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Current applications and future potential for bioinorganic chemistry in the development of anticancer drugs

Sabine H. van Rijt and Peter J. Sadler

Department of Chemistry, University of Warwick, Coventry CV4 7AL, UK

This review illustrates notable recent progress in the field of medicinal bioinorganic chemistry as many new approaches to the design of innovative metal-based anticancer drugs are emerging. Current research addressing the problems associated with platinum drugs has focused on other metal-based therapeutics that have different modes of action and on prodrug and targeting strategies in an effort to diminish the side-effects of cisplatin chemotherapy.

Introduction

Metals – in particular, transition metals – offer potential advantages over the more common organic-based drugs, including a wide range of coordination numbers and geometries, accessible redox states, 'tune-ability' of the thermodynamics and kinetics of ligand substitution, and a wide structural diversity. Medicinal inorganic chemistry is a thriving area of research [1–4], which was initially fueled by the discovery of the metallopharmaceutical cisplatin about 40 years ago. Today, more than 30 years after its approval as a chemotherapeutic agent, cisplatin is still one of the world's best-selling anticancer drugs. It is mainly used in the treatment of ovarian, head and neck, bladder, cervical and lymphomas cancers. Over the past decades, several cisplatin analogs have been screened as potential antitumor agents, but of these, only two (carboplatin and oxaliplatin) have entered worldwide clinical use [5].

Regardless of the achievements of current platinum drugs, there are some major drawbacks: they are efficient only for a limited range of cancers; some tumors can have acquired or intrinsic resistance; and they often cause severe side-effects, such as nausea, bone marrow suppression and kidney toxicity. Although approximately ten other platinum compounds are currently in clinical trials, the cisplatin derivatives have not been able to address sufficiently many of the disadvantages associated with cisplatin. There is a need, therefore, for new approaches that are purposefully designed to circumvent these drawbacks. The field of metal-based anticancer drug design can be divided into two different approaches: classical and nonclassical chemotherapeutics [6,7].

Cisplatin's mode of action involves distortion to DNA. Here, we use the term 'classical chemotherapeutics' to refer to drugs that target DNA. Classical drugs based on other metals can address the problems associated with platinum drugs and are attracting increasing interest. At present, several metal-based compounds are known to have promising antiproliferative effects in a wide range of tumors with novel modes of DNA binding; this will be discussed in the section 'Classical nonplatinum metal compounds'.

Corresponding author: Sadler, P.J. (p.j.sadler@warwick.ac.uk)

SABINE VAN RIJT

Sabine van Rijt was born in the Netherlands in 1981. She obtained her BSc in 2004 and MSc in 2006 at Leiden University. She is currently a PhD student working on the design of osmium arene anticancer complexes in Professor Peter Sadler's group at Warwick University. Her research interests are centered on the chemistry of metal complexes in biology and medicine.

PETER SADLER

Peter Sadler obtained his BA, MA and DPhil at the University of Oxford and then spent two years as a Medical Research Council Research Fellow in Molecular Pharmacology at the University of Cambridge and the National Institute for Medical Research. In 1973 he was appointed as a lecturer in Chemistry at Birkbeck College, University of London, where he subsequently became reader in Biological Inorganic Chemistry, and professor of Chemistry. In 1996 he was appointed to the Crum Brown chair of Chemistry at the University of Edinburgh, and in June 2007 took up a chair in Chemistry at the University of Warwick where he is also Head of Department. He is a fellow of the Royal Society of Edinburgh (FRSE) and the Royal Society of London (FRS). His research interests are centered on the chemistry of metals in medicine and the design of novel therapeutic agents.

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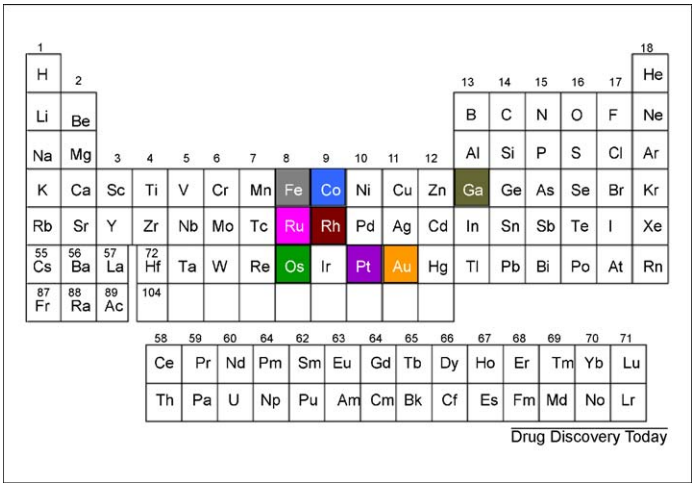

FIGURE 1

Periodic table with color coding for the metals discussed in this review.

