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CURRENT APPLICATIONS AND FUTURE TRENDS IN THE DEVELOPMENT OF ANTICANCER DRUGS FROM BIOINORGANIC METAL COMPLEXES

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ABSTRACT

This review illustrates notable recent progress in the field of medicinal bioinorganic chemistry with many new approaches to the design of innovative metal-based anticancer drugs emerging. Metals are endowed with unique characteristics that include redox activity, variable coordination modes and reactivity towards organic substrates. Due to their reactivity, metals are tightly regulated under normal conditions and aberrant metal ion concentrations are associated with various pathological disorders, including cancer. For these reasons, coordination complexes, either as drugs or pro drugs, become very attractive probes as potential anticancer agents. The use of metals and their salts for medicinal purposes, from iatrochemistry to modern day, has been present throughout human history. The discovery of cisplatin, *cis*-$[Pt^{II}(NH_3)_2Cl_2]$, was a defining moment which triggered the interest in platinum(II)- and other metal-containing complexes as potential novel anticancer drugs. Other interests in this field address concerns for uptake, toxicity and resistance to metallo drugs.

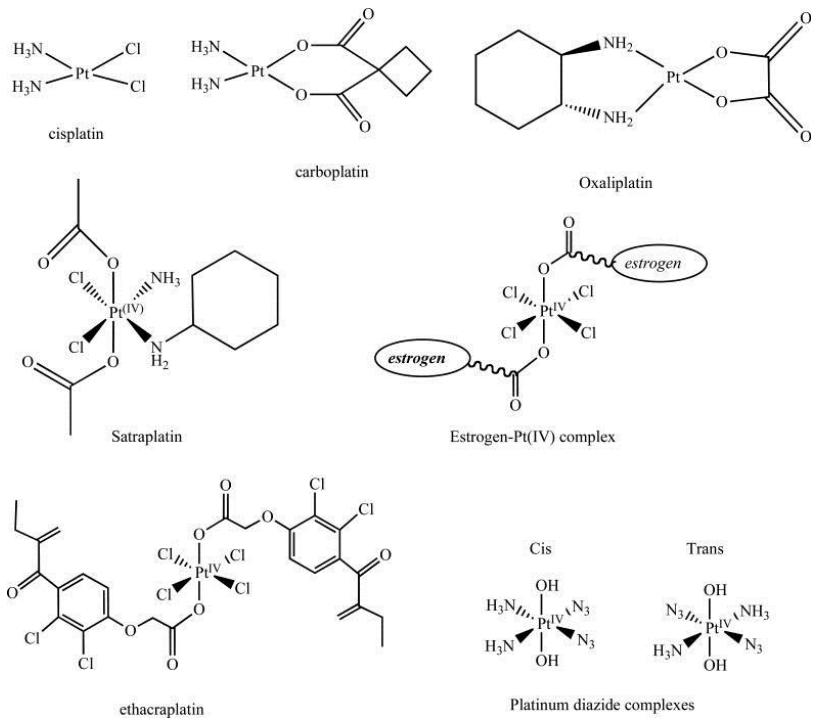
KEYWORDS: Cancer, metal, gold, anticancer, platinum, metal complex, Bioinorganic.

INTRODUCTION

In nature, many biological systems make extensive use of metal ions, such as zinc and copper, which play critical roles in the normal functioning of organisms.[1] Transition metals such as copper, iron and manganese, among others, are involved in multiple biological processes, from electron transfer to catalysis to structural roles and are frequently associated with active sites of proteins and enzymes.[2] However, dysregulation of some of these essential metals during normal biochemical processing has been implicated in the

development of various pathological disorders, such as cancer.[5] These cellular functions only require the "trace metals" in miniscule but tightly regulated amounts. By comparison, other metals such as arsenic, cadmium, chromium and nickel are less beneficial since they produce a wide range of toxic side-effects, including carcinogenesis.[4,6]

