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Digest

Anticancer platinum(II) complexes bearing *N*-heterocycle rings

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ABSTRACT

Starting from the pioneering discovery of picoplatin and phenanthriplatin, many efforts were realized by different research groups in the synthesis of different platinum(II) complexes, bearing a *N*-heterocycle moiety active as anticancer agents in different types of solid tumors. This review deals in particular with both the bifunctional and monofunctional platinum drugs, not only in dichloride platinum(II) complexes, but also in recent advances in modern platinum structures, i.e. cationic ones. Both the *in vitro* and *in vivo* studies of these anticancer agents are taken into account, with a special consideration for aggressive and orphan in treatment tumors.

Cancer is a leading cause of death worldwide, accounting for millions of cases every year. Among chemotherapeutics, platinum-based drugs are very potent agents for the successful treatment of many malignant tumors, since the pioneering Rosenberg's discovery[1] of cisplatin (*cis*-[$PtCl_2(NH_3)_2$]). Metal-based agents have the potential advantage over other small molecules to be fine-tuned in terms of reactivity and affinity properties in a distinct fashion upon modifying their coordination geometry, redox state and ligand exchange rate.[2]

As for all chemotherapeutics, unfortunately, cisplatin exhibits several drawbacks, including severe dose limiting side effects, along with intrinsic and acquired resistance that limits its use and negatively affects its cure rate (Fig. 1). Some of these safety issues have been partially solved with the introduction of carboplatin, a second-generation analogue of cisplatin, endowed with a similar cytotoxic activity, along with a milder side-effect profile.[3] The much more challenging goal to overcome cisplatin resistance, and to broaden its spectrum of activity, was finally achieved with the introduction of oxaliplatin, whose ability to overcome cisplatin resistance is likely due to the presence of the chelating diamine (1,2-Diaminocyclohexane, DACH) ligand and characterized by a distinct mechanism of action, compared to cisplatin and carboplatin.[4] The binding to the genomic DNA has been recognized as the principal way of cisplatin to exert anticancer activity; the resulting DNA damage, in fact was found responsible for aberrant transcription and/or replication processes, alterations, that by triggering a cascade of signaling modulators, have cell-death as the final event.[5,6] On the contrary, oxaliplatin forms 1,2-intrastand, and other cross-links on DNA, but it creates lesions on the DNA only in the absence of normal replication-bypass machinery, and results in significantly fewer double-strand breaks.[7,8] The significant differences regarding the mechanism of action among the platinum(II) complexes allowed to suggest that cisplatin and carboplatin could be defined as DNA-cross-linker compounds, while oxaliplatin results a transcription-translation-inhibitor-like compound. Oxaliplatin induced, in fact, a G1 cell-cycle arrest, causing a more rapid cell death than cisplatin. Its cytotoxicity resulted mediated by the ribosome-biogenesis-stress pathway and the expression of translation machinery plays a crucial role in the oxaliplatin sensitivity in specific cancer types, such as in breast cancer, in non-small-cell lung cancer and in colorectal cancer. This feature suggests the possibility to use oxaliplatin in a mechanism-targeted manner for the treatment of different cancers.[9]

However, a lack of selectivity towards the malignant cells, together with an unsolved resistance of the currently approved platinum drugs is still a challenge, thus evoking the need of novel platinum chemotherapeutics with a much higher tumor-targeting profile and with a higher resistance from the deactivation processes.

In the last decade, many platinum compounds containing different *N*-heterocyclic moieties have been synthetized and evaluated as anticancer agents on different cancer cell lines and the most promising ones were also tested *in vivo* with the aim of enlarging the spectrum of activity, overcoming the constraining issues related to cellular resistance and of lowering the toxicity of both first (cisplatin) and second (carboplatin) generation of platinum compounds.[10–13] A conventional way to classify these types of compounds relied on their capability to form mono- or bifunctional adducts in DNA binding. In this short review, some platinum(II)-based anticancer complexes with non-classical structures and containing one or more *N*-heterocycles as ligand are discussed.

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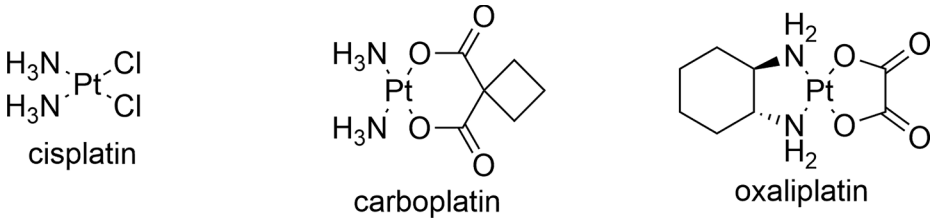


Fig. 1. Clinically approved anticancer platinum complexes.

