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Metals and Metal Derivatives in Medicine

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Abstract: Several chemical elements are required by living organisms in addition to the four elements carbon, hydrogen, nitrogen and oxygen usually present in common organic molecules. Many metals (e.g. sodium, potassium, magnesium, calcium, iron, zinc, copper, manganese, chromium, molybdenum and selenium) are known to be required for normal biological functions in humans. Disorders of metal homeostasis and of metal bioavailability, or toxicity caused by metal excess, are responsible for a large number of human diseases. Metals are also extensively used in medicine as therapeutic and/or diagnostic agents. In the past 5000 years, metals such as arsenic, gold and iron have been used to treat a variety of human diseases. Nowadays, an ever-increasing number of metal-based drugs is available. These contain a broad spectrum of metals, many of which are not among those essential for humans, able to target proteins and/or DNA. This mini-review describes metal-containing compounds targeting DNA or proteins currently in use, or designed to be used, as therapeutics against cancer, arthritis, parasitic and other diseases, with a special focus on the available information, often provided by X-ray studies, about their mechanism of action at a molecular level. In addition, an overview of metal complexes used for diagnosing diseases is presented.

Keywords: Metals, platinum, cisplatin, cancer, drug targets, therapy, mechanism of action, three-dimensional structure.

INTRODUCTION

Four elements, i.e., hydrogen, oxygen, carbon and nitrogen, account for 99% of the total human body weight; however, we require as many as 25 elements in total [1, 2]. The list of essential elements for human life comprises many metals, including iron, zinc, copper, manganese, sodium, potassium, calcium and magnesium, and also metals formerly thought of only as poisons, such as selenium, molybdenum, nickel, silicon, vanadium and, possibly, arsenic [3]. Different metals have different physical-chemical properties and perform diverse functions in the human body. As an example, sodium and potassium bind weakly to organic ligands and are used for the generation of ionic gradients across membranes and maintenance of osmotic balance. Magnesium stabilizes nucleic acids, participates in phosphoryl group transfer reactions and is a structural component of several enzymes. Calcium is an essential structural component of many proteins and of the bones, and is used as a charge carrier, trigger for muscle contraction and universal second messenger for signal transmission. Metal ions, such as iron and copper, bind strongly to organic ligands, participate in innumerable redox reactions and are required for oxygen transport.

Empirical evidence for the effectiveness of metal-based therapeutics has existed for centuries. The use of metals and metal-containing compounds in medicine dates back millenniums: copper was used by Egyptians and gold was utilized by Chinese and Arabic practitioners. Hippocrates (400 BC) employed copper and mercury in the treatment of diseases, while Paracelsus (XVI century) used Sb, As and Mg salts. More recently, $K[Au(CN)_2]$ has been used against tuberculosis, while arsenic-based Salvarsan has been considered to be the mainstay for the treatment of syphilis for the first decades of the XX century. However, the potential of metal-based compounds has been fully appreciated only after the discovery of the anticancer activity of cisplatin [4].

At present, metal-containing compounds are in use against several diseases, and are increasingly being studied by modern medicinal chemistry. Because of their unique features, including a wide range of redox states, charges, coordination geometries, thermodynamic and kinetic properties, metals can be exploited in the design of metal-based compounds alternative to fully organic molecules [5, 6].

Though many metals are essential to life, and many disorders affecting metal homeostasis and bioavailability are responsible for several human diseases, metals can be toxic at very low concentrations. Indeed, many metals are considered to be poisons although, as stated by Paracelsus, the right dose differentiates a poison from a medicine. Reaching a balance between potential positive impact and toxicity of an active formulation is therefore a particularly relevant issue in the design of metal-containing therapeutic and diagnostic agents [4].

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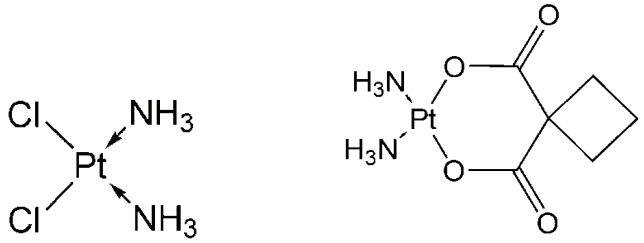
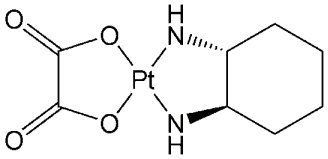
PLATINUM-BASED COMPOUNDS AGAINST CANCER

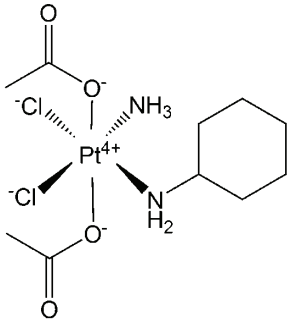
Cisplatin, *i.e.*, cis-diamminedichloroplatinum(II), a square planar compound containing Pt(II) complexed by anionic ligands (Fig. **1A**), has been the first metal-based agent to enter into worldwide clinical use for the treatment of cancer [7]. Currently, cisplatin is used either by itself or in combination with other drugs for treating lung, ovarian, bladder, testicular, head and neck, esophageal, colon, gastric, breast, prostate cancer and melanoma being particularly effective against testicular cancer [8]. Toxicity and resistance issues have prompted the design and clinical approval of second and third generation of cisplatin analogues with lower toxicity profiles, namely carboplatin and oxaliplatin (Fig. **1B**,**C**) [9]. Carboplatin is used in the treatment of ovarian carcinoma, lung and head and neck cancers, while oxaliplatin is used against colorectal cancer, which is resistant to cisplatin [10, 11].



A) Cisplatin **B**) Carboplatin



C) Oxaliplatin



D) Satraplatin

Fig. (1). Platinum-based drugs, targeting primarily DNA.