Many metal-containing compounds have been utilized throughout history to treat a wide variety of disorders.[7] In medicinal chemistry —traditionally dominated by organic chemistry— metal complexes have gained favor as diagnostic tools and anticancer agents.[7-8] Research in anticancer agents was stimulated by the accidental discovery of cisplatin, *cis*-$[Pt^{II}(NH_3)_2Cl_2]$ (Fig. (**1**). However, its clinical use is restricted due to dose-dependent toxicity and resistance coupled with a narrow spectrum of activity.[9,10] These limitations have triggered a search for platinum-based compounds that show lower toxicity, higher selectivity, and a broader spectrum of activity.[11-12] The complexes known as carboplatin and oxaliplatin, among others seen in Fig. **1** arose from this search. Nevertheless, in addition to numerous platinum analogs, other metal complexes containing metal ions such as zinc(II), copper(II), gold and copper chelating agents have received considerable attention as potential anticancer agents.[13-14] Additionally, the investigation of ruthenium-containing compounds in clinical trials attests to the rich potential of utilizing non-platinum metal-based compounds in the treatment of cancer.[15-16] Furthermore, metals that take advantage of their unique physiochemical properties have been utilized as powerful tools in cancer diagnosis.[17] This review discusses the role of selected metals in biological processes in cells as they pertain to malignancy and to highlight the medicinal applications of the metals and their complexes in the design and development of metallodrugs for the treatment of cancer. This article also places considerable emphasis on their cellular targets and mechanisms of action.



Ruthenium

Ruthenium compounds containing Ru^{II} or Ru^{III} are considered to be suitable candidates for anticancer drug design, since they exhibit a similar spectrum of kinetics for their ligand substitution reactions as platinum(II). A number of ruthenium compounds have been shown to display promising anticancer activity and two ruthenium(III) complexes have entered clinical trials, *trans*-[$RuCl_4$(DMSO)(Im)]ImH (NAMI-A, where Im = imidazole, Figure 2b), and *trans*-[$RuCl_4(Ind)_2$]IndH (KP1019, where Ind = indazol Figure 2c. NAMI-A is more active against metastases than against primary tumors. In contrast, the structurally-similar KP1019 is active against primary tumors. It is believed that the activity of the ruthenium(III) compounds is dependent on the *in vivo* reduction to the more reactive ruthenium(II) species This has led to increased interest in the anticancer potential of ruthenium(II) compounds. Much work has focused on the anticancer potential of half-sandwich Ru(II) arene complexes of the type, [(η^6-arene)Ru(YZ)(X)], where YZ is a bidentate chelating ligand and X is a good leaving group *e.g.* Cl, Figure 2d). These half-sandwich "piano-stool" complexes offer great scope for design, with the potential to vary each of the building blocks (arene, chelated ligand YZ and monodentate ligand X) to allow modifications of thermodynamic and kinetic parameters.

Some of the half-sandwhich Ru(II) arene complexes display promising *in vitro* and *in vivo* anticancer activity (Figure 2e and f). These monofunctional compounds bind