Bifunctional platinum drugs

Starting from the consideration that DNA represents the well-known primary target for cisplatin, it has been established that it reacts with many other different cellular constituents in the cytoplasm such as cytoskeletal microfilaments, RNA and the extensive pool of thiol-containing proteins, due to the high reactivity of platinum metal center towards soft *S*-donor nucleophiles.[14,15] Among these, the tripeptide glutathione (GSH), normally present in the cellular environment at high concentrations (0.5–10 mM), is probably the second most representative target. The coordination to GSH along with the binding to metallothioneins has been often exclusively associated to resistance phenomena.[16–18] The substitution of the metal center with one or more steric hindered groups could prevent the deactivation of platinum complexes by thiol-containing biomolecules, even if a reduction in DNA binding capability might occur, thus affording an alternative biological mechanism of action which is important for overcoming tumor cell resistance. In view of this idea, many efforts were realized in designing new anticancer platinum drugs, in which, based on classical structure–activity relationships, the possible ligands employed nitrogen as donor atom in the metal coordination. Nitrogen, in fact, guarantees a thermodynamically stable coordinative bond with platinum, especially when included in a ring, assuring the steric hindrance required for by-passing the common resistance mechanism, such as the well-known role of Ctr-1 in interfering with cisplatin uptake.[19] The replacement in cisplatin of one or both ammonia with other non-leaving *N*-donor ligands, in fact, generally effected the pharmacological behavior of the drug. The lead compound of the series was out of doubt considered picoplatin in which only one ammonia of cisplatin was substituted with a picoline ligand. (Fig. 2) Picoline influences the kinetic of interaction of the picoplatin with thiols and purine bases (GSH and DNA), resulting less active if compared to cisplatin against sensitive tumor cell lines but more cytotoxic in cisplatin-resistant ovarian cancer and small cell lung cancer both *in vitro* and *in vivo*.[20–22] Picoplatin also had specific toxicological properties with dose-limiting myelosuppression and low nephrotoxicity.[23–25] The preservation of *cis*-geometry was considered a necessary feature for antitumor activity of square planar platinum drugs considering that pharmacological studies on *trans*-platinum compounds revealed a lack of anticancer activity due to their different interaction with DNA and to the fast deactivation by thiol biomolecules.[26] Derivatives of cisplatin and transplatin containing 1-methyl-7-azaindole (Fig. 2, compounds **I** and **II**), in substitution for one ammonia, resulted in an increased *in vitro* cytotoxicity against cisplatin resistant cancer cell lines as ovarian carcinoma and breast cancer, particularly for *trans* isomer.[27]

Their activity could be associated to an increased level of cellular DNA platination even if the difference in biological activity between the two compounds could be correlated to their DNA binding mode and to the differences in the expression of transcription factors, leading to cell cycle arrest at S and G2/M phases.

An alternative strategy in bifunctional platinum complexes' development consisted in the substitution of the second ammonia introducing DMSO as coordinative ligand. The use of a sterically hindered sulfoxide instead of chloride was extensively studied, considering the labile behavior of the Pt–S bond due to its hydrolytic instability and to its resulting altered metabolism. Nevertheless, the loss of chlorine or sulfoxide did not alter the behavior of platinum(II) complexes in DNA bonding and towards the other targets.[28] A series of platinum(II) compounds bearing DMSO as a leaving group have been designed and synthesized, resulting in square planar transplatin derivatives. (Fig. 2, compounds **III**) These compounds were synthetized considering that rutaecarpine and tryptanthrin derivatives in metal complexes represented a selective c-myc G4 DNA ligands. The selectivity for quadruplex compared to double-stranded DNA could represent a promising drug target considering the involvement of G-quadruplex DNA (or RNA) in biological processes related to cancer. In particular the complex BrTry-Pt displayed a significant inhibition of human bladder cancer cell lines and it exhibited low toxicity in non-cancer human cell lines, arresting cell cycle progression at S phase and down-regulating cyclic A and CDK2 proteins.[29,30]

In the last decade, many efforts were realized for the substitution of the second ammonia considering the outstanding results obtained with the coordination of a bidentate ligand as DACH as in oxaliplatin in terms of cytotoxicity and ability of by-passing the resistance mechanism. Moreover, the use of aromatic *N*-heterocycles provided a larger surface able to interact more strongly with DNA base pairs and in lower inactivation of the complex by the thiols or thiol-transferring biomolecules. Two main approaches were applied: the first one for obtaining *cis*-square planar coordination mode in which the ligand was preferentially a bi-coordinated moiety and the second one that consisted in two different monodentate ligands able to assume a feasible *trans*-configuration. All these types of complexes are characterized by a binding mode to DNA different from that of cisplatin, so that they couldn't be considered as DNA-cross-linker compounds. A series of pydinecarboxaldimines of general formula *cis*-$PtCl_2$(*N*—*N*′R) (Fig. 3, **IV**) revealed to be promising for their *in vitro* cytotoxic properties against two human brain tumors: gliobastoma multiforme LN18 (IC_{50} from 11 to 31 μM) and LN405 (IC_{50} from 3 to 36 μM). The data obtained on its

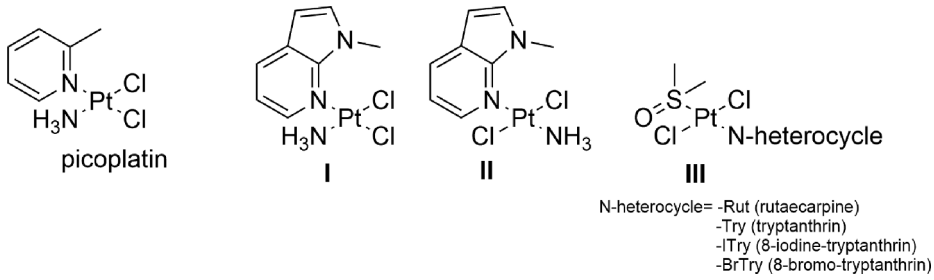


Fig. 2. Bifunctional platinum(II) complexes with ammonia.

