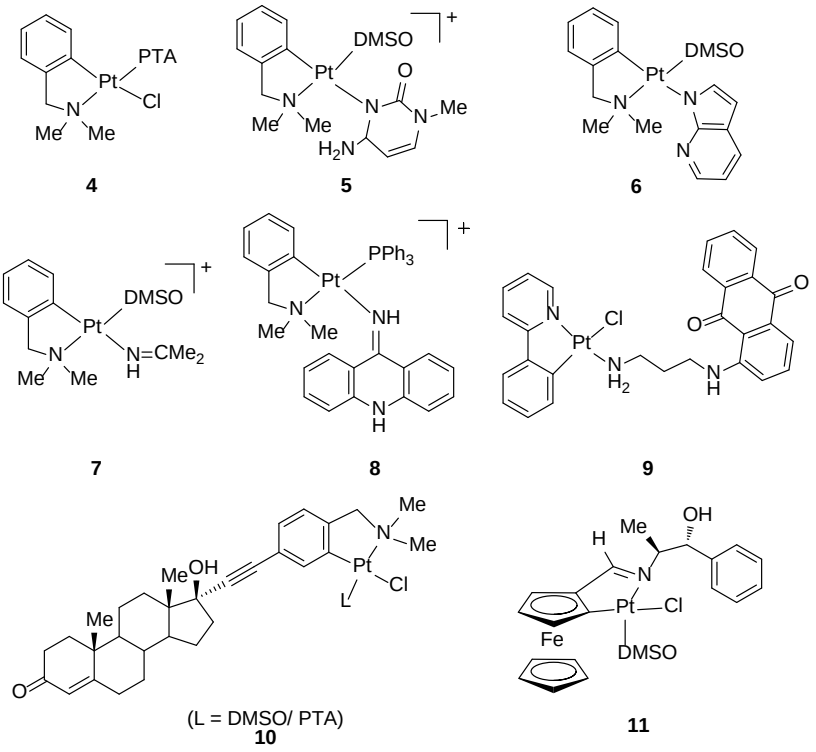


Fig. 4. Recently developed C–N cycloplatinated complexes.

In recent times, new strategies for functionalization of drug molecules have been identified to decrease the side effects and to increase the activity spectrum through more effective drug delivery to the desired

targets [60–62]. Biomolecules as delivery vectors are a possible functional adaptation and different molecules have been explored with varying degrees of success. Sex hormones such as estrogens and androgens have been attached to a range of different organometallic and coordination units with the aim of targeting estrogen receptors [63,64]. In this context, cycloplatinated steroidal conjugates of type **10** have recently been reported; these have comparable activity to their nonsteroidal counterparts and are more active than cisplatin in breast and ovarian cancer cell lines [65]. The steroidal carrier ligand retains an acceptable degree of relative binding affinity for androgen receptors. Very recently, López and co-workers reported pairs of isomeric 1,2-disubstituted ferrrocenylcycloplatinated complexes (e.g., **11**; Fig. 4) with different planar chirality [66]. Compound **11** exhibits cytotoxic activity against lung (A549), colon (HCT116) and breast (MDA-MB-231) human cancer cell lines and was even more potent than cisplatin, particularly in HCT116 cells. These complexes seem to change the tertiary structure of DNA.

The ubiquitin–proteasome pathway has become an important target in cancer therapy, as inhibition of proteasomal chymotrypsin-like activity is associated with tumor cell apoptosis [67]. Five coordinated cyclometalated platinum(II) complexes **12 (**Fig. 5) containing chelating biphosphine ligands exhibited more potent anticancer activity than cisplatin under *in vitro* and *in vivo* conditions [68]. They show proteasome inhibitory activity towards purified 20S and intact 26S proteasomes in human breast cancer cells, which is associated with apoptosis induction. In preliminary studies, these platinum complexes inhibited tumor growth in a mouse xenograft model and showed a more favorable toxicity profile compared to cisplatin. The binding mode to DNA and the relationship between the complex structures and their antitumor effects in relation to proteasome-inhibitory effects were reported on the basis of their inherent luminescence activity. More recently, fluorescence and UV/Vis studies have demonstrated that complexes **12** interact strongly with HSA and BSA. Hydrophobic interactions make the most important contributions to the binding process [69].

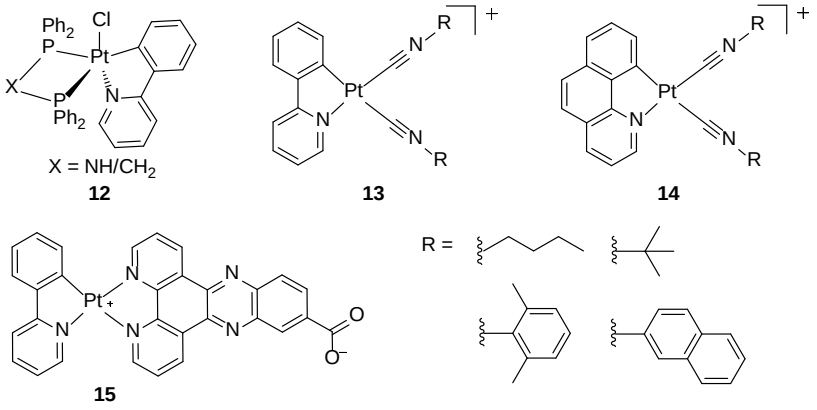


Fig. 5. Representative C–N cycloplatinated enzyme inhibitors.

Exploration of DNA topoisomerase IIα (TopoIIα) inhibition has been an efficacious anticancer strategy as TopoIIα is essential in sustaining cellular growth [70,71]. Terpyridine platinum(II) complexes were reported by Wang et al. that inhibit both TopoI- and TopoII-mediated DNA relaxation [72]. Che's group also reported an organoplatinum(II) complex with a nucleobase motif as an inhibitor of TopoIIα catalytic activity [73] as well as a series of complexes of types **13** and **14** that inhibit TopoIIα-mediated DNA relaxation [74]. These complexes bind to DNA at the major groove, stabilize the covalent TopoIIα–DNA cleavage complex, and induce cancer cell death with potency significantly higher than the known TopoIIα poison Vp-16. Inhibition of telomerase activity by inducing or stabilizing G-quadruplex formation has also arisen as a significant target for new anticancer drugs owing to its involvement in the regulation of telomerase activities [75,76]. Jamieson and Lippard showed that cisplatin and its derivatives have anti-telomerase activity [77]. To date, a number of platinum(II) complexes have been reported as potent telomerase inhibitors. Che et al. prepared a series of dipyridophenazine platinum(II) complexes such as **15**

that contain a ligand with a pendant COOH functional group, which may be involved in H-bonding interaction with the guanine in the external tetrad of G-quadruplex DNA, which accounted for the high binding selectivity and affinity of this complex towards the G-quadruplex, as well as its nanomolar potency against telomerase [78].