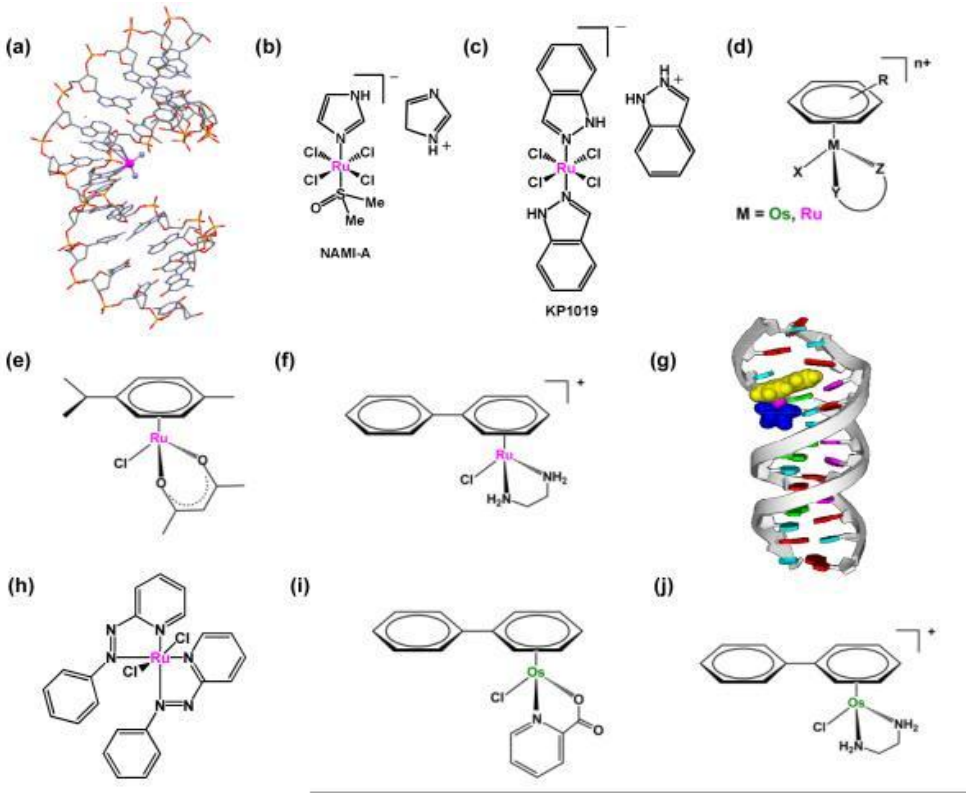
coordinatively to N7 of guanine in DNA which can be complemented by intercalative binding of an extended arene as well as specific hydrogen-bonding interactions between the chelating ligand and C6O of guanine. These additional interactions result in unique modes of binding to duplex DNA and structural distrortions that differ significantly from those caused by cisplatin (Figure 2g). This may explain why these compounds are not cross-resistant with cisplatin. Indeed, it has been found that increasing the size of the coordinated arene increases their activity in the human ovarian cancer cell line.[13] Changing the chelating ligand in these ruthenium arene complexes also appears to have an enormous effect on their kinetics and even changes their nucleobase selectivity. It is believed that *in vivo* the aquation of the chloro complex is largely suppressed in intracellular fluids where high chloride concentrations are found (100 mM), whereas in the cell nucleus, where the chloride concentration is lower (4 mM), the complex forms predominately the active aqua species.

Another interesting class of ruthenium compounds containing arylazopyridine (azpy) ligands shows promising cytotoxic activity that is structurally-dependent. Three of the five possible isomers of $[Ru(azpy)_2Cl_2]$ (α, β, λ, Figure 2h) have been reported, where the α isomer represents the *cis,trans,cis*, β the *cis,cis,cis* and γ the *trans,cis,cis* orientation of the chlorides, the pyridine and the azo nitrogens, respectively. The α and λ isomers show higher toxicities compared to the β isomer. Indeed, DFT calculations suggest that the ability of the isomers to intercalate into DNA decreases from λ >α > β isoforms Recently several isomeric forms of multinuclear ruthenium complexes with bridging azpy ligands have been reported[18]; the γ/γ isomeric form exhibits the highest cytotoxicity, over 30-fold higher than cisplatin in breast cancer cells.