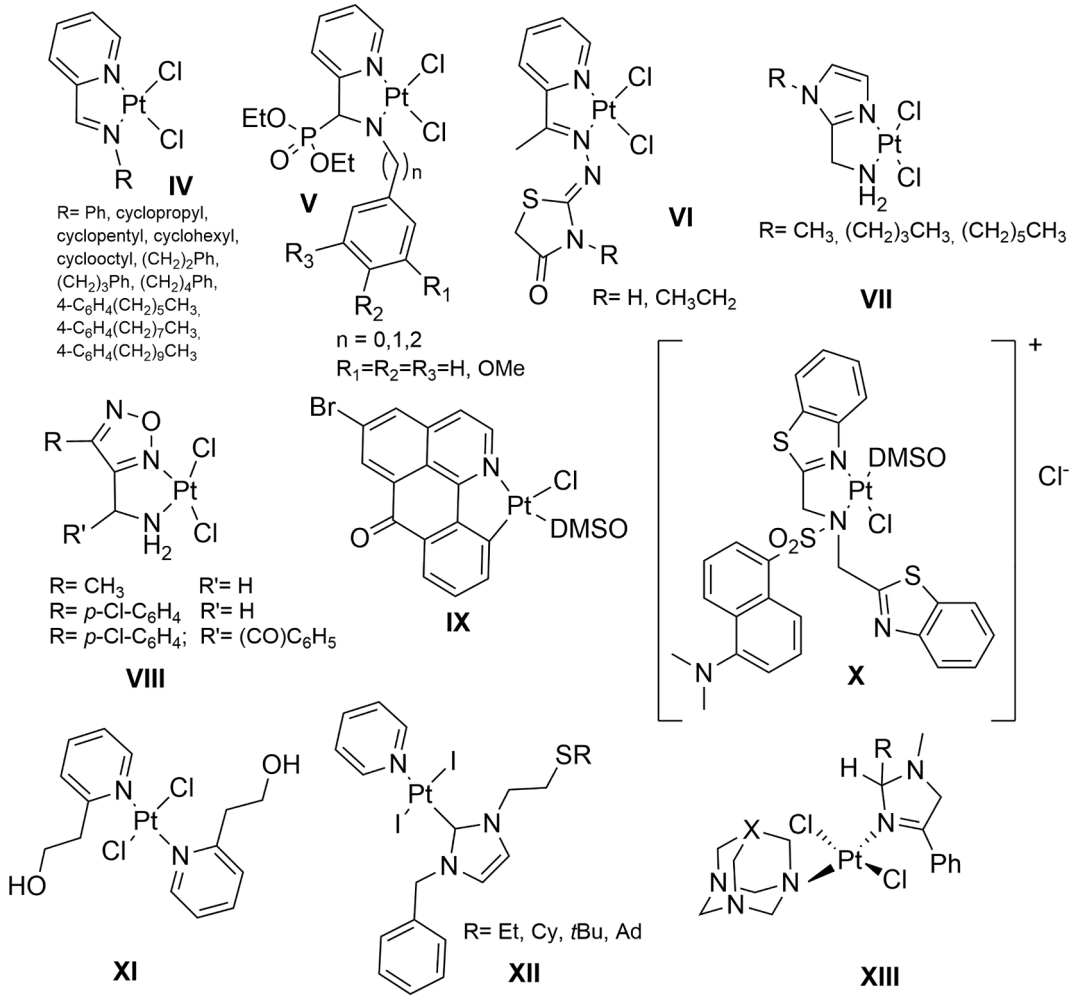


Fig. 3. Bifunctional platinum(II) series.

possible mechanism of action suggested that the cytotoxicity of this series was independent from DNA damage *in vivo* and maybe ascribable to a binding interaction with thiol groups in proteins.[31,32] The introduction of aminophosphonate ester in analogue series (Fig. 3, **V**) allowed to exert a considerable *in vitro* cytotoxic activity against 4 tumor cells lines: osteosarcoma MG-63 (IC_{50} from 18 to > 50 μM), ovary adenocarcinoma SK-OV-3 (IC_{50} from 18 to > 50 μM), hepatocyte carcinoma Hep-G2 (IC_{50} from 18 to > 50 μM) and hepatoma cells BEL-7404 (IC_{50} from 12.5 to 32.1 μM). The evinced cytotoxicity was due to cell apoptosis induction and cell cycle arrest at G1 phase. On the contrary these complexes resulted low cytotoxic on normal human liver cells HL-7702.[33] When an amino-thiazolidinone complex series was made by substitution of aliphatic amine (Fig. 3, **VI**), the cytotoxicity resulted noteworthy evident against Hep-G2 (IC_{50} from 3.8 to 48.9 μM), breast cancer cell line MCF-7 (IC_{50} from 8.8 to > 50 μM) and small lung cancer cell line NCI-H460 (IC_{50} from 7.8 to > 50 μM). It's important to underline that the best results in terms of cytotoxicity were however achieved with the cyclic tridentate platinum complex. The mechanism of action seemed to be related to the activation of the expression of Bax protein and the cleavage of caspase-3.[34]