Recent progress in the field of cell biology has resulted in the discovery of receptors and growth factors that are upregulated in cancer cells. These provide new targets for anticancer drug design. Examples of nonclassical chemotherapeutics with proteins and enzymes as targets are emerging; this will be discussed in the section 'Nonclassical metal compounds'.

In addition, there is continuing interest in designing drugs that can be activated selectively in the tumor by cellular processes or controlled external activation. Extensive studies on the behavior of metal complexes under biologically relevant conditions have revealed some promising approaches for targeted anticancer drug design with classical and nonclassical targets ('Prodrug strategies').

The metals discussed in this review are highlighted in Fig. 1.

Classical nonplatinum metal compounds

Nuclear DNA is considered to be the ultimate target of cisplatin and related platinum therapeutics. Before DNA attack, cisplatin undergoes aquation. Although the activated (aquated) cisplatin can interact with other biomolecules, its antitumor activity derives from its capability to form bifunctional DNA crosslinks, which causes the DNA to distort (kink, Fig. 2a [8]). The platinum-induced kink in the DNA is considered to be the crucial lesion that leads to a chain of events that includes protein recognition (e.g. by HMG) and eventual apoptosis [9].

In this section, some examples of other metal-based therapeutics that target DNA are given. Their exploration might result in drugs that produce distinctly different lesions on DNA and