The molecular mechanism of action of cisplatin and its analogues is quite complex (Fig. **2**). They are prodrugs whose activation occurs through dissociation of the anionic ligands, which is slow for *cis* compounds of Pt(II) [12, 13]. These compounds enter cells both by passive diffusion and transported by CTR1 the major copper influx transporter [14, 15]. Chloride ions play an important role in the mechanism of action of cisplatin and its analogues: inside the cell, the low chloride ion concentration allows the hydrolysis of these compounds; in the blood, this reaction is prevented by the high [Cl^-]. Cisplatin aquation, *i.e.* the replacement of chloride ligands with water molecules, generates the positively charged mono-aqua $[PtCl(H_2O)(NH_3)_2]^+$ ion and, more slowly, the di-aquo $[Pt(H_2O)_2(NH_3)_2]^{2+}$ ion. These species cross the nuclear membrane and bind to RNA, protein sulfhydryl groups, and DNA. The antitumour activity results from the coordination of the aquated compounds to DNA, with formation of intrastrand (less frequently interstrand) crosslinks to adjacent purine residues. Aquated cisplatin invariably reacts with the N^7 atom of purines, preferentially those of guanine residues, which bind 1,2-*cis*-$\{Pt(NH_3)_2\}^{2+}$. The chelation of two N^7 atoms of adjacent guanine residues in *cis* conformation produces a kink in the double-stranded DNA, which alters its secondary structure (Fig. **2B**). This effect is at the basis of the anticancer activity of these compounds, since it results in the inhibition of DNA replication and transcription and in the activation of signal-transduction pathways implicated in DNA-damage recognition and repair, cell-cycle arrest, and apoptosis [16-20].

Carboplatin and oxaliplatin are more water-soluble and have more favourable pharmacokinetic profiles with respect to cisplatin, mostly due to their slower rate of conversion into active aquated products [21, 22]. The rate of Pt(II)-DNA adduct formation is ten-fold slower for carboplatin, and several-fold higher doses of carboplatin can be administered compared to cisplatin. However, although carboplatin has fewer side effects with respect to cisplatin, the mechanism of action of the two drugs is the same, and the same mechanisms are involved in the onset of resistance towards both compounds. These include: decreased expression of CTR1; overexpression of the copper- and platinum-efflux proteins ATP7A and ATP7B; increased concentrations of glutathione and metallothionein, which form very stable Pt(II)-S adducts and, possibly, of enzymes involved in nucleotide excision repair and mismatch repair [15, 23-26]. Conversely, oxaliplatin retains anticancer activity against cisplatin-resistant cells [27-29]. The bulky diaminocyclohexane ligand of oxaliplatin forms DNA adducts with a narrow minor groove and a decreased kink with respect to cisplatin (Fig. **2C**), which bind mismatch repair proteins with lower affinity compared to cisplatin–GG adducts.

Toxicity, poor solubility, low bioavailability and resistance issues have prompted the search for novel platinum-based anticancer compounds containing either Pt(II) or Pt(IV), which is reduced to Pt(II) *in vivo* and can be coordinated by two additional ligands. Satraplatin (Fig. **1D**) forms intrastrand and interstrand Pt(II)-DNA adducts upon *in vivo* activation, as cisplatin does, can be administered orally, and is undergoing advanced clinical studies against hormone-refractory prostate cancer [30, 31].

Encapsulation of platinum compounds or of other metal-containing molecules into carriers has been carried out to improve drug cellular uptake or selective delivery to cancer cells. Major classes of such metal-based nanoparticles include drug conjugates and complexes, dendrimers, vesicles, micelles, core–shell particles, microbubbles, and carbon nanotubes (for a review, see Janib *et al.*, 2010 [32]).