Many research groups focused their attention on skipping from the series of pyridine based platinum(II) series to *N*-heterocycle differently hindered ligands as imidazole, oxadiazole, oxoisoaporphine or benzothiazole moieties. (Fig. 3, **VII-X**) The series of imidazole based platinum(II) complexes (Fig. 3, **VII**) was realized introducing differently long saturated and unsaturated chains at the *N*1 of the imidazole. The compounds displayed *in vitro* cytotoxic activity on different tumor cell lines as NCI-H460 (IC_{50} from 78.3 μM) and colorectal HCT-116 (IC_{50} from 38 to > 50 μM), blocking the cell cycle progression at G1/S phase. By the interaction study with Mets7 octapeptide, mimicking the *N*-terminal domain of *y*Ctr1, it was possible to confirm that this series could bypass the cisplatin resistance mechanism as for oxaliplatin.[35,36] The appropriate modifications of ligands introducing an 1,2,5-oxadizole moiety in the structure of the diamine ligands (Fig. 3, **VIII**) allowed to obtain a new series of platinum(II) complexes able to display an effective inhibition of signal traducer and activator of transcription 3 (STAT3) cascade.[37,38] These complexes exhibited an *in vitro* cytotoxicity on HCT-116 (IC_{50} from 7.8 to > 50 μM) and a stronger interaction with STAT3. *In vivo* experiments, in syngeneic murine Lewis lung carcinoma implanted in C57BL/6 mice, showed an antitumor activity with few side effects inducing a significant reduction of the tumor mass.[39] The use of 5-bromo-oxaisoaporphine ligand in *ortho*-metalated platinum(II) complexes (Fig. 3, **IX**) revealed *in vitro* IC_{50} values in a range of 5.06–31.09 μM in 11 different tumor cell lines, especially against Hep-G2 and resulting less toxic for human normal cells. They carried out the cell apoptosis mainly through the inhibition of telomerase activity by interaction with c-myc promoter and by the disruption of mitochondrial functions as evinced by the increase of ROS and the decrease of bcl-2 levels. The effects of a second ligand substitution were evaluated underlining a significant different behavior in cytotoxic activity.[40] The *in vitro* antitumor activity of platinum(II) complex bearing a danysl bis(2-benzothiazolylmethil)amine as ligand and a DMSO as leaving group (Fig. 3, **X**) resulted active in Hela, A-549 and MCF-7 cell lines (IC_{50} from 9.4 to 12.6 μM). The interaction study with calf thymus DNA (CT-DNA)

showed a groove binding mode with a moderate intercalation and a visible DNA conformational variation.[41]

Starting from the premise that *trans* geometry could improve the cytotoxic activity in resistant tumor cells since the coordination to DNA of the corresponding platinum-protein adducts resulted highly feasible,[42] many efforts were made in the synthesis of metal complexes bearing hindered *N*-heterocycle ligands in this configuration mode. (Fig. 3, **XI-XIII**) A symmetric *trans*-platinum(II) complex (Fig. 3, **XI**) was evaluated *in vitro* for its antitumor activity in mammospheres (Stem-cell enriched population) of breast CSCs (IC_{50} 31.9 μM). This complex prevented mammosphere formation and disrupted their structures in a dose-dependent manner. It promoted cell death pathways both involving apoptosis, as shown by the presence of caspase activity and the decrease of mitochondrial membrane potential and increasing the expression of pre-apoptotic genes, finally promoting necroptosis.[43] A series of *trans*-platinum(II) compounds (Fig. 3, **XII**) based on bidentate thioether-functionalized NHC ligands was evaluated *in vitro* against 3 different tumor cell lines: HCT-116 (IC_{50} from 16.6 to > 50 μM), MCF-7 (IC_{50} from 44.5 to > 50 μM) and in human prostate adenocarcinoma PC3 (IC_{50} from 23.6 to > 50 μM). The platinum drugs, providing in their coordination sphere an *S*-donor ligand able to act as a chemoprotectant group, were investigated for their ability to reduce side-effects and to prevent the coordination of GSH to the platinum center.[44] *Trans*-platinum oxadiazoline complexes with such a hindered ligand as 7-nitro-1,3,5-triaza-adamantane (NO_2-TTA) or hexamethylenetetramine (hmta) (Fig. 3, **XIII**) were tested *in vitro* for their cytotoxic activity especially in cervical cancer HeLa and in the poorly responsible to cisplatin lung cancer cell lines A549.[45] All mononuclear complexes showed a high cytotoxic activity.[46]