2.2. C–N–N complexes

Cyclometalated platinum(II) compounds containing tridentate π-conjugated organic ligands have attracted much interest for application as potent anticancer agents. The planar motifs of these platinum(II) complexes could insert between two adjacent DNA base pairs through non-covalent ligand–ligand π–π stacking interactions, thus rendering them DNA metallointercalators, apart from covalently cross-linking to the DNA base pairs [79,80]. Cycloplatinated tridentate C–N–N complexes are more stable compared to cisplatin and its derivatives. They display intriguing photoluminescence properties as well as anticancer activities. Che's group developed various types of C–N–N cycloplatinated complexes, focusing on anticancer activity [81]. The *N*-heterocyclic carbene platinum complex **16** (Fig. 6) is strongly emissive and stable under physiological conditions, with *in vitro* cytotoxic activity higher than cisplatin; it inhibited tumor growth in the nude mice model. Its cellular localization could be traced using emission microscopy. In contrast to common platinum-based antitumor agents, **16** did not accumulate in the vicinity of DNA but preferentially accumulated in cytoplasmic structures including sites where active survivin, an inhibitor of apoptosis, is located. More detailed experiments on this complex revealed that it significantly inhibited the expression of survivin, activated poly(ADP-ribose) polymerase (PARP) and induced apoptosis in cancer cells. *In vivo* results showed that injection of **16** at 3 mg kg^{-1} significantly inhibited NCI-H460 tumor growth, did not cause death of mice, and induced no significant weight loss compared to a vehicle control group [21]. Dinuclear cycloplatinated complexes **17** were more potent than cisplatin in human cervix epithelioid carcinoma (HeLa), human hepatocarcinoma (HepG2), and human nasopharyngeal carcinoma (CNE1) cell lines and in a normal human lung fibroblast cell line (CCD-19Lu). The planar configuration of complexes such as **17** facilitates their intercalation with DNA, involving a π–π stacking [81]. The same group reported that some C–N–N cycloplatinated complexes bearing acetylide ligands containing nucleobase motifs (adenine, thymine and 2-amino-6-chloropurine) (e.g. **18**, Fig. 6) play a critical role in inhibition of human TopoII [73]. All the complexes were cytotoxic against HeLa, HepG2, and CNE1 cell lines and less toxic against normal CCD-19Lu cells. Further studies revealed that these complexes intercalate into DNA and stabilize the TopoII–DNA cleavage complex, which is the major reason for their anticancer activity.

A limited number of transcription factors are overactive in most human cancer cells, which makes them targets for the development of anticancer drugs. A major approach for directly targeting transcription factors is to block the transcription factor–DNA interaction using DNA-binding agents. Metallointercalators interfere with the transcription factor–DNA interaction [82,83]. Che's group developed complex **19** as a DNA major groove binder [84]. It selectively blocks cAMP response element binding protein (CREB)–DNA binding in both cell-free and cellular assays. The selectivity is due to the higher affinity of **19** for CREB, while the substituents play the main role in governing the DNA binding mode and selectivity of the complexes against transcription factors. It was further reported that compounds similar to **19** can inhibit TNF-α-induced NF-κB-dependent gene transcription at micromolar concentrations [85]. Since NF-κB-dependent activation of prosurvival gene transcription blocks apoptosis, suppression of TNF-α-stimulated NF-κB-dependent transcription by **19** would further reinforce the efficacy of planar lipophilic cationic C–N–N cycloplatinated complexes as potent anti-cancer agents.

The López–Biot group reported that pyrazolyl C–N–N complex **20** exhibits higher cytotoxicity than cisplatin against lung (A549) and breast (MDA-MB-231 and MCF-7) cancer cell lines, but does not show any effect on plasmid DNA mobility, suggesting a different mechanism of action [86]. Crespo–Quirante group recently reported that a series of seven-membered cyclometallated Pt(II) complexes (e.g. **21**, Fig. 6**)** exhibits remarkable antiproliferative activity greater than that of cisplatin in three human cancer cell lines (A549, HCT116 and MDA-MB-231) [87]. Induction of S–G2/M cell cycle arrest and apoptosis was also

observed for **21**. The influence of lipophilicity (log *P*) was also investigated, as log *P* is an important lipophilic parameter associated with prediction of drug-like physical properties in ADME models.

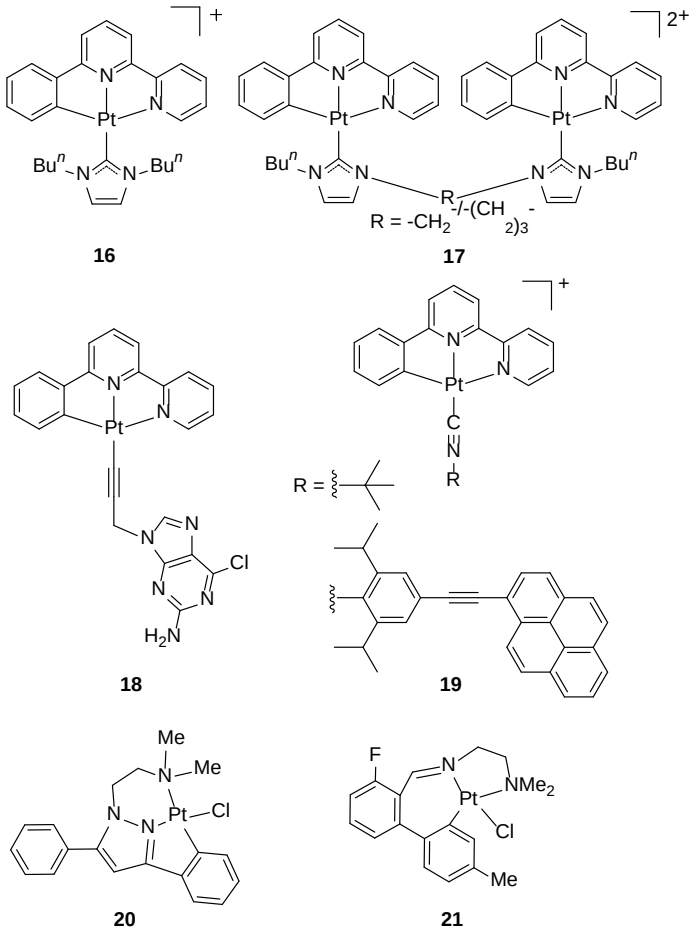
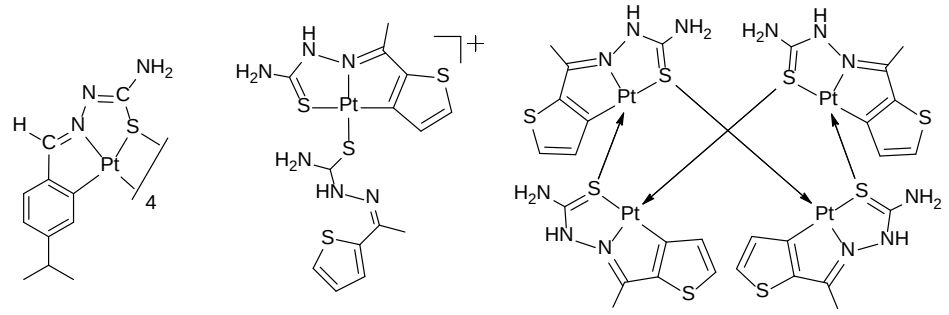


Fig. 6. Recently developed C–N–N cycloplatinated antitumor compounds.