Osmium

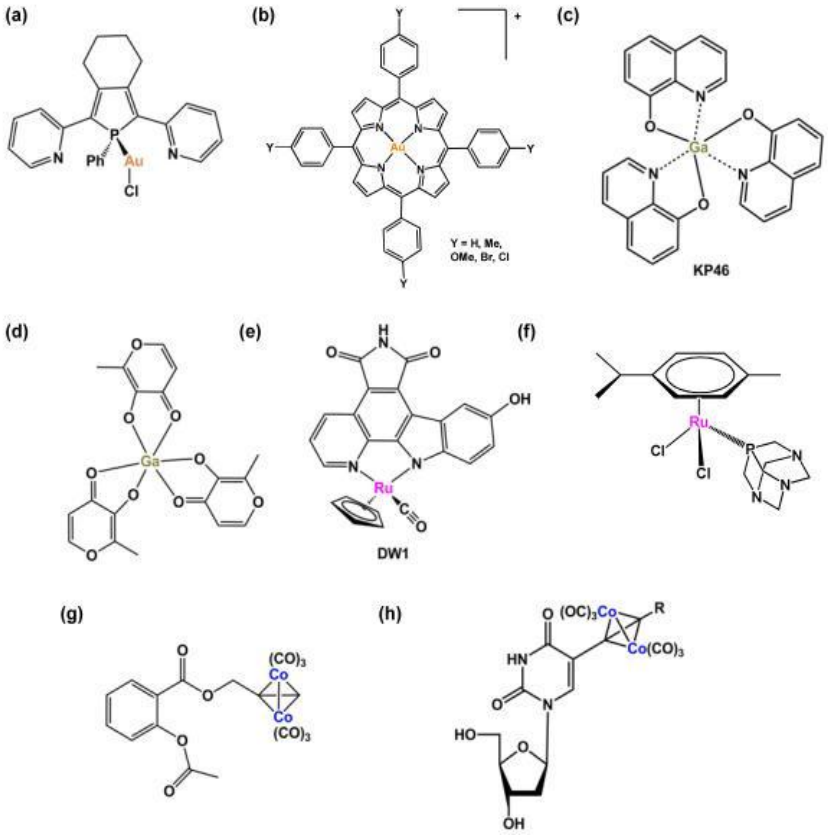
The anticancer potential of osmium, the heavier congener of ruthenium has recently been explored. Osmium complexes have a reputation for being either toxic (OsO_4) or substitution-inert (Os^{II} and Os^{III} complexes) and as a consequence their therapeutic potential has been little explored. However, Sadler and coworkers have synthesized some osmium(II) arene complexes with cancer cell cytotoxicity that is comparable to the clinical drugs carboplatin and cisplatin (Figure 2i and j).[19] This was achieved by systematically varying the nature of the chelating ligand to fine-tune both the kinetics and thermodynamics of reactions of the osmium compounds in aqueous solution.[20] The Os^{II} arenes are believed to interact with DNA in a similar fashion as their ruthenium analogs, *i.e.* binding to N7 of guanine in

combination with H-bonding and non-covalent arene DNA interaction. Interestingly, binding of Os^{II} arenes to calf thymus DNA gives rise to a large unwinding of double-helical DNA, unlike cisplatin which causes DNA bending. These osmium complexes do not display cross-resistance with cisplatin towards cancer cells, suggesting promise for addressing the problem of intrinsic or acquired resistance in chemotherapy.



Gold

Gold complexes are well known pharmaceuticals, mainly for their application as drugs to treat rheumatoid arthritis. Some tetrahedral Au(I) phosphine complexes display a wide spectrum of anticancer activity *in vivo*, especially in towards cisplatin-resistant cell lines. Their cytotoxicity is mediated by their ability to inhibit mitochondrial human glutathione reductase (hGR) and thioredoxin reductase (hTrxR) irreversibly.[21] In particular, phosphol-containing gold(I) complexes (Figure 3a) are highly potent, nanomolar inhibitors of both hGR and hTrxR.[28] hTrxR is associated with many cellular processes such as antioxidant defence and redox homeostasis and is found at elevated levels in human tumor cell lines.