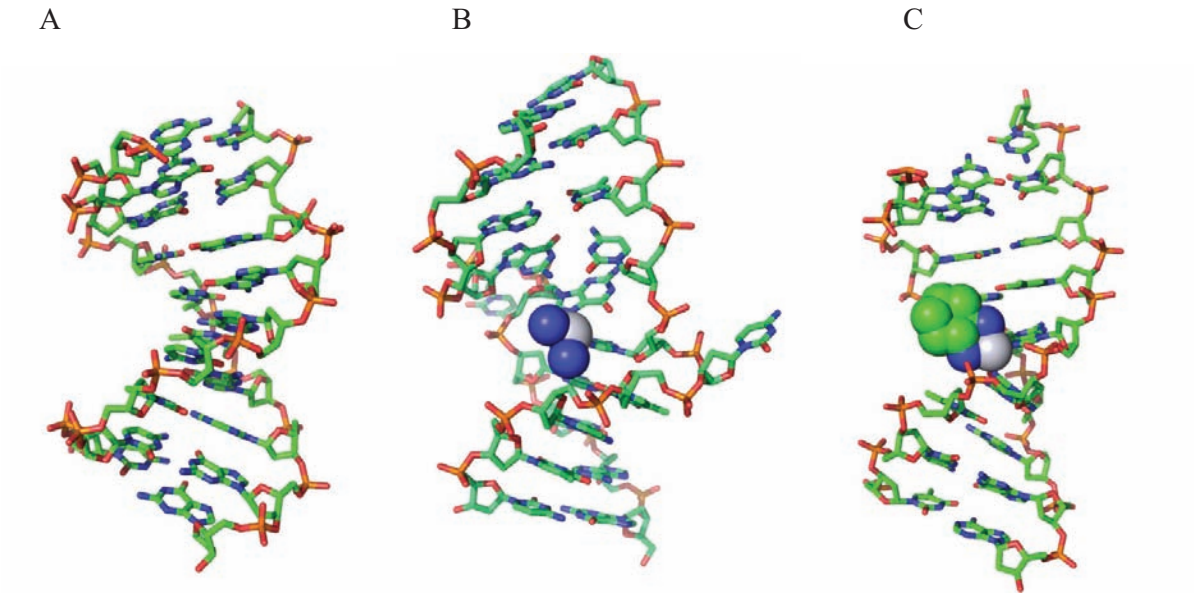


Fig. (2). Effect of cisplatin and oxaliplatin on the secondary structure of double-stranded DNA. **A**: X-ray structure of a DNA fragment (PDB ID: 2NQ1); **B**: cisplatin-GG adduct (PDB ID: 2KOT); **C**: oxaliplatin-GG adduct (PDB ID: 1A2E). Both DNA (shown in sticks), and cisplatin and oxaliplatin (both shown as spheres) are coloured by atom type: C, green; N, blue; O, red; P: orange; Pt, grey. The adducts formed by cisplatin and oxaliplatin with the N^7 atoms of two adjacent guanine residues determine a kink in the DNA double helix, which is the basis of the anticancer activity of these compounds. Significant conformational differences have been observed between the cisplatin-GG and the oxaliplatin-GG adducts, which may be related to the ability of various DNA binding proteins (e.g., DNA repair proteins and DNA polymerases) to discriminate between these adducts.

Cisplatin and oxaliplatin have been encapsulated in liposomes, within the ferritin protein, and in bacterial minicells labelled with specific antibodies [33-35]. Further, photo-activatable Pt compounds and pH-sensitive platinum-polymer derivatives have been obtained, while a Pt(IV) prodrug has been attached non-covalently to single-walled carbon nanotubes [36-38].

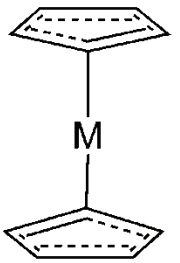
NON-PLATINUM METAL-BASED THERAPEUTICS TARGETING DNA

Like platinum, metals such as ruthenium, osmium, gallium and titanium can be coordinated by ligands. These metals undergo ligand substitution reactions whose mechanism and kinetics are similar to those of Pt(II) and, therefore, are suitable candidates for anticancer drug design.

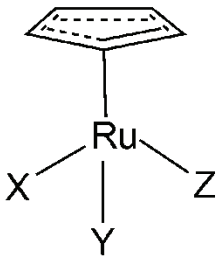
Recently, organometallic compounds, *i.e.* metal complexes containing at least one covalent metal-carbon bond, have been found to be promising anticancer drug candidates. Organometallic agents offer a wide structural variety (ranging from linear to octahedral geometries and beyond), are kinetically stable, often uncharged and rather lipophilic. Several classes of organometallics agents such as metallocenes (Fig. **3A**), half-sandwiches, carbene-, CO- or π-ligands, have been explored for the design of novel classes of drugs [39]. Half-sandwich Ru(II) arene complexes (Fig. **3B**) 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^-), have been widely explored by rational substitution of metal ligands. Some of these compounds have anticancer activity, due to the formation of adducts with DNA. Ru(II), like Pt(II), can coordinate the N^7 atoms of guanines; the extended arene moiety can intercalate within the double helix of DNA and the bidentate chelating ligand can establish additional hydrogen-bonding interactions with the C^6 carbonyl group of guanine. Such a binding mode determines distortions in the DNA double helix that are markedly different from those caused by cisplatin [40, 41]. As a consequence, these compounds are not cross-resistant with cisplatin.

Osmium(II)-arene complexes structurally analogous to Ru(II) complexes have recently been synthesized. They were shown to possess anticancer activity based on a large unwinding of double stranded DNA and not to be cross-resistant with cisplatin [42, 43].

Metal complexes have also been designed to bind specific DNA structures. Telomers, *i.e.* single-stranded ends of DNA consisting of TTAGGG repeats and known to fold into G-quadruplex structures, are interesting targets for drug design. Telomeric DNA shortens after every cell division, and telomerase, which maintains the length of the telomeric DNA, is needed to avoid cell death. In cancer cells, telomerase is overexpressed and cells have the ability to replicate indefinitely. Since telomerase accepts only single-stranded DNA, stabilization of the G-quadruplex structure is an attractive strategy to prevent telomerase from maintaining telomere length [5]. Metal-based molecules have been designed that are able to form stable complexes with G-quadruplexes. Both a Ni(II)–salphen complex and a manganese porphyrin (Fig. **3C**,**D**) have been shown to bind strongly to the telomeric quadruplex (Fig. **3E**), inhibit telomerase with IC_{50} below 1 μM and have very high selectivity for quadruplex over duplex DNA [44, 45].



A



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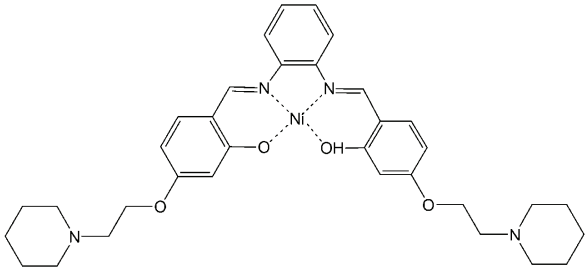