2.3. C–N–S complexes

Platinum complexes with a C–N–S tridentate ligand are among the first classes of cycloplatinated complexes explored for cytotoxic activity [88]. Navarro-Ranninger and co-workers investigated cycloplatinated complexes with various thiosemicarbazone ligands. Cycloplatinated complexes of *p*-isopropylbenzaldehyde thiosemicarbazone of type **22** (Fig. 7) exhibit important cytotoxic activity against HL-60 human leukemic cells, with IC_{50} values in the micromolar range [89]. Further investigations revealed that these complexes form DNA interhelical cross-links and have a good *in vitro* therapeutic index when comparing cytotoxicity in Pam-ras cells and normal murine keratinocytes (Pam 212 cells) [90]. It was subsequently discovered that *N*-substituted derivatives of **22** have important cytotoxic properties since they circumvent cisplatin resistance in tumor cells transformed by ras oncogenes (Pam 212-ras) and kill these cells by apoptosis [91,92]. Veith and co-workers reported that complex **23** is more cytotoxic than the corresponding free ligands against two different human tumor cell lines, HT-29 (colon adenocarcinoma) and HuTu-80 (duodenum adenocarcinoma), and was more effective in comparison to cisplatin [93]. The same group investigated the effect of the metal/ligand ratio on antiproliferative activity for cycloplatinated 2-acetylthiophene thiosemicarbazone derivatives and found that tetranuclear complexes with the general formula $Pt_4(L)_4$ **24** were more active than the corresponding mononuclear complex **23** against HT-29 and HuTu-80 cell lines [93]. The high cytotoxicity of **24** was related to intercalation of the metal complex

between nitrogen bases of the DNA in tumor cells, causing greater conformational changes in the double helix of DNA and then producing cell death.



22 **23** **24**

Fig. 7. Representative C–N–S cycloplatinated complexes.

3. Palladium(II)

Palladium derivatives have been explored as an alternative to platinum-based compounds owing to the obvious structural and thermodynamic analogy between platinum(II) and palladium(II) complexes [94–96]. However, the ligand-exchange kinetics of platinum(II) and palladium(II) derivatives are quite different: hydrolysis of palladium(II) compounds is much more rapid (10^5 times faster), leading to reactive species that cannot reach their pharmacological targets. The first palladium complexes had little or no application as antitumor compounds owing to their poor stability and fast hydrolysis in biological environments. Cyclopalladated complexes are less toxic, making them promising new antitumor compounds [97]. Complex **25** (Fig. 8) induced apoptotic cell death in human leukemia cells (HL-60 and Jurkat) by rupture of lysosomal membranes and release of cathepsin B into the cytoplasm (cathepsin B is an enzyme that is overexpressed in many cancer cell lines) [98,99]. The dimeric complex **26** showed promising antitumor properties against murine and cisplatin-resistant human tumor cells both *in vitro* and *in vivo* [97,100]. For this reason it was selected for further preclinical studies, including a gene therapy protocol in conjunction with plasmids [101]. Dimeric palladacycles **27**, **28** and **29** are also potent cathepsin B inhibitors [102–104]. Orthometalated complexes with thiosemicarbazones have a higher capacity than cisplatin to form DNA interstrand cross-links. Analogous to platinated derivatives, *p*-isopropylbenzaldehyde thiosemicarbazone cyclopalladated complexes such as **30** exhibit important cytotoxic activity against HL-60, with IC_{50} values in the micromolar range [88]. The iminophosphorane complexes **31** and **32**, which are stable in DMSO and DMSO–H_2O solutions under biological testing conditions, are cytotoxic against Jurkat-T leukemia and cisplatin-resistant Jurkat-shBak cells (Bax/Bak-deficient Jurkat cells) but less toxic to normal T-lymphocytes (PBMC) [95]. Interaction of **31** and **32** with plasmid pB*R*322 is much weaker than the cisplatin interaction, pointing to an alternative biomolecular target for these cytotoxic compounds.

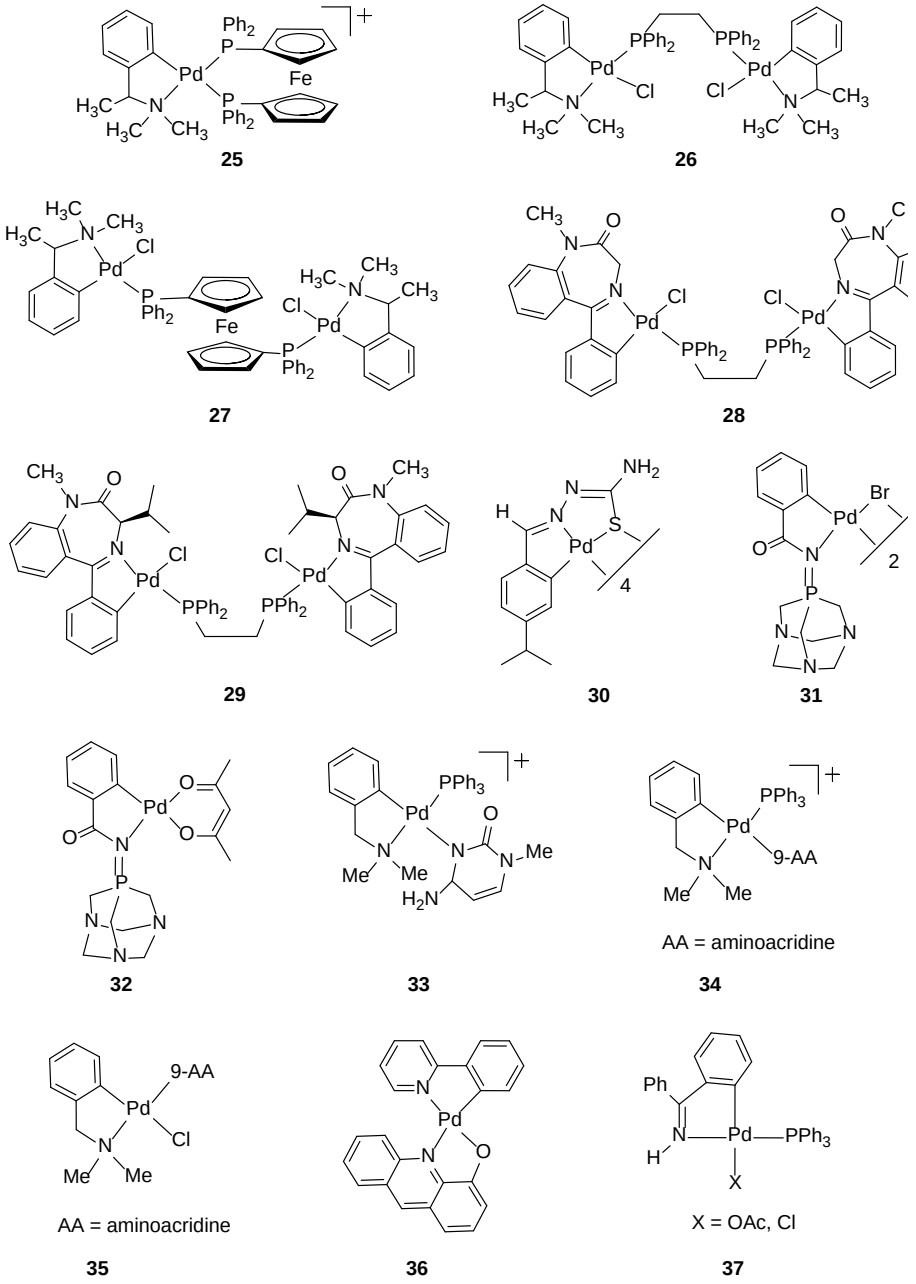


Fig. 8. Representative C–N palladium(II) complexes.

Palladacycles **33–35** developed by Ruiz and co-workers were highly active towards HL-60 tumor cells after 24-h incubation and were more active than cisplatin (up to 30-fold in the case of **34**). These complexes interact strongly with DNA and induced apoptosis [47,57]. Complex **36** showed higher cytotoxic activity than cisplatin against human ovarian cancer cells lines (A2780, OVCAR 5 and OVCAR 8) that are sensitive or resistant to cisplatin [105]. More recently, Albert et al. prepared compounds **37**, which are more potent than cisplatin in MDA-MB231 and MCF-7 cell lines. Electrophoresis studies demonstrated that these complexes modify DNA helicity, although to a lesser extent than cisplatin. In addition, DNA–ethidium bromide fluorescence quenching and viscometry experiments have excluded an intercalating DNA-binding mode for these compounds [106].