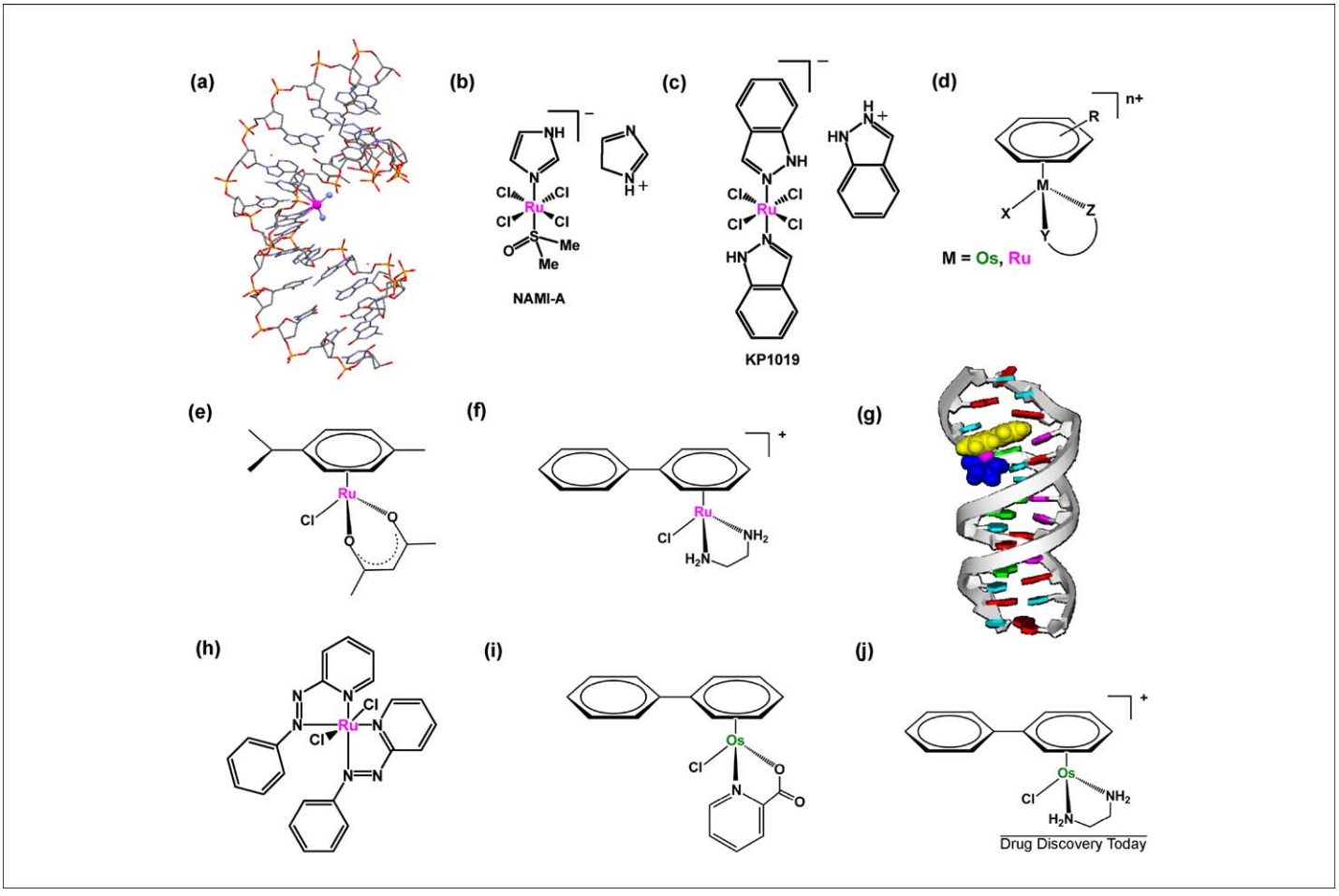

FIGURE 2

Examples of metal-based compounds that target DNA. **(a)** X-ray structure showing the kinking of DNA by cisplatin (pdb1aio). **(b)** NAMI-A. **(c)** KP1019. **(d)** General structure of organometallic ruthenium(II) and osmium(II) arene complexes. **(e,f)** Examples of cytotoxic Ru^{II} arene complexes. **(g)** Model showing intercalation of a Ru^{II} arene complex into DNA. **(h)** [γ-Ru(azpy)$_2$Cl$_2$]. **(i,j)** Examples of cytotoxic Os^{II} arene complexes.

overcome acquired or inherent cisplatin resistance or might prove to be more active toward tumors that are nonresponsive to current chemotherapy.

Ruthenium

Ruthenium compounds containing Ru^{II} or Ru^{III} are considered to be suitable candidates for anticancer drug design because they exhibit a similar spectrum of kinetics for their ligand substitution reactions as platinum(II). Several ruthenium compounds display promising anticancer activity, and two ruthenium(III) complexes have entered clinical trials: *trans*-[$RuCl_4$(DMSO)(Im)]ImH (NAMI-A, where Im = imidazole, Fig. 2b) and *trans*-[$RuCl_4(Ind)_2$]IndH (KP1019, where Ind = indazole, Fig. 2c). NAMI-A is more active against metastases than against primary tumors [10]. By contrast, the structurally similar KP1019 is active against primary tumors [11]. 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 [12]. 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, Fig. 2d). These half-sandwich 'piano-stool' complexes offer much scope for design, with the potential to vary in each of the building blocks (arene, chelated ligand YZ and monodentate ligand X) to enable modifications of thermodynamic and kinetic parameters.

Some of the half-sandwich Ru(II) arene complexes display promising *in vitro* and *in vivo* anticancer activity [13] (Fig. 2e,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 [14]. These additional interactions result in unique modes of binding to duplex DNA and structural distortions that are distinctly different from those caused by cisplatin [15] (Fig. 2g). This might explain why these compounds are not crossresistant 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 seems to have an enormous effect on their kinetics and even changes their nucleobase selectivity [16]. 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 [17].

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 and γ, Fig. 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 γ isomers show higher toxicities than the β isomer [18]. Indeed, DFT calculations suggest that the ability of the isomers to intercalate into DNA decreases from γ > α > β isoforms [19]. Recently, several isomeric forms of multinuclear ruthenium complexes with bridging azpy ligands have been reported [20]; the γ/γ isomeric form exhibits the highest cytotoxicity, more than 30-fold higher than cisplatin in breast cancer cells.

Osmium

The anticancer potential of osmium, the heavier congener of ruthenium, has been explored recently. 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 (Fig. 2i,j) [21,22]. 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 [23,24]. The Os^{II} arenes are believed to interact with DNA in a similar manner to their ruthenium analogs (i.e. binding to N7 of guanine in combination with H-bonding and noncovalent 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 [25]. These osmium complexes do not display crossresistance with cisplatin toward cancer cells, suggesting promise for addressing the problem of intrinsic or acquired resistance in chemotherapy.