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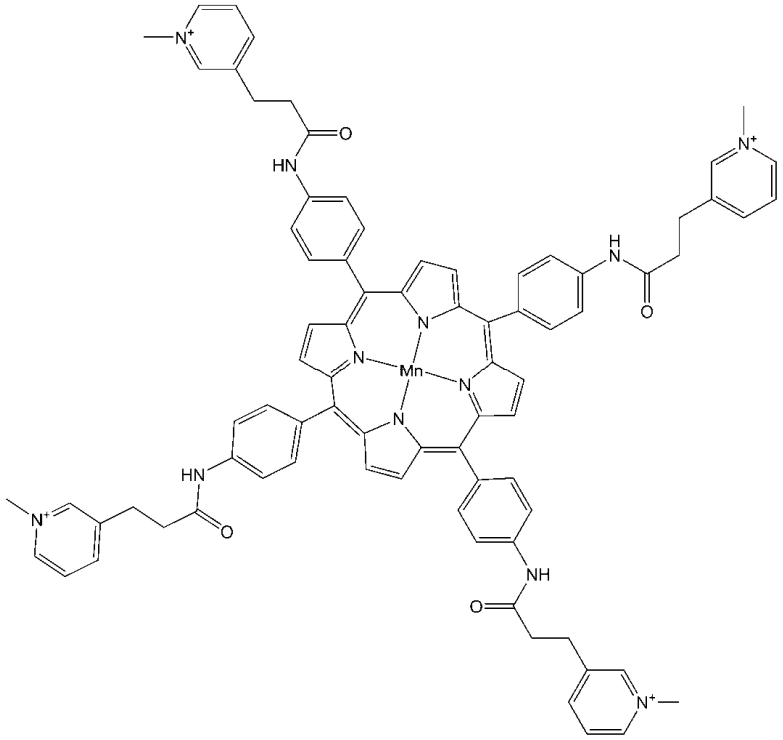

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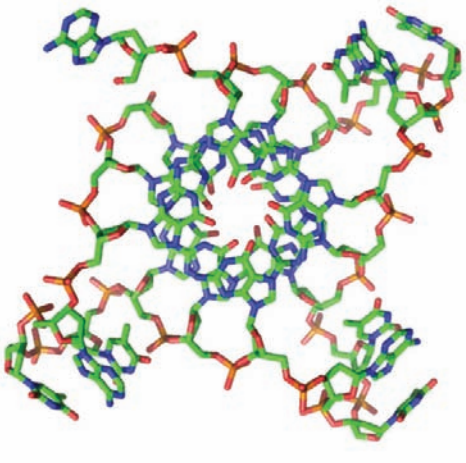

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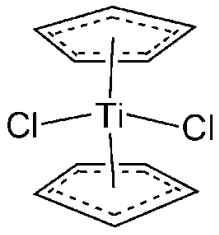

F

Fig. (3). Ruthenium-based and other metal-based anticancer compounds. **A**: Structure of metallocenes. **B**: Structure of organometallic Ru(II) arene complexes. **C**: Ni(II)-salphen compound and **D**: Mn-containing porphyrin compound designed for quadruplex-stabilization. **E**: G-quadruplex telomeric DNA (PDB ID: 1KF1). DNA is shown as sticks. **F**: Titanocene dichloride.

Ti(IV) compounds, such as titanocene complexes and budotitane, are studied as potential drugs against cancer. Titanium complexes are very reactive and unstable, and bind to DNA by intercalation and to many protein targets [46-48]. Kőpf-Maier and collaborators have studied the anticancer properties of metallocenes containing Ti, Mo, V and Nb. Based on these studies, titanocene dichloride (Fig. **3F**) was shown to be active against melanoma, prostate cancer and colon carcinoma, resulted to be less toxic than cisplatin and showed no nephro- or myelotoxicity. Therefore, it was selected as the first nonplatinum metal complex to enter clinical trials.

METAL COMPOUNDS AGAINST PROTEIN TARGETS

DNA is not always the primary target of metal-containing anticancer agents. Many of these compounds actually bind proteins more strongly than DNA [49, 50], indicating that different modes of action occur depending on the specific type of metal complex.

Eight of the amino acids commonly found in proteins, namely aspartic and glutamic acid, tyrosine, histidine, lysine, methionine, cysteine and selenocysteine, have electron-donor atoms in their side chains that are potential targets for coordination by metallo-drugs. According to Pearson's classification [51], large and polarizable ions (soft acids) and small, compact and less-polarizable ions (hard acids) form highest affinity complexes with large and polarizable ligands (soft bases) and compact and less-polarizable ligands (hard bases), respectively. In particular, aspartate, glutamate, lysine and tyrosine are considered to be hard bases, and prefer binding to hard acids such as sodium, calcium, magnesium, iron and cobalt. Methionine, cysteine and selenocysteine are soft bases, and form stable complexes with soft-acid metal ions like platinum, gold, copper, zinc and cadmium. Histidine is considered to be intermediate between soft and hard bases [51].

A number of three-dimensional (3D) structures of proteins in complex with metal-based compounds have been solved by X-ray crystallography, including: the selenoenzyme thioredoxin reductase; the cysteine proteases cathepsins; ribonucleotide reductase; topoisomerases; histone deacetylases; protein kinases; and proteasome [52-61]. Although binding to proteins and peptides contributes to drug toxicity and lack of specificity, many metal-binding proteins represent interesting anti-cancer targets.

Thioredoxin reductase (TrxR) and glutathione reductase (GR) are redox enzymes essential for antioxidant defence and redox homeostasis. Since they are overexpressed in many tumour cell lines and associated with apoptosis and cancer proliferation, TrxR and GR are regarded as valuable targets for anticancer therapy [62]. Au(I) compounds are strong inhibitors of TrxR, since they bind with high affinity to selenocysteine residues at the enzyme active site. Phosphole–gold(I) complexes inhibit both TrxR and GR at nanomolar concentrations (Fig. **4**). Au(III) porphyrins exhibit potent *in vitro* and *in vivo* anticancer activity towards hepatocellular and nasopharyngeal carcinoma, while Au(III) thiocarbamates are more cytotoxic than cisplatin *in vitro*. Gold compounds induce mitochondria-dependent apoptosis, probably via proteasome inhibition [63-69]. The crystal structure of the Au(I)-phosphole-GR complex, where two gold atoms are bound to the enzyme, is shown in (Fig. **4**).