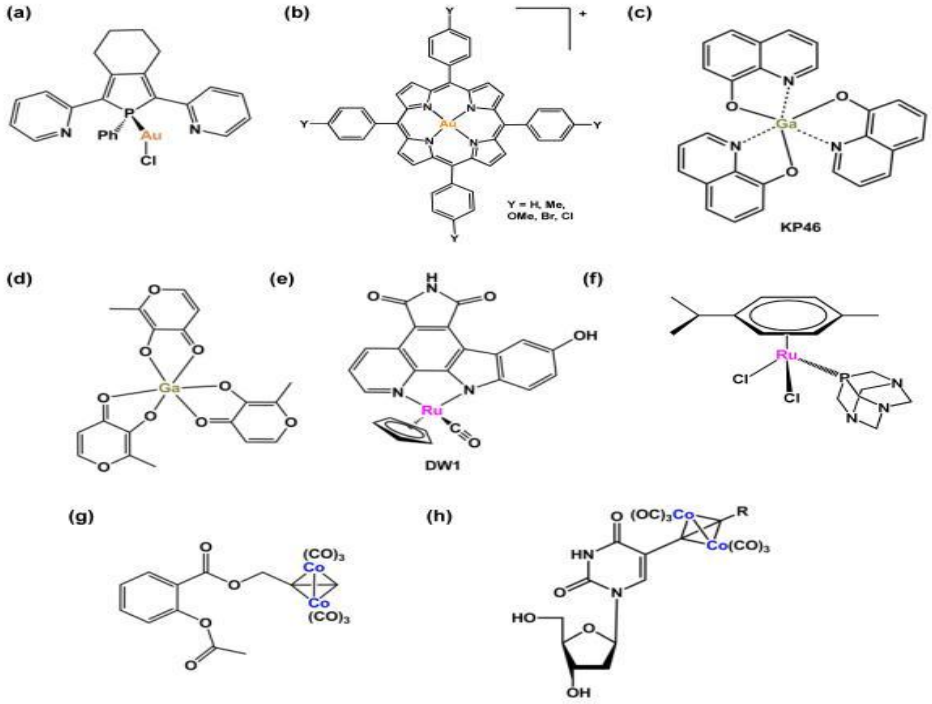


Gold (III) is isoelectronic and isostructural with Pt(II), therefore gold(III) analogues of Pt(II) drugs were investigated for their biological potential soon after the appearance of cisplatin in the clinic. Unfortunately they were found to be relatively unstable as well as easily reduced to metallic gold under physiological conditions. In recent years, however, several gold(III) compounds that incorporate ligands to increase the stability to the gold(III) centre have been reported. For example, gold(III) porphyrins(Figure 3b) exhibit *in vitro* and *in vivo* activity in hepatocellular and nasopharyngeal carcinoma. Other Gold(III) compounds with promising biological activity include gold(III) bipyridyl compounds, dinuclear gold(III) oxo complexes and gold(III) dithiocarbamates. For these compounds the mitochondria and the proteasome are thought to be targets.[22]

Gallium

The chemical behavior of gallium (III) is similar to that of ferric iron (Fe^{III}), but differs in that Ga^{III} is non-reducible under physiological conditions whereas Fe^{III} is readily reduced to Fe^{II}. This difference provides therapeutic potential for gallium (III). Currently, two compounds, gallium tris-8-quinolinolate (KP46) and gallium tris-maltolate (Figure 3c and d) are being investigated in clinical trials.[23] Their mechanism of action is associated with the inhibition

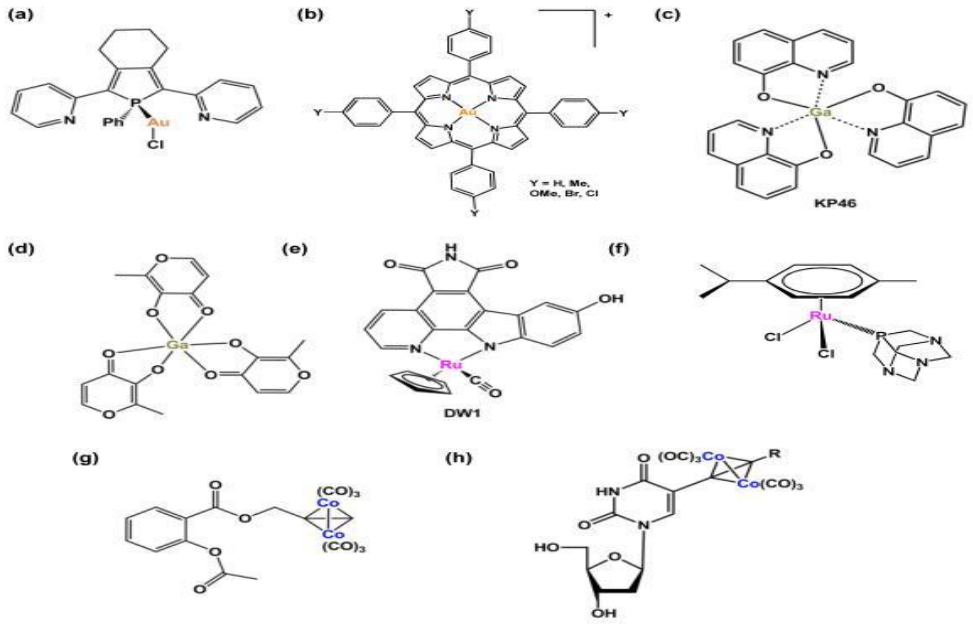
of ribonucleotide reductase (RR). The enzyme RR catalyses the conversion of ribonucleotides to deoxyribonucleotides and is produced during the transition from the G1 to the S phase of the cell cycle as a prerequisite for DNA replication and is highly expressed in tumor cells.