4. Gold(III)

Although Au(III) and Pt(II) are isoelectronic and isostructural, the use of Au(III) complexes as antitumor agents has not been similar to platinum compounds because Au(III) complexes are generally strong oxidizing agents and potentially toxic in biological systems, where reduction can easily be driven by thiols [14]. However, the anticancer properties of the anti-arthritic Au(I) phosphine drug auranofin on HeLa cells *in vitro*, as reported by Lorber et al. [107], triggered extensive interest in the search for novel gold compounds as potential anticancer drugs [108,109]. It has been proposed that the mechanisms of action of these compounds are DNA-independent, but implicate interactions with a variety of target proteins inside cells [12,110,111]. With the aim of stabilizing the trivalent oxidation state, several research groups have synthesized a number of C–N cyclometalated compounds, as well as N–C–N and C–N–N pincer derivatives of gold(III).

4.1 C–N complexes

Parish and co-workers described antitumor activity for the mononuclear gold(III) complex **38** in 1996 (Fig. 9) [112,113]. This compound displayed similar cytotoxicity to that of cisplatin against several human tumor cell lines. When the two chloride ligands were replaced by acetate or malonate anions, the resulting complexes also exhibited good selective cytotoxicity *in vitro* against a panel of human tumoral cell lines and displayed moderate *in vivo* antitumor activity in human tumor xenograft models [113]. However, their mechanism of action is different from that of cisplatin [37]. The role of hydrolysis as an activation step for this class of compounds is not yet clear. Compound **38** and the acetato and malonato analogs inhibit cathepsin B, with IC_{50} values of 0.6–1.36 μM [114–116], and are very potent inhibitors of TrxR [117]. Importantly, high levels of Trx have been clinically associated with aggressive tumor growth and therefore with lower patient survival, making the Trx–TrxR redox system an attractive target for anticancer therapies [118].

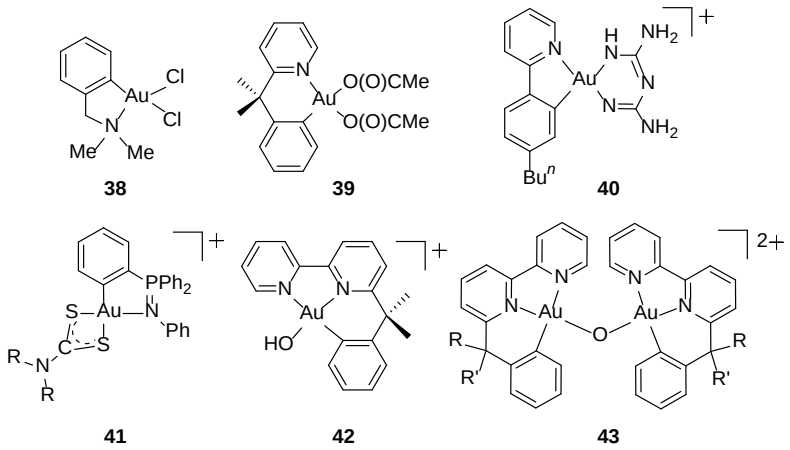


Fig. 9. Representative C–N and C–N–N pincer cycloaurated complexes.

Results for complex **39** against the A2780 cell line were very promising, with a similar profile to that of cisplatin, although with significant cross-resistance. However, **39** promotes apoptosis to a greater extent than cisplatin and oxaliplatin [119]. Studies of **39** solutions under physiological-like conditions showed that the hydrolytic specie is stable for several hours. Moreover, evaluation of **39** as an inhibitor of mitochondrial TrxR suggested that the complex is highly selective for this enzyme [120–122]. The same group studied enzyme inhibition by this type of gold(III) complex by mass spectrometry (MALDI-TOF MS) combined with biochemical assays. They found that inhibition only occurs after pre-reduction of the enzyme with NADPH, indicating that TrxR inhibition is the result of protein structure modifications occurring on cofactor binding. Furthermore, on the basis of biotin-conjugated iodoacetamide assays, it has been suggested that there is progressive oxidative damage of cysteine and selenocysteine residues [122]. Che

and co-workers recently reported the synthesis of **40**, which combines a lipophilic ligand with another one that has polar H-bonding groups to improve the aqueous solubility [123]. This complex displays high toxicity against HeLa cells and low toxicity towards CCD-19Lu normal cells. The authors found that **40** caused S-phase cell cycle arrest and had an anti-angiogenic effect at sub-cytotoxic concentrations. The biological activities of some iminophosphorane complexes (e.g. **41**, Fig. 9) have recently been reported [124–127]. An advantage is that the P atom in the PR_3 fragment can be used as a spectroscopic marker to study the *in vitro* stability (and oxidation state) by $^{31}P\{^{1}H\}$ NMR [125]. Compound **41** was highly active against HeLa and Jurkat-T cell lines, and exhibited low toxicity against normal T-lymphocytes. Mechanism-of-action studies suggest that reactive oxygen species (ROS) production at the mitochondrial level is a critical step in the cytotoxic effect of these compounds [124].

4.2. C–N–N pincer derivatives

Messori and co-workers reported that complex **42** (Fig. 9) is cytotoxic and stable under pseudo-physiological conditions. Studies on BSA showed that a metal–protein adduct was formed, suggesting that it occurred through coordination at the level of surface histidines [128]. Compound **42** formed small amounts of metal–protein adducts with cytochrome *c* and lysozyme in which the gold(III) centre and the C–N–N tridentate ligand were conserved [129]. Furthermore, the interaction of **42** with calf thymus DNA was weak and reversible [130]. It was recently observed that **42** forms stable adducts with the copper chaperone Atox-1 [131]. Similar compounds in which the OH is substituted by bulkier ligands, such as 2,6-xylidine-H and *p*-toluidine-H, have also been described. For these analogs, hydrolysis may represent an activation step [119]. These compounds did not induce significant changes in the cell cycle phases but induced apoptosis [120]. The authors studied the inhibitory effects on TrxR and suggested that mitochondrial pathways were directly involved in the apoptotic process and the cytotoxicity [13,121,132]. Compound **42** showed good activity and a high degree of selectivity against a panel of 13 human tumor cell lines. Inhibition of mTOR, the proteasome, and/or DNA synthesis has been suggested as possible mechanism of action [133].

The dinuclear Au(III) complexes **43** are stable in the presence of reducing agents such as ascorbic acid or glutathione, but partial rupture of the oxo-bridge in phosphate buffer gives the corresponding mononuclear hydroxo complexes. Studies against a representative panel of 12 human tumor cell lines showed rather moderate cytotoxicity towards the majority of them, although the complexes were particularly active against the human breast cancer 401NL cell line. The reactions of **43** with hen egg white lysozyme and horse cytochrome *c*, used as model proteins, were followed through ESI-MS, and the results indicated that both form monomeric adducts of gold(III), although the reaction with cytochrome *c* proceeds to a lesser extent [134].