Monofunctional platinum drugs

Cationic platinum(II)-based anticancer agents containing only one substitution-labile ligand and thus referred to as “monofunctional”, have recently drawn significant attention due to their unique mode of action, distinctive anticancer spectrum and promising antitumor activity both *in vitro* and *in vivo*.[47,48,2,49] For such cations no indication of ammonia or *N*-heterocycle loss was detected so that the characteristic monofunctional DNA adducts may be responsible for the different spectrum of activity observed for these compounds in comparison to those for clinically used bifunctional platinum drugs. Although the monofunctional lesions do not significantly bend DNA, they resulted able to effectively destabilize the double helix structure and impede DNA replication and transcription thus triggering apoptotic cell death. The possibility of a secondary interaction afforded by an aromatic *N*-heterocycle ligand with DNA appeared essential for having antitumor activity. Even if DNA interaction remains a secure action mechanism, DNA is not the only cellular target of these types of complexes. The possibility to interact with different targets could allow to improve their antineoplastic activity specially to fight against aggressive and/or orphan cancers. Due to their positive charge, monofunctional platinum complexes uptake seems to be enhanced, more than by a passive diffusion, by OCTs thus avoiding the traditional view that neutrality is required for platinum drug uptake. After the synthesis of the very first and inactive $[PtCl(NH_3)_3]^+$ and $[PtCl(dien)]^+$ (Fig. 4, compounds **XIV** and **XV**), the field of monofunctional platinum compounds have known a renewed interest with the discovery of pyriplatin (Fig. 4), a metallodrug structurally similar to cisplatin in which a pyridine replaced one chloride ligand.[50,51]

Pyriplatin binds to the *N*7 of the guanine residues thus creating only a slight distortion in DNA double helix that however results extremely efficient in inhibiting transcription and eluding repair. Recently the X-ray structure of RNA polymerase II stalled on pyriplatin-DNA adduct revealed that the growing RNA strand terminated at the post-translocation step of transcription in contrast to cisplatin ability to block RNA polymerase II procession at the translocation step. Moreover, pyriplatin was identified as a specific substrate of the OTCs thus opening the possibility of a selective delivery of the drug to those tumor tissues where OTCs are overexpressed such as in the colon-rectal where pyriplatin resulting 87-fold more cytotoxic in OCT1(+) than OCT1(-) cells, whereas oxaliplatin was only 12-fold more effective. The presence of the aromatic pyridine appeared essential for determining such a type of lesion that makes pyriplatin able to induce a cellular response different from that exerted by the bifunctional neutral platinum drugs.

In addition, the inactivity of the analogue enpyriplatin (Fig. 4, **XVI**), that differs from pyriplatin by an ethane-1,2-diamine ligand, shed light on the importance of the proper lipophilicity of the complex for exerting cytotoxicity: the slight contribution of the chelating ligand to the lipophilicity of the complex is enough to determine a significant difference in terms of activity. **XVI** resulted in fact inactive against DLD-1 cancer cell line (IC_{50} > 300 μM) if compared to pyriplatin that showed comparable activity (IC_{50} 6.5 μM) to cisplatin (IC_{50} 2.9 μM) on the same cancer cell line. For these reasons the cytotoxicity profile of pyriplatin resulted distinct from that of both cisplatin and oxaliplatin in a panel of 10 cancer cell lines and by the NCI single-dose screen. The cell lines in which pyriplatin resulted most active (IGROV1, HOP-92, HOP-62, and COLO205), although with IC_{50} values that are 16 to 270 times higher than for cisplatin and oxaliplatin, are different from those in which cisplatin resulted the leader (HCT-116, HOP-92, HOP-62, and OVCAR-3) or those in which oxaliplatin is the most cytotoxic (HCT-116, OVCAR-3, HOP-92, and MCF7).[52] In view of these results pyriplatin can be considered as the exploratory lead compound of the monofunctional platinum-based drugs candidates. Starting from the observed reduced deactivation of pyriplatin by GSH and other cellular nucleophiles and in order to obtain monofunctional platinum(II) complexes endowed with a higher cytotoxic effect, a progressive substitution for pyridine with more steric hindered *N*-heterocycle ligands was realized.[52]