Nonclassical metal compounds

The traditional platinum-based therapeutics and the organometallic complexes discussed in the previous section owe their anticancer activity to their nonrepairable interaction with DNA and make use of the fast replication and mitotic processes of malignant cells. Drugs that are able to target cellular signaling pathways overexpressed in cancer cells provide attractive approaches for anticancer drug design. Although less studied than the metallodrug–DNA interactions, some examples of metallodrugs that interact with specific proteins and enzymes are given below.

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 cisplatin-resistant cell lines [26]. Their cytotoxicity is mediated by their ability to inhibit mitochondrial human glutathione reductase (hGR) and thioredoxin reductase (hTrxR) irreversibly [27]. In particular, phosphol-containing gold(I) complexes (Fig. 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) analogs 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 and easily reduced to metallic gold under physiological conditions [29]. In recent years, however, several gold(III) compounds that incorporate ligands to increase the stability to the gold(III) center have been reported. For example, gold(III) porphyrins (Fig. 3b) exhibit *in vitro* and *in vivo* activity in hepatocellular and nasopharyngeal

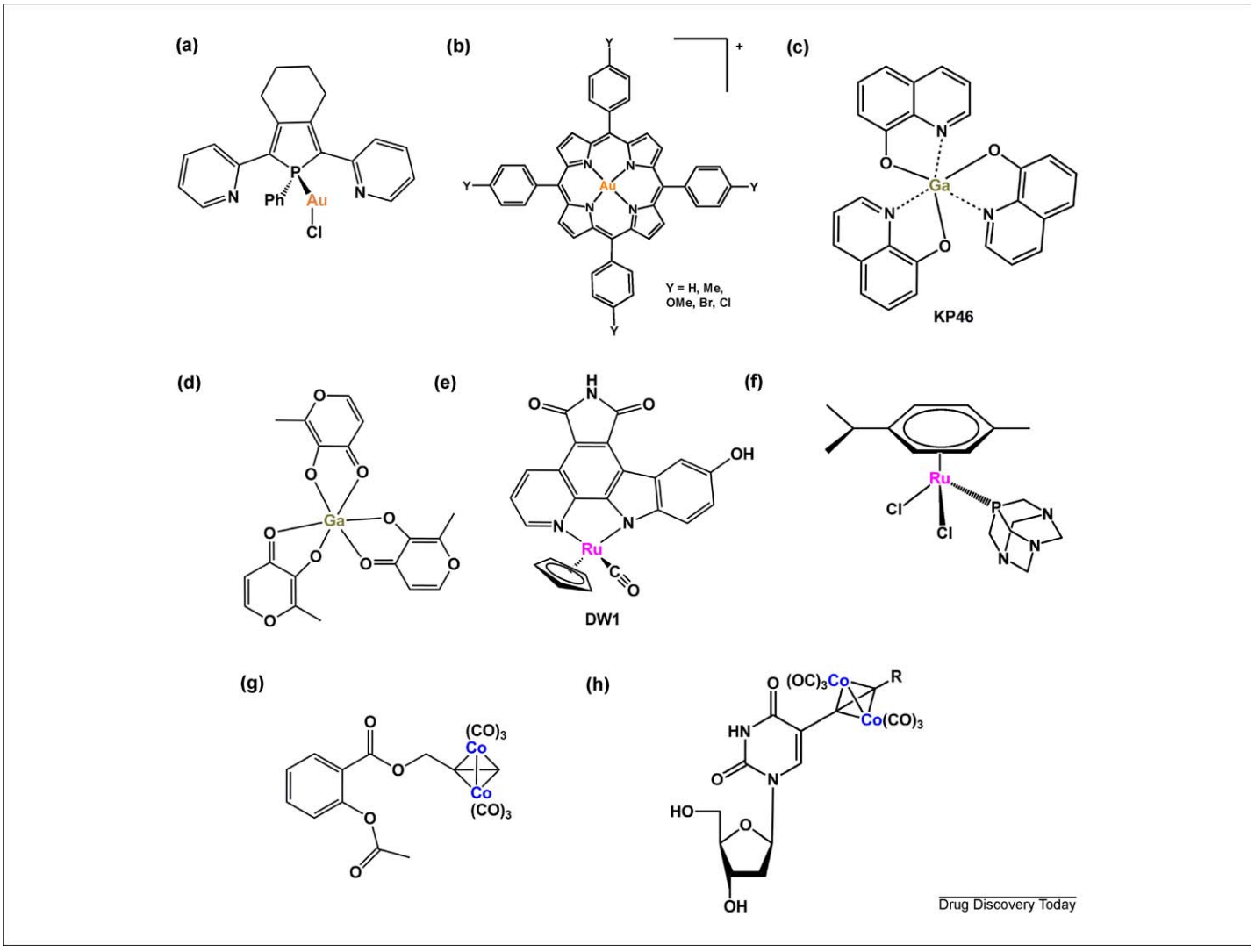

FIGURE 3

Examples of metal-based anticancer drugs that target proteins and enzymes. **(a)** Gold(I) phosphole complex. **(b)** Gold(III) meso-tetraarylporphyrins complexes. **(c)** KP46. **(d)** Gallium tris-maltolate. **(e)** DW1. **(f)** Ru^{II} arene complex containing a monodentate phosphaadamantane (pta) ligand. **(g)** Cobalt–alkyne analog of the anti-inflammatory drug aspirin. **(h)** Hexacarbonyl dicobalt complex containing a nucleoside ligand.

carcinoma [30]. Other gold(III) compounds with promising biological activity include gold(III) bipyridyl compounds [31], dinuclear gold(III) oxo complexes [32] and gold(III) dithiocarbamates [33]. For these compounds, the mitochondria and the proteasome are thought to be targets [34].

Gallium

The chemical behavior of gallium(III) is similar to that of ferric iron (Fe^{III}) but differs in that Ga^{III} is nonreducible 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 (Fig. 3c,d) – are being investigated in clinical trials [35]. Their mechanism of action is associated with the inhibition of ribonucleotide reductase (RR). The enzyme RR catalyzes 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; it is highly expressed in tumor cells.

Ruthenium

Interestingly, Meggers *et al.* [36] have developed kinetically inert organometallic complexes that act as scaffolds to mimic the organic enzyme inhibitor staurosporine, a potent inhibitor of various kinases. In these metal-based inhibitors, the carbohydrate unit of staurosporine is replaced with ruthenium fragments [36] (Fig. 3e). Structural variation by substitution of the ligands on the metal results in picomolar protein kinase inhibitors. They are highly toxic toward human melanoma cells. The ruthenium staurosporine bioconjugate was recently investigated as an inhibitor for glycogen synthase kinase, a major regulator of p53 localization and expression. The ruthenium staurosporine complex acts as a potent p53 activator and induces apoptosis in otherwise chemoresistant melanoma cells [37].