4.3. C–N–C pincer derivatives

Che and co-workers have described a series of mononuclear cyclometalated gold(III) complexes (e.g. **44**, Fig. 10) based on the tridentate ligand 2,6-diphenylpyridine [135]; these are stable under physiological conditions and in aqueous solutions containing 2 mM GSH for at least 24 h. The cytotoxicity of **44** and analogs is similar to that of cisplatin but they do not exhibit cross-resistance with cisplatin against nasopharyngeal carcinoma, and the resistance factors were less than 1. Flow cytometry assays indicated that **44** causes cell death by apoptosis and cell-cycle analysis revealed S-phase cell arrest. Furthermore, studies with calf-thymus DNA showed that **44** binds strongly by intercalation and enhances G-quadruplex assembly, suggesting that it could act as an inhibitor of telomerase [136]. Studies of human DNA topoisomerase inhibition indicated that **44** inhibits the topoisomerase I cleavage reaction since it prevents binding of the DNA substrate [137].

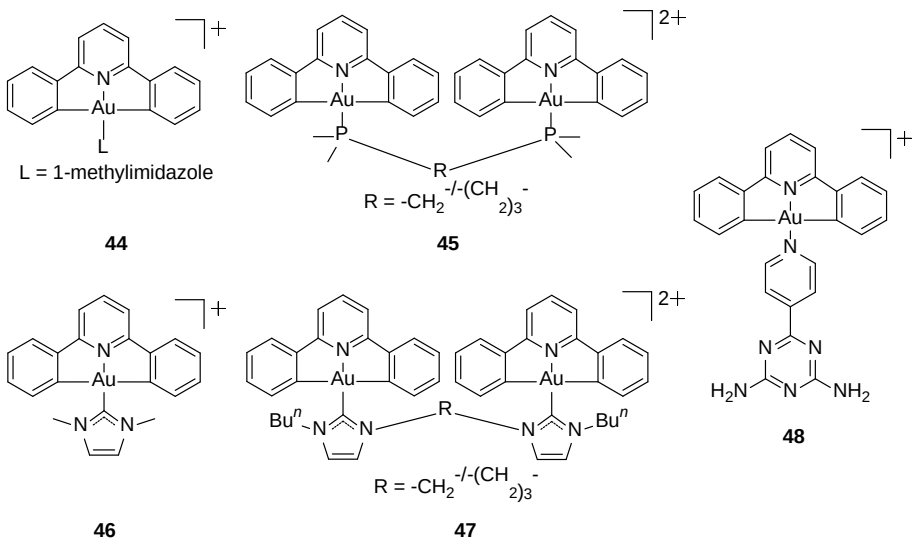


Fig. 10. Representative C–N–C pincer cycloaurated complexes.

The dinuclear complexes **45** (Fig. 10) are much more active than their mononuclear counterparts. The 1,2-bis(diphenylphosphino)propane (dppp) derivative has an IC_{50} value ~250 times lower than that of cisplatin towards HeLa cells and reacted only weakly with ctDNA. This complex did not induce cell-cycle arrest [136]. *In vivo* studies in rats bearing HCC orthografts indicated that the dppp derivative effectively prolongs survival, since it is a nanomolar inhibitor of TrxR [109,138]. *N*-Heterocyclic carbene analogs **46** and **47** have been reported, of which **46** is the most active. *In vitro* cytotoxicity studies showed that **46** was 167-fold more cytotoxic to non-small lung carcinoma cells (NCI-H460) than to normal lung fibroblast cells (CCD-19Lu). *In vivo* treatment of nude mice bearing PLC (hepatocellular carcinoma) cells inhibited tumor growth without causing apparent toxic effects in the test period. It has been found that **46** binds to DNA by intercalation and has potent poisoning activity against topoisomerase I [139]. Che and co-workers recently developed complex **48** containing the anti-angiogenic ligand 2,4-diamino-6-(4-pyridyl)-1,3,5-triazine (4-dpt) (Fig. 10) [140]. Compound **48** induced 80% cell death within 24 h in human B16 melanoma cells and exhibited cytotoxicity through an apoptotic pathway. Solution studies under relevant biological conditions indicated degradation of the species by release of the 4-dpt ligand and formation of adducts with GSH. Compound **48** formed a supramolecular polymer when dissolved in CH_3CN to a concentration of 20 mM at 323 K and then cooled to 298 K. The polymer was cytotoxic towards B16 cancer cells, and to a lesser extent towards CCD-19Lu normal cells, after a prolonged time. The authors proposed that sustainable release of the free 4-dpt ligand and the formation of adducts with GSH may explain the sustained cytotoxicity. The same group also suggested the possibility of directly implanting the polymer in a solid tumor to obtain localized and sustained release of the drug, which would increase its efficiency and safety [140].

5. Ruthenium(II)

Ruthenium-based drugs have recently attracted a great deal of attention. Scientists working in bioinorganic medicinal chemistry often make a point of comparing them favorably to cisplatin for the following reasons: (i) their analogous ligand exchange abilities; (ii) several accessible oxidation states in biological fluids [Ru(II), Ru(III) and perhaps Ru(IV)]; (iii) binding to biologically relevant proteins; (iv) lack of cross-resistance with cisplatin; and (v) lower toxicity against healthy tissues, probably explained by transport into tumor cells by transferrin (which is often overexpressed in many tumor cells), given the presumed higher iron requirement of these rapidly dividing cells [141].

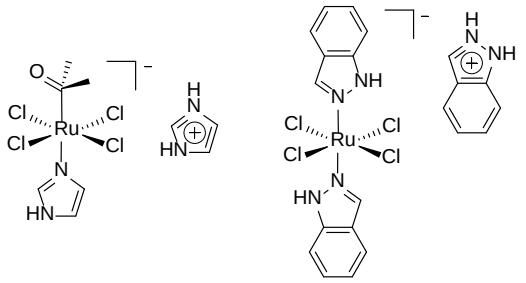


Fig. 11. Chemical structure of NAMI-A and KP1019.

Compared to many organic compounds, ruthenium-based drugs offer the advantage of relatively low costs for their synthesis and purification. Certain ruthenium complexes possess a strong ability to inhibit metastases of solid invasive cancers [142,143]. Two anionic Ru(III) coordination compounds, NAMI-A [144] and KP1019 (Fig. 11) [145–147], have successfully completed phase I clinical trials and entered phase II [22].

Ru(II)–arene complexes with promise for clinical trials have been synthesized. Sadler and co-workers prepared complexes of the formula [(η^6-arene)RuCl(en)]PF_6 (en = ethylenediamine) (Fig. 12) that are cytotoxic towards cancer cells, including cisplatin-resistant cell lines [18,148]. The RAPTA family complexes prepared by Dyson et al. contain the hydrophilic and monodentate PTA phosphine ligand and show selectivity towards metastatic cancers (Fig. 12) [19,149,150]. At first glance, the structural similarity of the half-sandwich "piano-stool"-type organometallics in Fig. 12 might suggest an analogous mechanism of cytotoxic action. However the mechanisms appear to be very different [18,19,22] and are still a matter of debate [150].

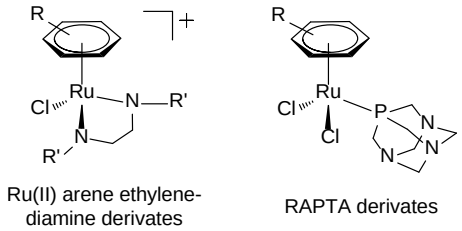
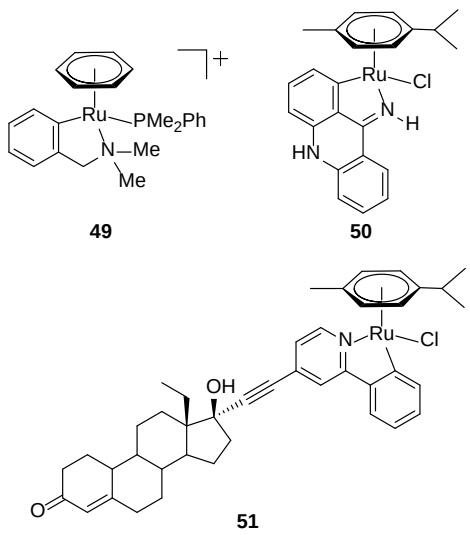


Fig. 12. Representative (η^6-arene) ruthenium anticancer complexes.