As observed by X-ray diffraction of pyriplatin, the plane of the heterocyclic ligand results perpendicular to the platinum coordination sphere so that the *N*-heterocycle with its steric hindrance furnishes protection against the eventual attack of any deactivating nucleophilic agent such as GSH and metallothioneins. These observations led to the development and discovery of phenanthriplatin (Fig. 4), *cis*-$[Pt(NH_3)_2$(phenanthridine)Cl$]NO_3$, in which the pyridine ring was replaced by a more expansive phenanthridine ring thus resulting in a complex exhibiting an efficacy 7–40 fold higher than cisplatin towards the most of established human cancer cells.[53,54] Phenanthriplatin stands out for the presence of a chiral center and therefore it can form diastereomeric complexes with guanine residues with one diastereomeric form preferred over the others.[55] To understand the right mechanism behind the binding of phenanthriplatin to DNA, the *trans* analogue phenanthridine platinum(II) complex was prepared (Fig. 4, **XVII**)[56] showing that only the *cis* isomer had the right stereochemistry for affording an irreversible DNA covalent binding and thus explaining the more potent cytotoxicity of *cis*-phenanthriplatin in cisplatin resistant ovarian cancer A2780CP70 (IC_{50} 0.29 μM for *cis*-phenanthriplatin *vs* 6.5 μM for the *trans* isomer) and in the breast cancer cell line MCF-7 (IC_{50} 0.80 μM for *cis*-phenanthriplatin *vs* 14.9 μM for **XVII**).[57] Phenanthriplatin-DNA monofunctional adducts sterically hindered the DNA major groove thus blocking the transcription process. Site specifically-platinated DNA studies revealed that the insertion of cytosine triphosphate (CTP) opposite to the platinated guanine residue took place without errors but downstream from that the RNA polymerase resulted unable to go ahead with the mRNA strand synthesis.[9]

Indeed, phenanthriplatin was recently associated to oxaliplatin for its transcription/translation inhibitory activity as a result of a ribosome biogenesis stress more than a DNA dependent process. Focusing the attention on the rRNA synthesis, a nearly 50% decrease in pre-rRNA was observed within 30 min in response to both phenanthriplatin and oxaliplatin. From a functional genetic point-of-view, the p53 dependent cell death induced by phenanthriplatin exposure is a consequence of a ribosome biogenesis damage that lead to an excess of RPL11

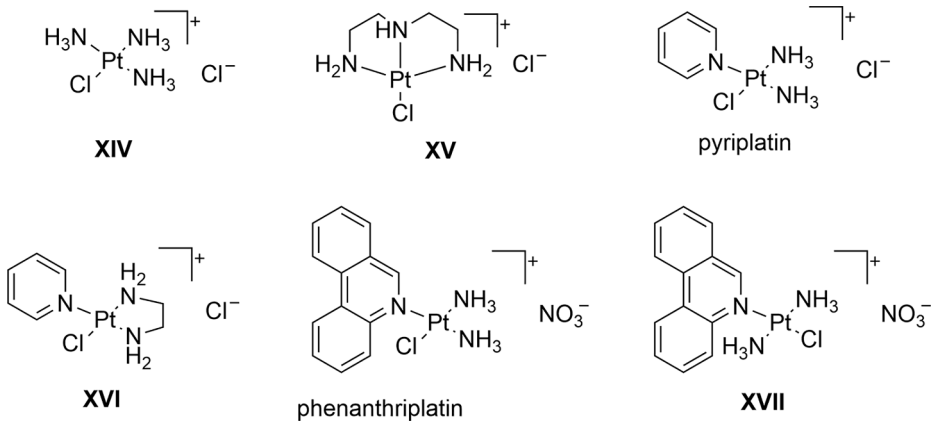


Fig. 4. Monofunctional platinum(II) complexes.

(Ribosomal Protein L11) subunits able to inhibit Mdm2 binding to p53 thus triggering apoptosis. Conversely, because of the diastereoselectivity induced on the polymerase adduct by the heterocyclic ring, phenanthriplatin induced lesions resulted able to inhibit DNA polymerase η, a repair enzyme, allowing to overcome the 1,2-intrastrand lesions created by cisplatin.[58]

A very interesting series of water soluble cationic platinum(II) compounds relied on the substitution of the non-labile *N*-donor ligands with a chelating 2,9-dimethyl-1,10-phenanthroline. The coordination sphere of the platinum complex was indeed completed by either a 2-picoline, or its derivative 6-amino-2-picoline or by 1-methyl cytosine respectively (Fig. 5, **XVIII**).[59] The presence of the two *ortho*-methyl substituents on the phenanthroline ligand, along with the shielding properties furnished by the aromatic ring of the third nitrogen ligand, contributed to protect the platinum center making the complexes resistant from deactivation reactions by platinophiles. The 1-methyl cytosine derivative exhibited a remarkable growth inhibitory activity on a variety of human tumor cell lines (NCI-H460, A549/ATCC, MCF7, MDA, HCT-116, KM12, Colo205, A2780, 41M, OVCAR-8) included some cell lines characterized by intrinsic (SKOV-3) or acquired (A2780cisR and 41McisR) resistance to cisplatin affording IC_{50} from 0.15 to 7.2 μM. Its cytotoxic properties resulted strictly related to its capabilities to cross cell membrane thanks to the hydrophobic phenanthroline respect to its analogue bearing a 1,8-naphthyridine ligand that it was however up taken at a similar extent by LoVo cells.[60] Compound **XIX** (Fig. 5) resulted in turn more active than quinoplatin **XX** and endowed with an antiproliferative profile comparable to the oxaliplatin's one underlining the importance of an extra nitrogen atom in acting as H-bond donor/acceptor for targeting DNA or proteins more selectively.