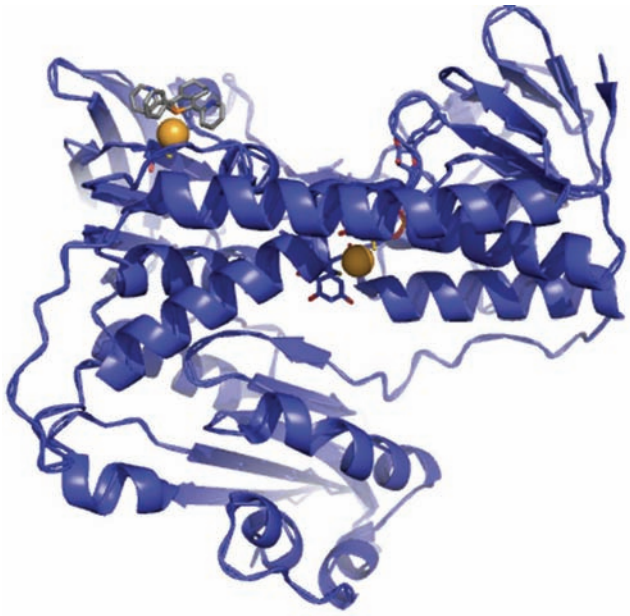

Fig. (4). Gold(I) inhibits human glutathione reductase. The 3D structure of human GR in the presence of Au(I)-phosphole contains two gold atoms (shown as spheres) bound to the enzyme (PDB ID: 2AAQ). α-Helices and β-strands are shown as ribbons and arrows, respectively.

Two Ru(III) complexes are currently in clinical trials (Fig. **5A**,**B**), namely trans-[$RuCl_4$(DMSO)(Im)]ImH (NAMI-A, where Im = imidazole) and trans-[$RuCl_4(Ind)_2$]IndH (KP1019, where Ind = indazole). Both compounds are prodrugs, which need to be reduced *in vivo* to Ru(II) to be active [70]. However, they have a different spectrum of interaction with targets, since NAMI-A has been shown to be active against metastases as well, while KP1019 is active mostly against primary tumors [71, 72]. NAMI-A interacts with DNA *in vitro*, but its pharmacological activity relies mostly on its interaction with specific proteins. It inhibits neoangiogenesis by modulating the action of protein kinase C, dephosphorylating the extracellular signal-regulated kinase (ERK) and inhibiting c-myc transcription. Additionally, it has powerful anti-invasive properties depending on its ability to interact with and activate β1 integrins.

Compounds such as gallium nitrate and the orally administrable gallium maltolate (Fig. **5C**) have antitumour, immunosuppressive and anti-inflammatory activity, and do not cross-react with other chemotherapeutics. Gallium compounds, used for the treatment of hypercalcemia associated with malignancies, interfere with iron metabolism and inhibit the iron-dependent activity of the enzyme ribonucleotide reductase, which plays a key role in DNA synthesis. Additionally, they induce apoptosis in human lymphoma cell lines through an intrinsic mitochondrial pathway that involves the activation of the proapoptotic Bax protein, loss of mitochondrial membrane potential, release of cytochrome c from the mitochondria, and the activation of caspase-3 [73].

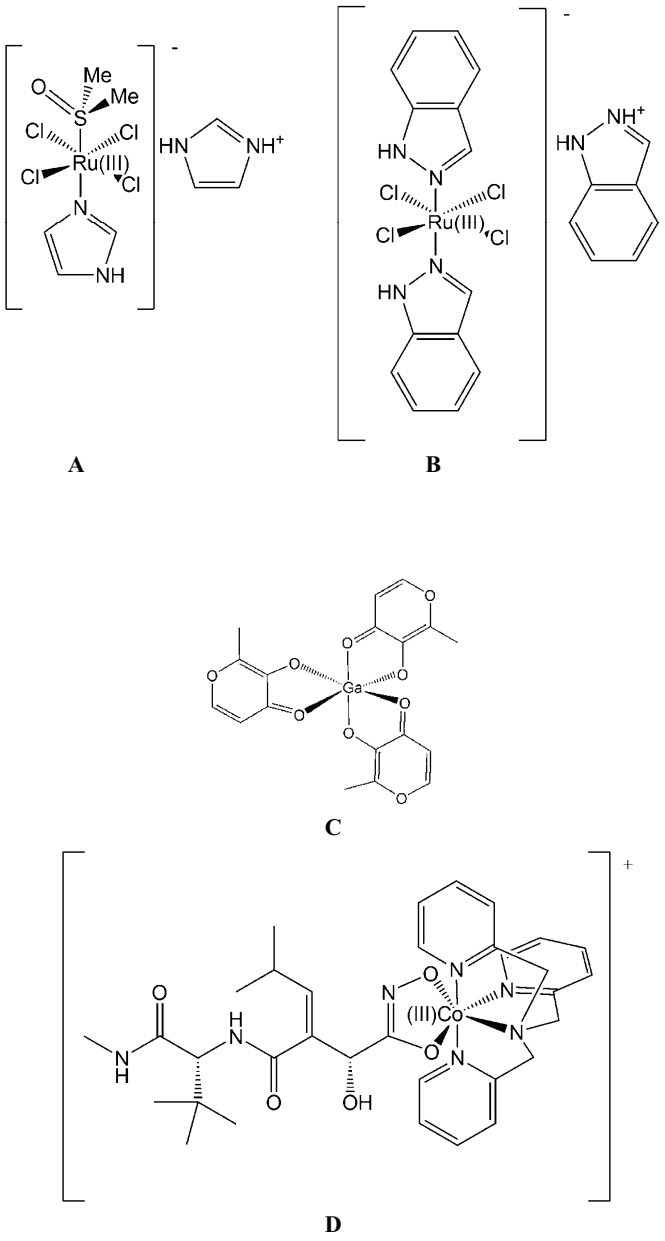

Fig. (5). Anti-cancer metal compounds interacting primarily with protein targets. **A**: NAMI-A; **B**: KP1019; **C**: gallium maltolate; **D**: marimastat-Co(III)-derivative.