5.1. Arene C–N complexes

The phosphine arene C–N cycloruthenated complex **49** (Fig. 13) is cytotoxic in glioblastoma (A172 and HS683), neuroblastoma (N2A and SH5Y) and lymphoblastoma (RDM4 and TK6) cell lines [151], and can induce both cell arrest in G1 phase and apoptosis. Moreover, the novel ruthenium(II) arene-based intercalator **50** derived from 9-aminoacridine exhibits good activity towards a variety of cell lines (T47D, MCF-7, A2780 and A2780*cis*R) [152]. The influence of **50** on the tertiary structure of DNA was determined according to its ability to modify the electrophoretic mobility of the covalently closed circular (ccc) and open (oc) forms of pB*R*322 plasmid DNA. Ruiz and co-workers reported the synthesis of a highly potent ruthenium(II) anticancer conjugate bearing the lipophilic steroid group 17-α-[2-phenylpyridyl-4-ethynyl]-19-nortestosterone **51**, which was more efficient than its nonsteroidal analog [Ru(η^6-*p*-cymene)(ppy)Cl], which is not active in the same cell lines [153]. Especially noteworthy is the very low resistance factor of **51** at 48 h (RF = 0.8) against the A2780*cis*R cell line, indicating efficient circumvention of cisplatin resistance. Reactions of complex **51** with 9-ethylguanine, as followed by ESI-MS, gave the monoadduct [Ru(η^6-*p*-cymene)(LEVppy)(9-EtG)]$^+$.



49 **50** **51**

Fig. 13. Representative C–N cycloruthenated anticancer complexes.

5.2. Non-arene C–N complexes

5.2.1. The RDC family

A large and original library of ruthenium-derived compounds (RDCs) was recently synthesized by the Pfeffer–Gaiddon group [154,155]. This includes C–N cyclometalated compounds, as well as N–C–N and N–N–C pincer tridentate monoanionic derivatives of ruthenium (Fig. 14). Several of them pass the symbolic barrier of the nanomolar IC_{50} range [151]. The group first checked whether their solutions (in neat DMSO diluted with the required amount of cell culture medium) were stable for at least 2 days. They found that the level of activity shows tentative correlation to physicochemical properties of the compounds such as their Ru(III/II) redox potential and their lipophilicity (log *P*) that will allow entry into cells. The acetonitrile compound **52** (RDC11, Fig. 14) inhibited the growth of various cancers implanted in mice more efficiently than cisplatin [156]. Importantly, in striking contrast to cisplatin, **52** did not cause severe side effects on the liver, kidneys, the neuronal sensory system or blood cells. Therefore, **52** represents a suitable ruthenium-based candidate for clinical trials that would first target cisplatin-resistant cancers, such as cisplatin-resistant ovarian cancers [27,154,156]. The interactions between **52** and DNA were studied using different techniques, which revealed that this molecule intercalates dsDNA [157], although the modes of action of these RDC compounds could also involve DNA-independent mechanisms. In this context, the redox potential of the compounds was crucial for deregulation of several cellular redox enzymes (glucose oxidase and PHD2, among others) and activation of the endoplasmic reticulum stress pathway (through transcription factors such as CHOP and DDIT3) that leads to cancer cell apoptosis in the absence of p53 [156–158]. The authors have now optimized these molecules by improving their cytotoxicity and water solubility, and demonstrated that by changing the ligands around the ruthenium, the ability of the compounds to interact with DNA can be modified. Furthermore, depending on their structures, these compounds can target several pro-apoptotic signaling pathways leading to ROS production and caspase 8 activation [158]. Addition of a second phenanthroline ligand significantly increased the cytotoxicity of the new compound **53** (Fig. 14) in comparison to **52**, with an IC_{50} often in the nanomolar range, confirming the important role of the phenanthroline residue in the cytotoxic properties of RDCs. Compound **53** is also more toxic than **52** when given to mice [27]. The increased toxicity of **53** could be related to its high lipophilicity [154], a property that might favor cellular uptake and distribution in the body after dosing. Addition of the spermine chain to **54** improves the water solubility of **53**, as indicated by its log *P* value [158].

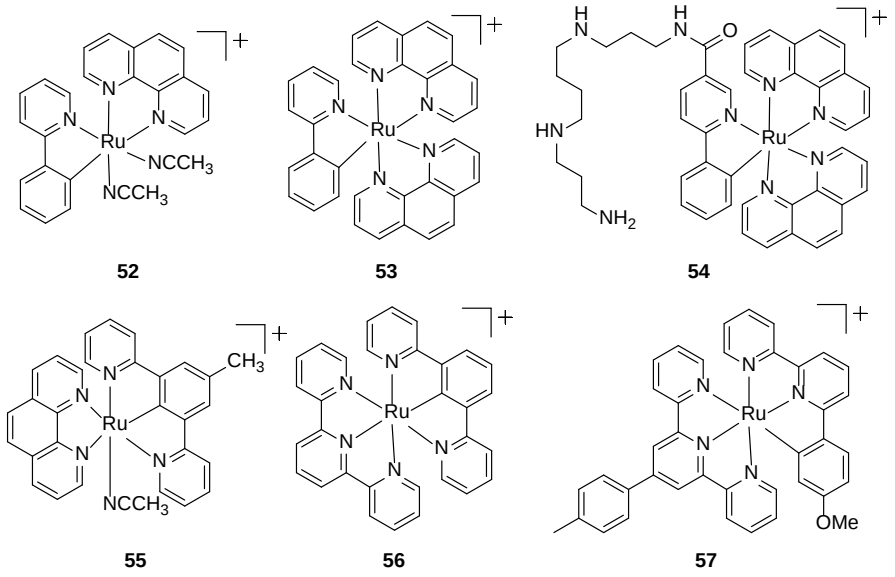


Fig. 14. Representative RDC anticancer compounds.

IC_{50} values for **55–57** in HCT116 cancer cells are analogous (within one order of magnitude) to those for other C–N derivatives (**52**–**54**). The group thus concluded that the coordination sphere of the compounds, which is of the Ru(NNNN,NC) type, is likely to be responsible for their activity rather than substitution of the C–N ligand.

5.2.2. C–N kinase inhibitors

Meggers et al. recently prepared a library of *C,N*-cycloruthenated protein kinase inhibitors (**58**–**60**, Fig. 15) [159–161]. They are characterized by the strong similarity with staurosporine. The racemic complex **58** displays an IC_{50} value of 83±20 nm (1 μm ATP) against p21-activated kinase 1 (PAK1). Interestingly, the pyridylphthalimide ligand itself is not an inhibitor of PAK1 (IC_{50}>100 μm), and thus the entire coordination sphere is important for protein kinase binding. The key feature is a 3-(2-pyridyl)-1,8-naphthalimide pharmacophore chelate ligand, which is designed to form two hydrogen bonds with the hinge region of the ATP-binding site. This emphasizes the broad range of possibilities for fitting octahedral metal complexes in the active site of an enzyme. To date, the ruthenium phthalimide complex **58** (Fig. 15) is among the most potent ATP-competitive inhibitors known for PAK1, demonstrating the advantages of filling large or open pockets with globular octahedral metal complexes. It is worth noting that the facile C–H activation and robustness of the metal–carbon bond formed can be attributed to the highly electron-deficient nature of the phthalimide moiety, which is functionalized with electron-withdrawing pyridyl and maleimide substituents.