A family of organometallic Ru^{II} compounds containing monodentate phosphaadamantane (pta) ligands exhibits moderate *in vitro* activity, and some compounds show no activity in healthy cells up to millimolar concentrations. The pta compounds show little activity against primary tumors *in vivo*, although they exhibit

some capacity to reduce lung metastases derived from a mammary carcinoma xenograft grown in mice [38]. The cytotoxicity of the Ru^{II} pta compound, [Ru(η^6-*p*-cymene)Cl_2(pta)] (Fig. 3f), in EAC cells is thought to be mediated by mitochondrial and Jun-N (amino)-terminal kinase (JNK)–p53 pathways [39].

Cobalt

Some hexacarbonyl dicobalt complexes exhibit promising activity against several human cancer cell lines [40]. In particular, a cobalt–alkyne analog of the anti-inflammatory drug aspirin is potently active in breast cancer cell lines (Fig. 3g). Its toxicity has been attributed to its ability to inhibit cyclooxygenase-1 and -2 [41]. This seems to be a promising approach because the inhibition of cyclooxygenase delays tumor growth and improves response to conventional cancer therapies.

Another hexacarbonyl dicobalt series of compounds containing nucleoside ligands (Fig. 3h) displays antiproliferative activities with IC_{50} values in the range of 5–50 μM in human breast cancer cell lines [42].

The family of cysteine cathepsin proteases has been validated recently as an important enzymatic class to target in cancer. More specifically, cathepsin B and L have been 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 [43], dinuclear palladium complexes (biphosphinic palladacycle complexes) [44] and several oxorhenium(V) complexes [45].

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 [46–48].

Prodrug strategies

Delivery of metal-based drugs to their targets poses one of the biggest challenges in cancer chemotherapy. A drug needs to be sufficiently reactive to bind to the biological target but not so reactive that it will be deactivated by the many biomolecules encountered on the way. One strategy involves the design of prodrugs. Prodrugs are drug derivatives that can undergo a transformation *in vivo* to release the active species, with improved physiochemical, biopharmaceutical and pharmacokinetic properties. For metal-based therapeutics, this prodrug activation might be realized by a photochemical process [49], by oxidation or reduction of the metal or a ligand, or by ligand substitution. This requires extensive knowledge of ligand substitution rates, redox potentials, photochemistry and choice of metal and, in addition, the effect of the other coordinated ligands in the complex.