A different approach uses the toxic metal as a chaperone for selective delivery of established inhibitors to target proteins that are overexpressed in cancer cells. An example is provided by the complex of the matrix metalloproteinase (MMP) inhibitor marimastat to a Co(III)-derivative [74] (Fig. **5D**). MMPs are overexpressed in tumours with poor prognosis. Cobalt provides an inert scaffold for marimastat transport to the target cells. *In vivo* reduction of the prodrug yields the more labile Co(II)-complex, which releases the inhibitor. Cobalt–alkyne analogues of the non-steroidal anti-inflammatory drug acetylsalicylic acid inhibit cyclooxygenase and are highly toxic in breast cancer cell lines [75]. Other interesting drugs include the kinetically inert organometallic ruthenium complexes designed to mimic staurosporine, a natural inhibitor of protein kinases that controls signalling pathways involved in cancer (e.g., GSK-3 and Pim-1). One of these half-sandwich compounds inhibits Pim-1 in picomolar concentrations by binding to the protein ATP-binding site (Fig. **6**). Additionally, it activates p53 and induces apoptosis in human melanoma cells [76-78].

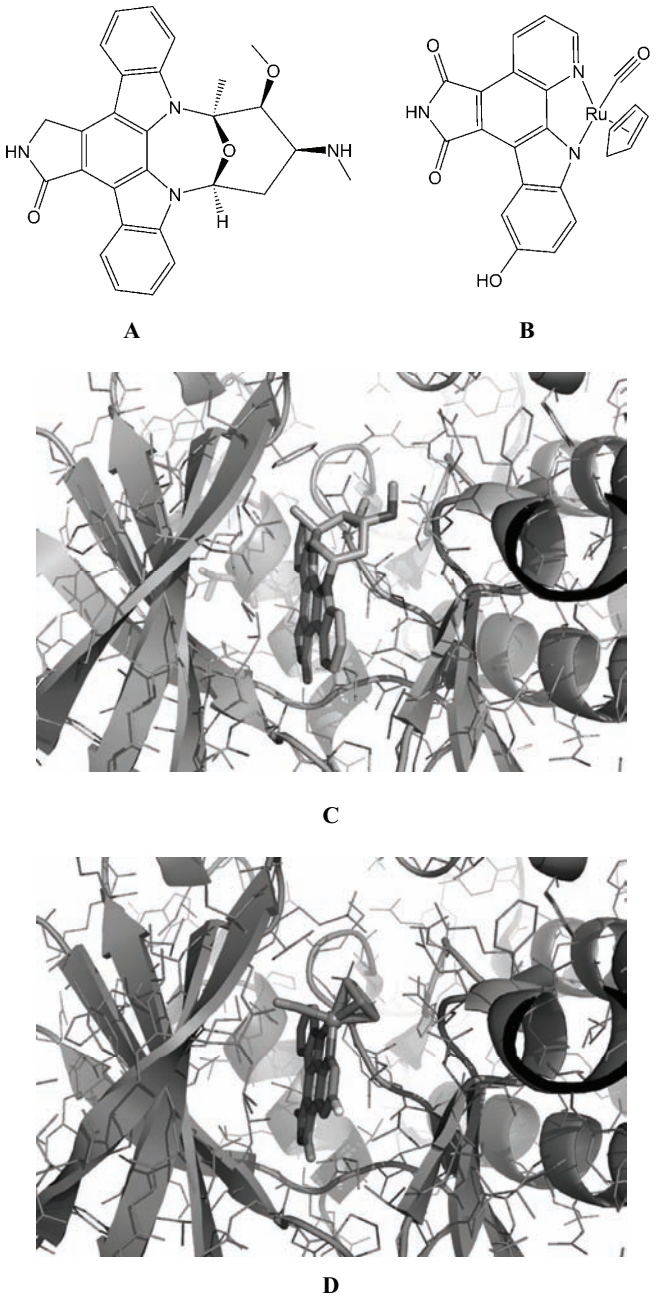

Fig. (6). Organometallic compounds mimicking staurosporine, a specific inhibitor of enzymes important for cancer onset. **A**: staurosporine; **B**: Ru complex mimicking staurosporine; **C**: Crystal structure of Pim-1 in complex with staurosporine (PDB ID: 1YHS) **D**: Crystal structure of Pim-1 in complex with the organometallic inhibitor (PDB ID: 2BZI). In both panels C and D the inhibitor is shown as sticks and protein residues, α-helices and β-strands are shown as lines, ribbons and arrows, respectively.

METAL-CONTAINING COMPOUNDS AGAINST OTHER DISEASES

Gold(I) complexes such as auranofin [1-thio-β-D-glucopyranosato-(triethylphosphine)gold 2,3,4,6-tetraacetate] (Fig. **7A**), gold sodium thiomalate, gold thioglucose and others have been used for decades against rheumatoid arthritis. These gold-thiol drugs act on multiple targets. They inhibit many enzymes, including the serine esterases elastase and cathepsin G; can inactivate the first component of complement (C1); inhibit lysosomal hydrolytic enzymes, such as acid phosphatases and ß-glucuronidase; reduce all classes of immunoglobulin and serum rheumatoid factors; and hamper lymphoblastogenesis *in vitro* by directly inhibiting mononuclear phagocytes. In particular, auranofin has a strong inhibitory effect on lymphocyte functions (for a review, see Kean and Kean, 2008 [79]).