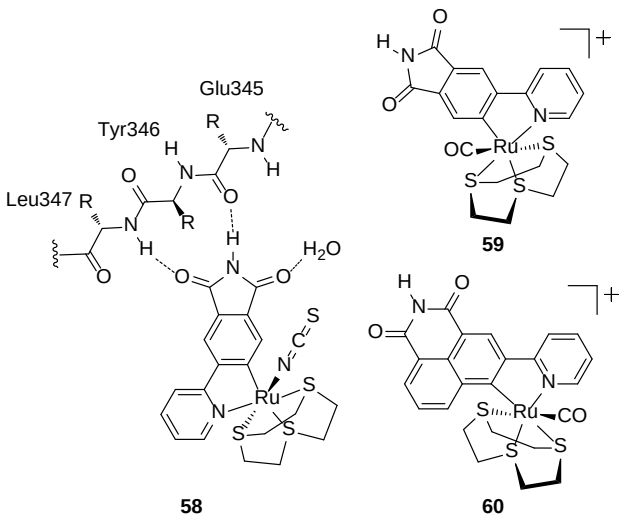


Fig. 15. Representative ruthenium-templated inhibitors of the protein kinase PAK1.

6. Rhodium(III) and iridium(III)

In contrast to their Ru(II) congeners, the isoelectronic Rh(III) and particularly Ir(III) complexes were generally considered as being unlikely candidates for anticancer agents until recently owing to the typical kinetic inertness of their metal centers [17,162,163]. However, there has been recent interest in luminescent iridium(III) polypyridine complexes as chemical and biological probes [164–166].

6.1. Cyclopentadienyl C–N complexes

Sadler et al. recently showed that replacement of the *N*,*N*-chelating ligand 2,2′-bipyridine (bpy) in the complex $[(\eta^5\text{-}C_5Me_5)Ir(bpy)Cl]^+$ with the *C*,*N*-chelating ligand ppy to give complex **61** (Fig. 16) switches on cytotoxicity towards A2780 cells (IC_{50} 10.8 μM after 24 h) [167]. The same group investigated the effects of changing the negatively charged *C*,*N*-chelating ligand and the nature of the cyclopentadienyl ligand (complexes **62** and **63**) on the hydrolysis of the chlorido complexes, acidity of the aqua adducts, nucleobase binding, and cancer cell cytotoxicity [168]. They found that introduction of a phenyl or biphenyl substituent significantly improved the cytotoxicity, especially for complex **63**.

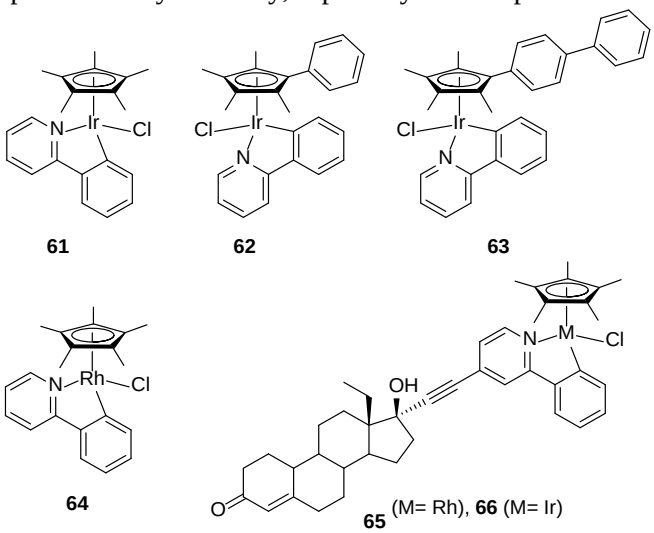


Fig. 16. Representative anticancer cyclopentadienyl metal(III) complexes.

Ruiz and co-workers reported on the anticancer activity of the related pentamethylcyclopentadienyl complexes **64–66** (Fig. 16) [169]. The steroidal conjugates **65** and **66** are isostructural and isoelectronic to the ruthenium complex **51** (Fig. 13); compound **66** is twice as active as the non-steroidal complex **61** [167]. Theoretical DFT calculations for complexes **65** and **66** showed that the lipophilic steroidal moiety is located far away from the metal centre and the strongest bond to the metal atom is the η^5-interaction to the pentamethylcyclopentadienyl ligand. Furthermore, both of them have a rather strong metal–chlorine bond that is significantly stronger than that displayed by the analogue complex **51**. Steroidal conjugates **65** and **66** can bind to DNA according to Hoechst 33258 displacement experiments and ESI-TOF MS spectrometry studies. They are also cathepsin B inhibitors.

6.2. Non-cyclopentadienyl C–N complexes

To design new biological probes for BSA, Lo and co-workers prepared the luminescent Ir(III) complex **67** (Fig. 17) containing an indole derivative, which was highly cytotoxic towards HeLa cells [170]. Iridium(III) complexes containing an alkyl chain such as **68** are also cytotoxic towards HeLa cells [171]. The same group appended different sugars (galactose, glucose, lactose and maltose) to various Ir(III) complexes to give a series of sugar-containing Ir bioconjugates **69** [172]. The glucose-containing Ir conjugates showed better cellular uptake than their non-glucose analogs, which are extremely cytotoxic. It is possible that glucose transporters present on the cell membrane can specifically transport the glucose bioconjugates. Lo and co-workers recently reported the synthesis of some cyclometalated iridium(III)–polyamine complexes using branched poly(ethyleneimine) (bPEI) as ligands (**70** and **71**; Fig. 17) [173]. Cyclometalating ligands and polyamines both play a role in the photophysical properties, lipophilicity, cellular uptake, and cytotoxicity of the complexes towards HeLa and HEK293T (human embryonic kidney 293T) cell lines. On internalization, complexes of types **70** and **71** were localized in the lysosomal compartment. The high cytotoxicity of the branched complexes **70–72** is most likely associated with disruption of the cytomembrane and mitochondrial membranes of the cells, which is common to bPEI and its derivatives. Complex **72** was conjugated to various proteins and polymers. The conjugate with the amine-containing polymer poly(ethyleneimine) (PEI) was very highly cytotoxic (IC_{50} = 0.11 μM) [174].