In recent years, there has been a focus on making prodrugs selective. To achieve this, the prodrug has to be activated by specific physiological characteristics of tumors, such as the reducing environment of the cell, pH or cancer cell permeability. Some examples of different prodrug strategies, including tumor selectivity and drug delivery strategies, will be discussed in the following paragraphs.

Photoactivation as a prodrug strategy

The activation of a metal-based prodrug can be realized by photochemical means. The advantage of using light as an external stimulus is that it enables local treatment of the tumor, minimizing side-effects. The poor penetration of tissue by short-wavelength light, however, is a serious limitation: longer wavelength light (red) penetrates more deeply than UVA light. For a photochemical treatment to be effective in the clinic, the wavelength of activation should be within the range 350–900 nm; shorter wavelengths cause damage to tissue, and higher wavelengths usually carry insufficient energy to activate the prodrug. Currently used in the clinic, photodynamic therapy (PDT) treats readily accessible tumors (i.e. skin, neck and bladder) by the administration of a nontoxic photosensitizer and subsequent irradiation of the tumor site [50]. Upon irradiation, the photosensitizer, typically a porphyrin, becomes excited and this energy is transferred to ground-state triplet oxygen ($^3O_2$) to form highly reactive singlet oxygen ($^1O_2$), leading to cell death. Metal-bound porphyrins can have marked effects on the tumor-localizing properties of the photosensitizer. Indeed, metal-containing photosensitizers for cancer treatment are currently well represented in clinical trials and include a lutetium porphyrin derivative (Lutetium texaphyrin) [51,52], CGP55847 (Zn), Photosense (Al) and Purlytin (Sn) [53]. All these photosensitizers need oxygen to generate their cytotoxic effects; however, cancer cells are often deficient in oxygen.

Rhodium

Recently, several Rh and Ru complexes that exhibit oxygen-independent light-induced anticancer activity, have been reported. For example, Barton *et al.* have shown that several octahedral Rh^{III} complexes with extended diimine ligands (Fig. 4a) bind only weakly to DNA in the absence of light but on photoactivation bind to DNA and cleave the DNA backbone with high specificity for mismatched DNA [54,55]. Recently, the effects of variation of the ancillary ligand on the ability of these compounds to target DNA mismatches *in vitro* and *in vivo* have been explored [56].

Platinum

The general kinetic inertness of Pt^{IV} complexes compared to Pt^{II} complexes has been widely exploited in the design of potential prodrugs. The Pt^{IV} compound satraplatin, [Pt(cha)$Cl_2(OAc)_2(NH_3)$] (where cha is cyclohexylamine; Fig. 4b), has been abandoned recently in phase III clinical trials for the treatment of hormone-refractory prostate cancer [57]. Substitution reactions of Pt^{IV} complexes under physiological conditions are very slow or do not take place at all. Therefore, intracellular reduction to Pt^{II} is thought to be essential for cytotoxic activity. This reduction might be achieved by cellular reducing agents (discussed in the next section) or by irradiation with light, enabling site-specific activation of the drugs [58].

trans-Dihydroxido platinum(IV) prodrugs containing two azido ligands in *trans* or *cis* positions relative to each other are nontoxic in the dark but show cytotoxicity toward various human cancer cell lines upon irradiation [59,60]. In particular, a Pt^{IV} diazido complex containing pyridine *trans* to ammonia, *trans*,*trans*,*trans*-[$Pt(N_3)_2(OH)_2(py)(NH_3)$] (Fig. 4c), is up to 80 times more cytotoxic than cisplatin in ovarian cancer cells upon irradiation but inactive and stable toward biological reductants in the dark. One photoactivation pathway for these complexes (among several possibilities) involves ligand-to-metal charge transfer from the azido ligands to Pt^{IV}, resulting in reduction to the reactive Pt^{II} species.