Only a few drugs are effective against parasitic diseases like malaria, trypanosomiases and leishmaniases. The most widely used antimalarial drug is currently chloroquine (CQ). However, after twenty years of successful use, CQ-resistant malarial parasites have started to emerge and spread. Metal-chloroquine complexes like Ru(II)-CQ and Au(I)-CQ, and organo-Ru(II)-CQ compounds are effective against several *Plasmodium* species resistant to CQ [80, 81]. Ferroquine (FQ) is the ferrocenyl analogue of CQ, is currently undergoing clinical studies (Fig. **7B**). FQ derivatives are strong antimalarial compounds, which couple iron-dependent radical generation with the inhibition of β-hematin formation, essential to the survival of the malaria parasite. Powerful trioxaferroquine compounds have also been synthesized, which contain a 1,2,4-trioxane moiety covalently linked to FQ. As a result, these compounds combine, within a single structure, an iron(II) species, a 1,2,4-trioxane, as in artemisinin, and a substituted quinoline, as in chloroquine [82, 83]. Other metallodrugs such as auranofin, aurothiomalate, triethylphosphine gold(I) chloride, cisplatin, the Ru(III) complex NAMI-A, mononuclear and dinuclear gold(III) complexes, and compounds containing bismuth or antimony are endowed with antiplasmodial properties [84].

Many metal-based agents have been developed against trypanosomatides, the aetiological agents of trypanosomiases and leishmaniases. These compounds belong to three classes: i) metal complexes of trypanocidal ligands (e.g., clotrimazole, ketoconazole, 5-nitrofuryl and 5-nitroacroleine containing thiosemicarbazones; 2-mercaptopyridine N-oxide); ii) metal complexes of DNA intercalators, such as (2,2':6'2''-terpyridine)-Pt(II); iii) metal compounds acting as direct inhibitors of parasite enzymes (e.g., Pd(II) and Au(III) cyclometallated complexes; Re(V) complexes, which inhibit cruzipain, the major cysteine protease of *Trypanosoma cruzi* [84-86]). These metal-based agents have been shown to be effective against *Trypanosoma* parasites *in vivo* or *in vitro*.

To date, the classic first-line treatment against *Leishmania* species relies on pentavalent antimonial derivatives, such as meglumine antimonate and sodium stibogluconate, which have been used for decades (Fig. **7C**,**D**). Both are prodrugs that become active upon *in vivo* reduction to Sb(III). The determination of the 3D structure of *Leishmania infantum* trypanothione reductase (TR) in complex with NADPH and Sb(III) by X-ray crystallography [87] revealed the mechanism of enzyme inhibition by antimonial agents. Upon NADPH binding, the trivalent antimony ion binds to the protein active site residues Cys52, Cys57, Thr335 and His461' (from the symmetry related subunit) with high affinity, strongly inhibiting enzyme activity (Fig. **8**).

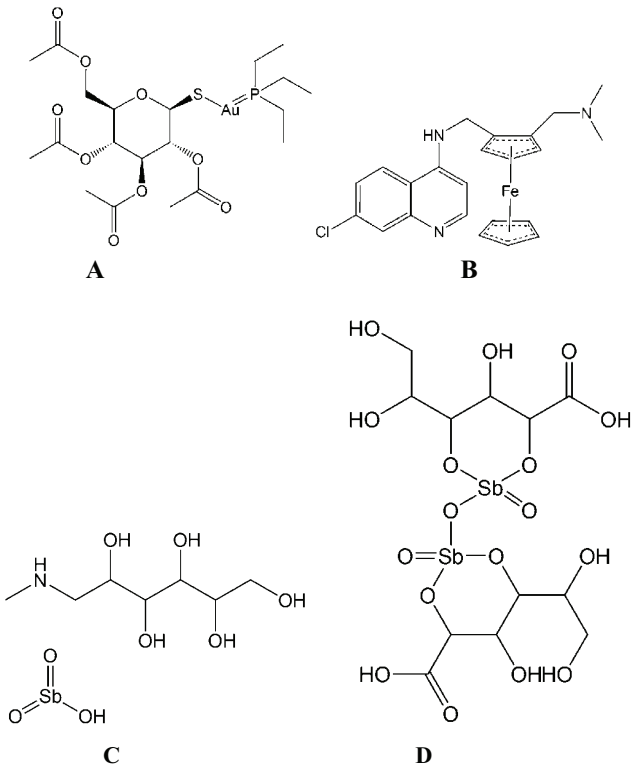

Fig. (7). Metal compounds against diseases. **A**: Auranofin. **B**: Ferroquine, the ferrocenyl analogue of Chloroquine; **C**: meglumine antimoniate (Glucantim); **D**: sodium stibogluconate (Pentostam).

METAL COMPLEXES FOR DIAGNOSING DISEASES

Many metals are used in medical diagnosis. The most extensively studied paramagnetic metal ions are transition metal ions (*i.e.*, high-spin Mn(II) and Fe(III), each having five unpaired electrons) and lanthanides (essentially Gd(III), having seven unpaired electrons). Gadolinium is quite toxic to mammals but chelated Gd(III) compounds are far less toxic. The contrast agent Gd-DTPA has been administered to more than 20 million patients. To improve the diagnostic efficacy of contrast agents many approaches have been attempted, including coupling to: i) antibodies against membrane receptors selectively expressed by specific cell types; ii) transferrin, whose receptor is over-expressed by tumour cells; iii) annexin V, a protein that binds to phosphatidylserine, as a marker of apoptosis [2].