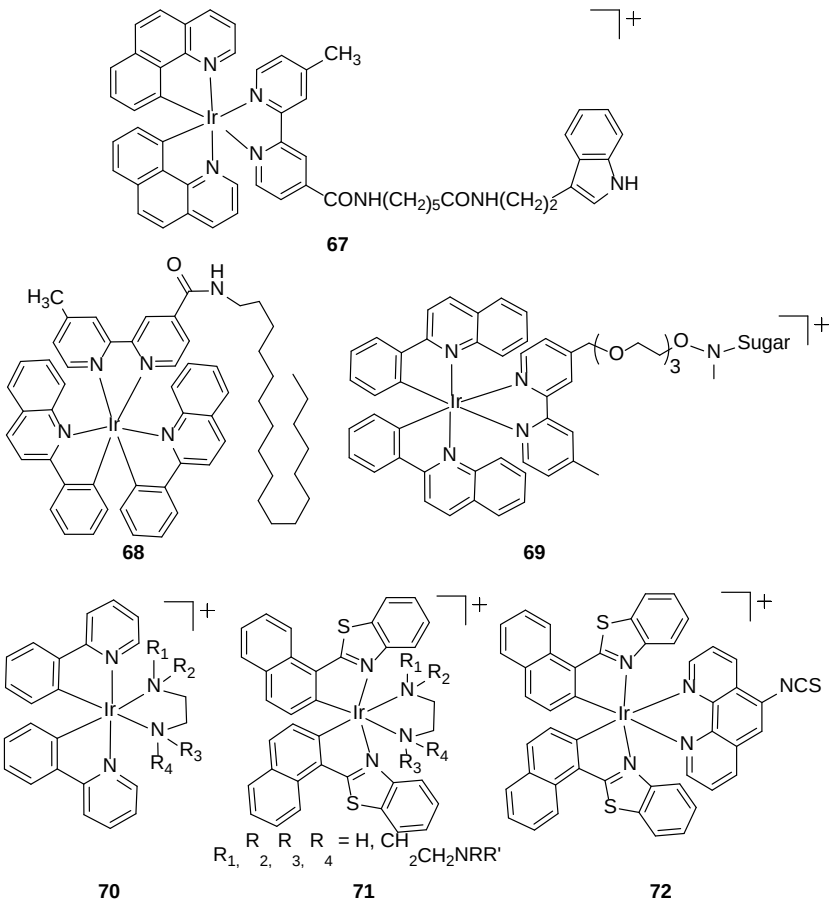


Fig. 17. Representative anticancer iridium(III) complexes.

Velders and co-workers recently reported the preparation of a series of luminescent amino acid-functionalized Ir(III) neutral complexes (**73**, Fig. 18) [175]. Only the lysine complexes showed reduced cell viability towards a murine breast cancer cell line (4T1). The same group reported the synthesis of Ir(III) complexes **74**, which are functionalized with three Ac-TZ14011 peptide moieties that bind to the chemokine receptor 4 (CXCR4) [176].

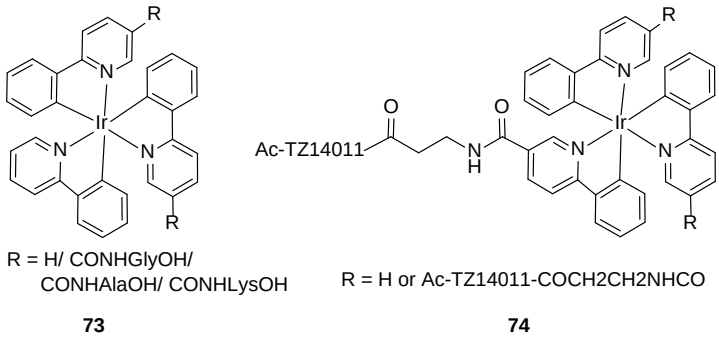
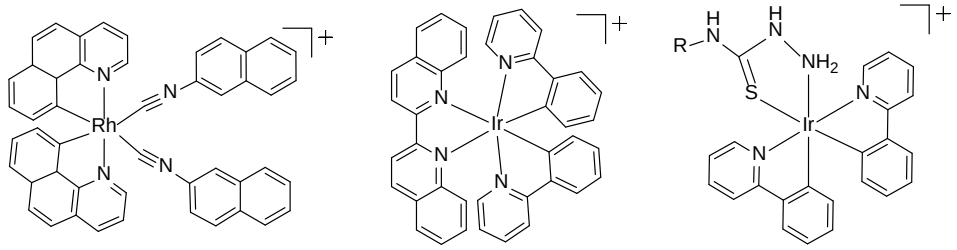


Fig. 18. Representative amino acid- and peptide-functionalized iridium(III) complexes.

Leung et al. recently synthesized some cyclometalated rhodium(III) complexes (e.g. **75**, Fig. 19) [177]. These derivatives inhibited Janus kinase 2 (JAK2) enzyme phosphorylation activity, reduced JAK2 autophosphorylation *in cellulo* and exhibited cytotoxicity towards human erythroleukemia (HEL) cancer cells. The same group synthesized the iridium(III) biquinoline complex **76**, which targets the protein–

protein interface of TNF-α [178]. Ruiz and co-workers recently described a series of organoiridium(III) complexes containing a thiosemicarbazide ligand bound to the iridium atom as an *N*,*S*-chelate **77**. Cytotoxicity studies showed that they are more active than cisplatin (~5-fold) in T47D. They bind strongly to HSA and inhibit cathepsin B. Furthermore, as shown by Hoechst 33258 displacement experiments, these complexes are able to bind to DNA in the minor groove. No reaction with 9-EtG was observed by ^{1}H NMR in the conditions assayed [179].



75 **76** **77**

Fig. 19. Representative metal(III) inhibitors.

7. Summary

We summarized recent developments of cyclometalated anticancer compounds of platinum group metals and gold. Cyclometalated complexes show improved stability and enhanced cytotoxicity because of endowed organic scaffold, versatile stereochemistry, and the redox properties of the metal. The metal along with the C–N, C–N–N, C–N–C or C–N–S pincer ligands and co-ligands collectively play a role in determining the anticancer properties of the complex. Promising bioactivities have been observed for many complexes, although their mode of action is not completely clear at this stage. Besides DNA, protein/enzyme interactions represent a major mode of action, while some complexes exhibit completely novel modes of action. Moreover, cyclometalated compounds are suitable for rational drug design and thus could solve many of the challenges in turning a structural lead into a drug candidate with improved efficacy and tolerability. Many research groups believe that the advent of organometallic complexes in clinical trials will improve the acceptance of cyclometalated compounds in the pharmaceutical industry and support further research into anticancer metallodrugs. Until then, efforts to find new compounds with improved profiles will continue.

Abbreviations

4-dpt	2,4-diamino-6-(4-pyridyl)-1,3,5-triazine
9-EtG	9-ethylguanine
ATP	adenosine-5′-triphosphate
BSA	bovine serum albumin
cisplatin	*cis*-diamminedichloridoplatinum(II)
ctDNA	calf thymus DNA
dmba	2-(dimethylaminomethyl)phenyl
DMSO	dimethyl sulfoxide
dppp	1,2-bis(diphenylphosnino)propane
dsDNA	double-stranded DNA
ESI-MS	electrospray ionization mass spectrometry
ESI-TOF MS	electrospray ionization time-of-flight mass spectrometry
GSH	reduced gluthatione
HSA	human serum albumin
IC_{50}	half-maximal inhibiting concentration
JAK2	Janus kinase 2

MALDI-TOF MS	matrix-assisted laser desorption/ionization time-of-flightmass spectrometry
mTOR	mammalian target of rapamycin
NAMI-A	imidazolium *trans*-[tetrachlorido(1*H*-imidazole)(*S*-dimethylsulfoxide)ruthenate(III)]
NF-κB	nuclear factor κB
PAK1	p21-activated kinase
pB*R*322	plasmid DNA
ppy	2-phenylpyridine
PTA	1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane or 1,3,5-triaza-7-phosphaadamantane
RDC	ruthenium-derived compound
TNF-α	tumor necrosis factor-α
TopoIIα	DNA topoisomerase IIα
Trx	thioredoxin
TrxR	thioredoxin reductase

Acknowledgements

This work was supported by the Spanish Ministerio de Economía y Competitividad and FEDER (Project SAF2011-26611), by Fundación Seneca-CARM (Project 08666/PI/08) and was in part funded by the European Union Seventh Framework Programme – Marie Curie COFUND (FP7/2007-2013) under UMU Incoming Mobility Programme ACTion (U-IMPACT) Grant Agreement 267143.

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