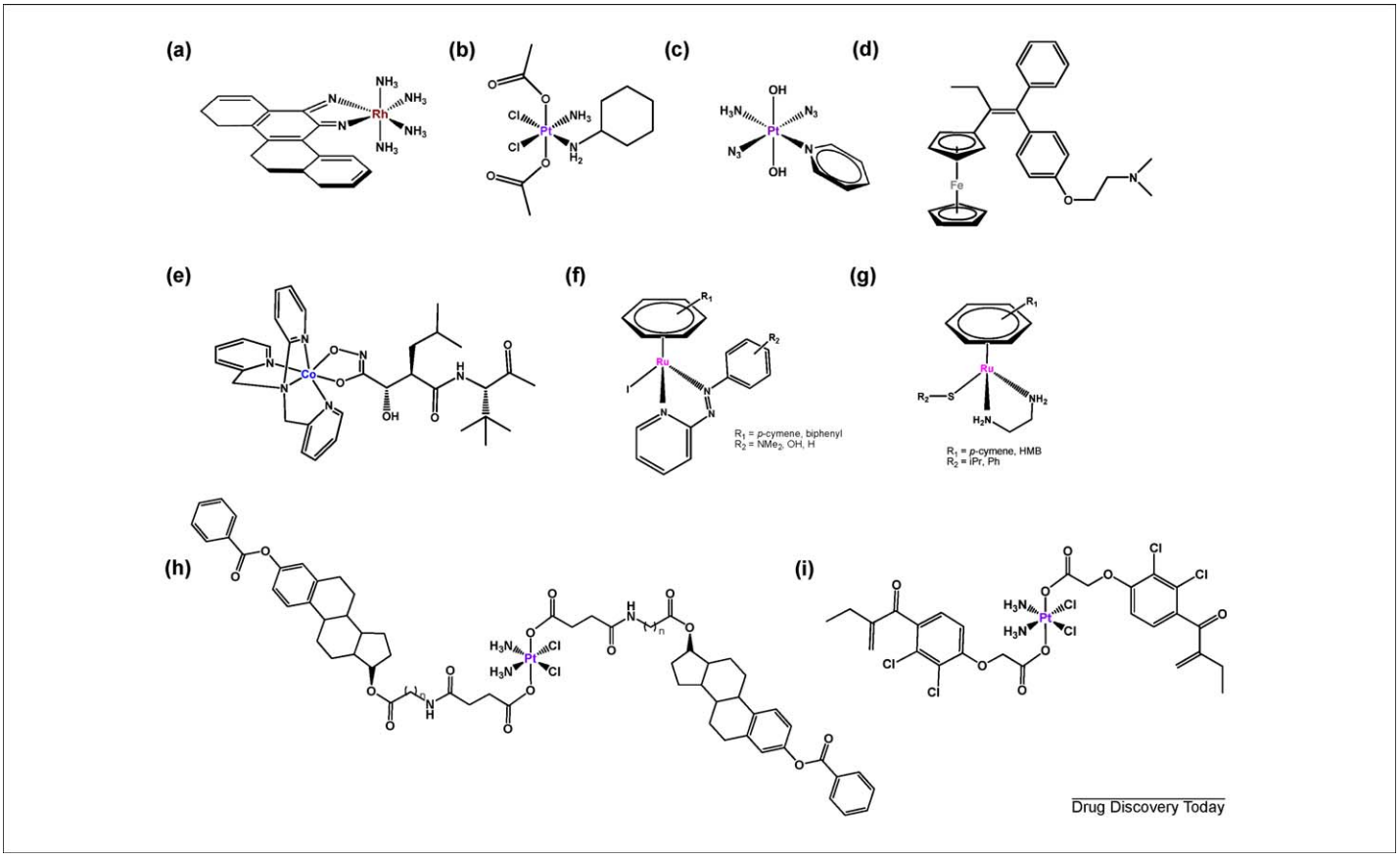

FIGURE 4

Prodrug strategies. **(a)** Example of a photoactivatable octahedral Rh^{III} complex with an extended diimine ligand. **(b)** Satraplatin. **(c)** Example of a photoactivatable *trans*-azido platinum(IV) prodrug. **(d)** Ferrocifen. **(e)** Cobalt–marimastat bioconjugate. **(f)** Ru^{II} arene complexes containing iodo and phenylplazopyridine ligand. **(g)** Ru^{II} arene complexes containing a thiolate ligand. **(h)** Pt(IV)–estradiol bioconjugate. **(i)** Ethacraplatin.