A recent series of monofunctional platinum compounds based on imidazole moiety was prepared and evaluated in different cancer cell lines unresponsive to cisplatin (Fig. 5, **XXI**).[61] Compound carrying the hexyl group, resulted the most active of the series with an IC_{50} of 61.9 μM in the triple-negative breast cancer cell line MDA-MB-231 and showing a promising 57.4 μM in the colorectal DLD-1 cancer line. Moreover, its *in vitro* antiproliferative properties were investigated against three aggressive and still orphan-drug tumors: malignant pleural mesothelioma (NCI-H28), glioblastoma multiforme (U87 MG) and pancreatic adenocarcinoma (CFPAC-1). The obtained results

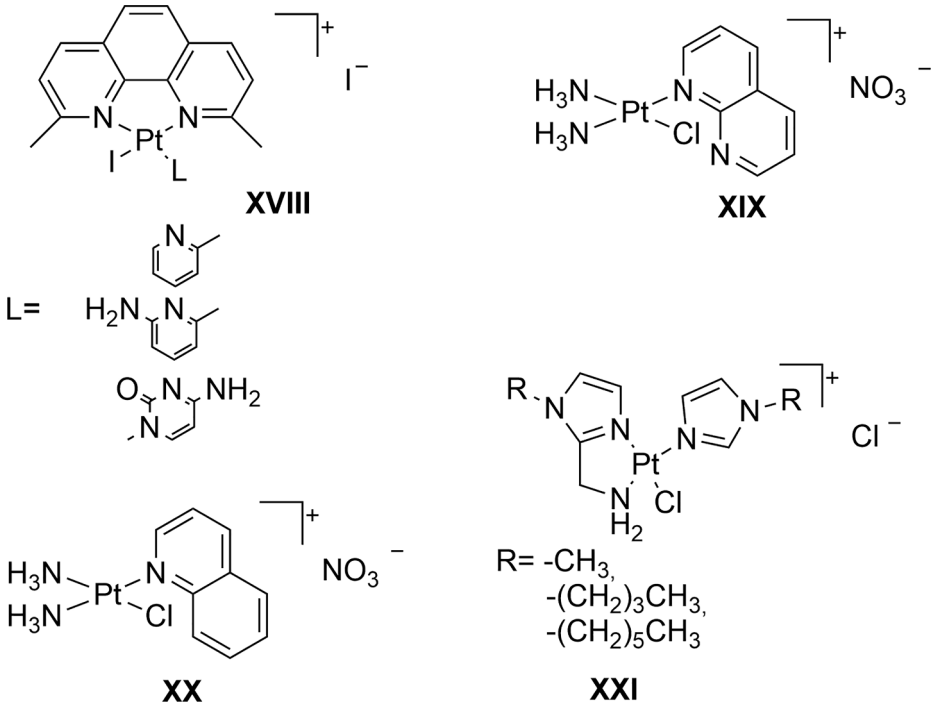


Fig. 5. Cation monofunctional platinum(II) series.

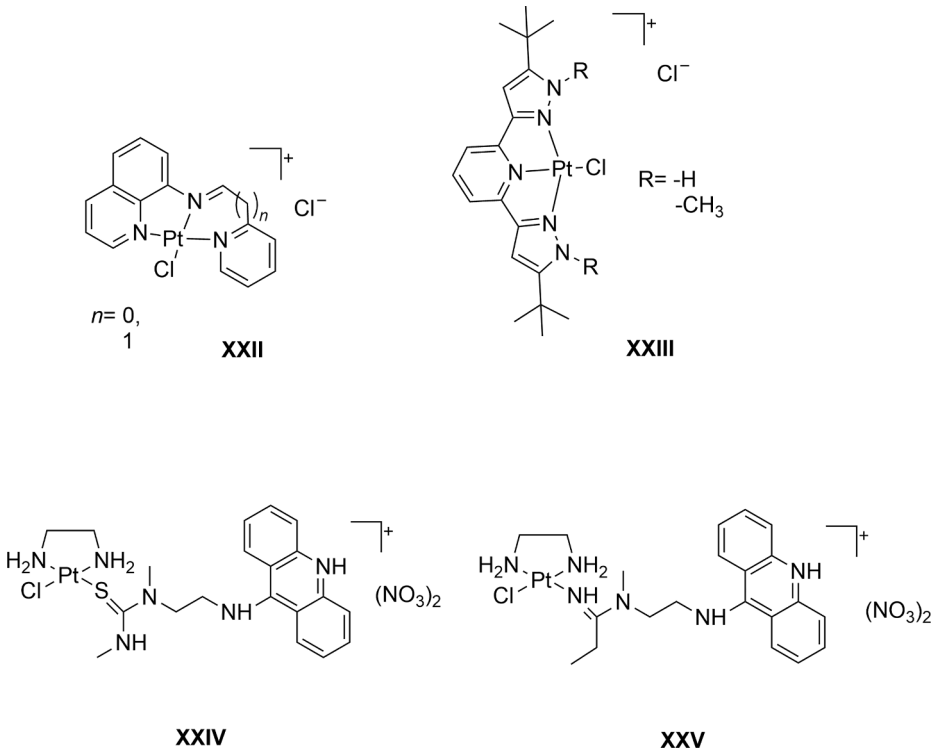


Fig. 6. Additional examples of cationic monofunctional platinum(II) series.