Cobalt

Some hexacarbonyl dicobalt complexes exhibit promising activity against several human cancer cell lines.[24-25] In particular, a cobalt-alkyne analogue of the anti-inflammatory drug, aspirin, is potently active in breast cancer cell lines (Figure 3g). Its toxicity has been attributed to its ability to inhibit cyclooxygenase (COX-1 and 2).[41] This appears to be a promising approach, since inhibition of cyclooxygenase delays tumor growth as well as improves response to conventional cancer therapies. Another hexacarbonyl dicobalt series of compounds containing nucleoside ligands (Figure 3h) displays antiproliferative activities with IC_{50} values in the range of 5–50 μM in human breast cancer cell lines.[26] The family of cysteine cathepsin proteases has recently been validated as an important enzymatic class to target in cancer. More specifically, cathepsin B and L have been shown to be involved in multiple stages of tumor development. Metal-based compounds reported to show promising inhibition of cathepsin B include linear gold(I) complexes containing thiolate and phosphine ligands[27], dinuclear palladium complexes (biphosphinic palladacycle complexes)[28] and several oxorhenium(V) complexes . Other metal-based drugs in preclinical or early phase of

clinical development not mentioned in the previous two sections contain vanadium, rhodium, copper, bismuth and lanthanide metals.[29-30]



CONCLUSION

Metal coordination complexes offer a very versatile platform for the design of novel anticancer agents. Their properties can be quite distinct from those of purely organic compounds. Particularly attractive for study are the first, second and third row transition metals, with their variable oxidation states, coordination numbers and ability to bind to a wide variety of types of ligands (*e.g.* halides, O, S, N, P, C). In particular metals in the second and third rows often exchange their ligands relatively slowly, on minutes-to-hours timescales which allow at least some of the original ligands to remain bound to the metal en route to the target site. In general (with some exceptions) because they can undergo ligand exchanges, metal complexes are pro drugs, ligand substitution can activate the metal complex towards binding to target molecules. A key element in the design process is the control of both the thermodynamics (state of equilibrium) and kinetics of ligand substitution events which can occur *in vivo*, for example the aquation of metal-chloride bonds as the concentration diminishes from extracellular to intracellular (cytoplasmic and nuclear) compartments. of interest too are both metal-centered and ligand-centered redox processes. The former can trigger activation by ligand release (*e.g.* reduction of substitution inert Co^{III} to labile Co^{II}), and the latter the initiation of the production of reactive oxygen species (e.g. azopyridine Ru^{II} arenes) as part of the cytotoxic mechanism. The possibility of using light to activate

metal complexes selectively in tumor cells is also an intriguing one. Reactions of excited-state metal complexes can be distinctly different from those of ground-state complexes, giving rise to the possibility of interfering in biochemical pathways with highly reactive novel species. Cisplatin and the successive generations of platinum-based anticancer drugs (carboplatin and oxaliplatin) have demonstrated that metal coordination complexes can play an important part in anticancer treatment regimes in the clinic. The exploration of other transition metal complexes, as well as targeting and activation strategies, should lead to future generations of drugs which can overcome some of the disadvantage.

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