Technetium is the lowest atomic number element without any stable isotopes: every form of it is radioactive. Nearly all available technetium is produced synthetically and only trace amounts are found in nature [88]. The vast majority of the Tc-99m ("m" indicates that this is a metastable nuclear isomer) used in medicine is produced upon decay of Mo-99

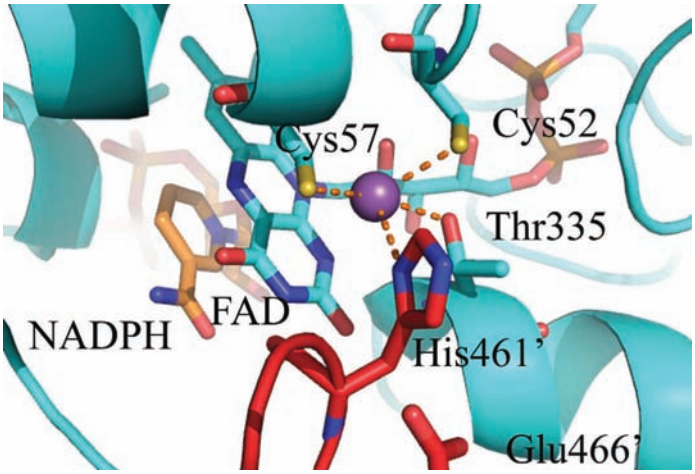

Fig. (8). Antimonial compounds inhibit TR from *Leishmania* parasites. Crystal structure of the complex between *Leishmania infantum* TR, NADPH, FAD and Sb(III). The two symmetry related subunits of the enzyme are shown as ribbon and coloured cyan and red, respectively; residues in the TR active site, NADPH and FAD are shown as sticks and coloured by atom type: N, blue; O, red; S, yellow; C, cyan in FAD and residues from the first TR subunit, red for residues from the second TR subunit and orange in NADPH; Sb(III) is a purple sphere. Sb(III) binds directly to the TR active site residues Cys52, Cys57 and Thr335 from one subunit and His461' from the other, thereby blocking hydride transfer and trypanothione reduction.

Table 1. Mechanisms of Anticancer Actions and Side Effects of Metal-Containing Compounds.

Compound	Mechanism of Action	Side Effects	References
Au(I), Au(III) compounds (porphyrins, thiocarbamates)	Inhibition of thioredoxin reductase and glutathione reductase	Protein binding	[62-69]
Co(II) compounds (Cobalt alkynes)	Analogue of acetylsalicylic acid: inhibition of cyclooxygenase		[75]
Co(III) compounds	Reduced *in vivo* to Co(II), with release of marimastat: inhibition of matrix metalloprote	Induction of metastases	[74]
Ga(III) compounds (nitrate, maltolate)	Inhibition of ribonucleotide reductase, apoptosis		[73]
Mn(III)-porphyrin	Stabilization of G-quadruplex telomeric structure		[45]
Ni(II)-salphen complex	Stabilization of G-quadruplex telomeric structure		[44]
Os(II) compounds	DNA intrastrand crosslink; inhibition of DNA replication and transcription, apoptosis	Binding of proteins and RNA; resistance	[42,43]
Pt(II) complexes (Cisplatin, Oxaliplatin, Carboplatinum)	Prodrugs. DNA intrastrand crosslink; inhibition of DNA replication and transcription, apoptosis	Binding of proteins and RNA; resistance	[15-26]
Pt(IV) complexes Satraplatin	Prodrug, reduced *in vivo* to Pt(II). DNA intrastrand crosslink; inhibition of DNA replication and transcription, apoptosis	Binding of proteins and RNA; resistance	[30,31]
Ru(II) complexes	DNA intrastrand crosslink; inhibition of DNA replication and transcription, apoptosis	Binding of proteins and RNA; resistance	[40,41]
Ru(II) structural complexes	Ru(II): scaffolding role in a complex mimicking staurosporine: inhibition of GSK-3 and Pim-1, activation of p53, apoptosis		[76-78]
Ru(III) complexes (NAMI-A, KP1019)	Reduced *in vivo* to Ru(II); DNA intrastrand crosslink, binding of kinases and integrins.		[70-72]
Ti(IV) compounds (titanocene, budotitane)	DNA intercalation	Protein binding	[46-48]

Table 2. Mechanisms of Action of Metal-Containing Compounds for Therapy against Rheumatoid Arthritis and Parasite Infections.

Compound	Mechanism of Action	Side Effects	References
Au(I), Au(III) compounds (auranofin, gold thiomalate, gold thioglucose)	Anti-arthritic effect: Inhibition of many protein targets. Anti-parasitic activity (Plasmodium, Leishmania …)	Aspecific protein binding	[79, 84]
Bi(III), Bi(V) compounds	Antiparasitic activity (Plasmodium); Many targets: proteins, DNA	Aspecific protein binding	[84]
Fe(II) compounds: ferroquines	Antimalaria. Many targets: lipids, hematin (inhibition of hemozoin formation), generation of reactive oxygen species		[80-83]
Pd(II) cyclometallated complexes	Antitrypanosoma, antileishmania. Inhibition of cysteine protease		[86]
Pt(II) compounds	DNA metallointercalator with antileishmanial activity	Binding of proteins and RNA	[84,85]
Re(V) cyclometallated ompounds	Antitrypanosomal and antileishmanial activity. Inhibition of cysteine protease		[86]
Sb(V) compounds)	Prodrugs. Bioreduction to Sb(III). Binding to trypanothione reductase; binding to trypanothione.	Aspecific protein binding. Resistance. Cardiotoxicity, renal insufficiency, anemia, pancreatitis, leucopenia.	[87]

from an instant generator. Tc-99m is used in radioactive isotope medical tests as a radioactive tracer that medical equipment can detect in the human body. It emits 140 keV gamma rays, and its half-life is 6.01 hours (about 94% of this isotope decays in 24 hours). At least 31 commonly used radiopharmaceuticals for imaging and functional studies of the brain, myocardium, thyroid, lungs, liver, gallbladder, kidneys, skeleton, blood, and tumours are based on Tc-99m [89].

CONCLUSIONS

The significant progress in the use of metals in medicine that has taken place in recent years has been mostly based on a deeper understanding of the mechanism of action and pharmacological effects of metal-based compounds. The rational design of new metal-based drugs has yielded many new molecules with reduced toxicity and high specificity. Application of new methodologies, including the screening of large libraries of compounds, such as those generated by combinatorial chemistry, which has been extensively used in organic drug discovery, will be beneficial for the development of novel classes of metal-based compounds as therapeutics.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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