demonstrated a potent and higher cytotoxicity than cisplatin against both NCI-H28 (19.37 μM versus 34.66 μM for cisplatin) and U87 MG (19.85 μM versus 54.14 μM for cisplatin).[62,63] Mechanistic studies confirmed for this compound a p53-independent mechanism of cytotoxicity affecting the G2/M more deeply than the S phase and thus suggesting a mitochondrial apoptotic pathway activation. Moreover, the monofunctional complex resulted able to elude the cellular transporters CTR-1, ATP7a and ATP7b found to be involved in cisplatin resistance occurrence. The ability of this cationic platinum complex to be up taken without any loss of activity along with a higher stability than cisplatin makes it a possible candidate for the development of new cell mediated therapies.[63]

A promising strategy in the search of new metal-based anticancer drugs relies on the possibility to exploit biologically active molecules as ligands in coordination complexes with transition metals.[64] Starting from the premise that a metal ion can reshape the biochemical properties of such ligands, two monofunctional platinum complexes (Fig. 6, **XXII**) bearing 8-substituted and bioactive quinoline alkaloid ligands were developed and investigated for their *in vitro* and *in vivo* antiproliferative activity.[65,66] The one endowed with the better lipophilicity profile, *i.e.* a higher membrane permeability, resulted also endowed with a higher anticancer activity if compared to its analogue against CT-26, SK-OV-3, Bel-7404, MGC-803 and HL-7702 cancer cell lines with IC_{50} values and toxicity lower than cisplatin. It's worth noting that this compound showed a certain selectivity of action, displaying a lower antiproliferative effect on normal human liver HL-7702 cell line than on the cancerous counterpart. Mechanistic experiments proved that it accumulates in mitochondria causing both a mitochondrial metabolism dysfunction and a TrxR (thioredoxin reductase) inhibition with a consequent ER (endoplasmic reticulum) stress that triggers a simultaneous induction of apoptosis and autophagy in A549 cells. Moreover, the same data were confirmed by *in vivo* study in KM mice. A similar bimodal mechanism of cell death involving both apoptotic and autophagic pathways was established for new tridentate pyrazol-3-yl-pyridine based monofunctional platinum complexes **XXIII** (Fig. 6).[67] The reactivity of these complexes against a series of biologically relevant sulphur and nitrogen nucleophiles was realized in order to expand information about the structural features involved in the pharmacological response. The results showed a high binding affinity to DNA with an established $K_b = 10^4\ M^{-1}$ but also to BSA, usually responsible for the toxicity of metallodrugs, along with a moderate selective cytotoxicity against HeLa (IC_{50} from 57 to 70 μM) over PANC-1 cancer cells (IC_{50} from 146 to 168 μM) in comparison to cisplatin (IC_{50} 9 μM against HeLa and IC_{50} 16 μM on PANC-1) after 48 h of exposure.

With the same idea to exploit the intrinsic biological properties of the nitrogen ligands, platinum(II)-acridine hybrid agents deserve to be mentioned.[68,69] These types of monofunctional complexes are among the most cytotoxic anticancer agents with nanomolar IC_{50} values against several cancer cell lines due to both a monofunctional binding to guanine (80%) or adenine (20%) and an intercalation of the acridine moiety into the base pair adjacent to the site of platination. Complex **XXIV** (Fig. 6) exhibited a high cytotoxic profile in a broad range of solid tumors *in vitro* but its inhibitory effect on cell proliferation resulted particularly decreased *in vivo*. The replacement of the thiourea sulfur atom with a nitrogen amidine donor as realized in **XXV** (Fig. 6) resulted in a greatly enhanced DNA binding kinetics as a result of the hydrogen bonding between the imino hydrogen and exocyclic groups of the DNA bases. This simple but not trivial chemical modification turned out in a reduction of the tumor growth at a sublethal dose close to the MTD in H460 tumor xenograft model.

Conclusion and perspectives

The choice to use different *N*-heterocycle rings, mainly the aromatic ones, resulted to influence not only the electronic and steric coordination sphere around the platinum metal center but also to offer the possibility to target different biological pathways involved in such a multifactor pathology as cancer. The first attempt was focused on the substitution of one ammonia with a monodentate aromatic amine both in *cis* and *trans* configurations, underlining that the *cis* configuration is not fundamental for exhibiting cytotoxic activity. The substitution of the second ammonia, especially with bidentate ligands, allowed to

explore new ligand design maintaining the platinum(II) pharmacophore. These structural changes resulted in improving the pharmacological profiles as in oxaliplatin. The introduction of DSMO as coordinative ligand represented a valid way to improve the activation process in physiological conditions. The development of monofunctional platinum(II) complexes, as in phenanthriplatin, suggested the possibility to by-pass many issues related to the use of cisplatin as intrinsic and acquired resistance and they shed light on new types of DNA lesions and on the interaction with non-DNA targets. Extensive research work on the synthesis of new metal complexes bearing *N*-heterocycle ligands could represent a valid alternative tool especially in the treatment of orphan and drug resistant tumors.

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