The produces azidyl ($N_3^{\bullet}$) radicals that rapidly combine and decompose to produce nitrogen gas. Aquation of the Pt^{II} compound and subsequent binding to DNA (and possibly proteins) leads to its cytotoxic effect. Notably, the mechanism of DNA platination by the *trans*-azide complex is different from cisplatin, and cell death is not solely dependent on activation of the caspase 3 pathway [61]. It is apparent that photoactivation can produce excited states with unusual reactivity and provide routes to intervening in biological pathways not available to ground-state drugs.

Redox activation as a prodrug strategy

The redox behavior of metal complexes offers chemical reactivity that is not accessible to purely organic molecules and, therefore, can yield novel metallodrugs with new mechanisms of drug action. For the prodrug to be successful, the metal complex should possess biologically accessible redox potentials. Tuning their properties to the reducing environments of tumor cells might lead to novel targeted strategies.

Iron

Well-established examples are ferrocene derivatives of the breast cancer drug tamoxifen [62,63] (Fig. 4d). They display potent activity against both estrogen-dependent and estrogen-independent breast cancer cells, whereas tamoxifen alone is active only against estrogen-dependent cells. The activity of the ferrocene tamoxifen derivatives (ferrocifens) in estrogen-independent cells is attributed to the redox properties of the Fe^{II} complex, leading to oxidative damage to DNA. The mechanism of action of ferrocifens in estrogen-dependent cells is likely to be similar to that of tamoxifen itself. It is noteworthy that one of the most active ferrocene derivatives exhibits less toxicity than tamoxifen itself. A recent study on ferrocene tamoxifen derivatives with modified side chains has established the minimal structural requirements to obtain cytotoxicity [64].

Cobalt

A prodrug approach for the inhibition of enzymes by cobalt complexes has been explored by Hambley *et al.* [65]. Their strategy involves the complexation of the matrix metalloproteinase (MMP) inhibitor marimastat to a Co^{III} complex to achieve selective delivery of MMP to the tumor (Fig. 4e). The resulting Co^{III} complex provides an inert carrier system for the transportation of the inhibitor. The prodrug is activated by a bioreduction pathway producing a labile Co^{II} complex, which results in the release of the MMP inhibitor. The hypoxic nature of the tumor should prevent oxidation back to the cobalt(III) complex, thus achieving selective release in tumor cells. Indeed, increased cytotoxicity was observed for the cobalt prodrug in *in vivo* tumors in mice compared to the MMP inhibitor alone. Unfortunately, both the inhibitor and the prodrug promote metastasis.

Ruthenium

Half-sandwich ruthenium arene complexes containing iodo and phenylazopyridine ligands (Fig. 4f) exhibit remarkable inertness toward ligand substitution in aqueous solution but are highly toxic in human ovarian and lung cancer cells. Whereas azopyridine ligands alone are difficult to reduce, these azopyridine Ru^{II} complexes have reduction potentials that are biologically accessible. The toxicity of these complexes can be attributed to their ability to induce redox reactions inside the cell leading to reactive oxygen species. Interestingly, the redox cycle involves the oxidation of the strong reducing agent glutathione present in millimolar concentrations, in the presence of micromolar concentrations of the ruthenium complex [66].

Organometallic ruthenium arene complexes containing thiolato ligands (e.g. Fig. 4g) can be activated by oxidation [67]. Under physiologically relevant conditions, the monodentate thiolato ruthenium complex is capable of efficient acceptance of an oxygen atom from an intermediate in glutathione (GSH) oxidation. This shows that GSH can act as a source of reactive oxygen species, able to induce oxidation of organometallic complexes that are themselves stable in air [68]. Ruthenium sulfenate adducts seem to be more labile than the parent thiolato complexes (e.g. toward DNA binding), perhaps through protonation of the sulfenato oxygen atom.

Platinum

The relative kinetic inertness of six-coordinate octahedral Pt^{IV} complexes can be used as a prodrug approach to overcome some of the problems associated with (four-coordinate, square-planar) cisplatin. For this, intracellular reduction to Pt^{II} is essential for activation and cytotoxic activity. The two extra ligands in the axial positions enable the inclusion of different kinds of bioactive ligands, which might lead to platinum anticancer complexes with improved efficacy.

In one such approach, an attempt to target specifically estrogen-positive malignancies (such as breast and ovarian cancers) led to the design of several estrogen-tethered platinum(IV) complexes [69] (Fig. 4h). This is a cancer drug target because estrogen-receptor-positive breast cancer cells treated with estrogen are more sensitive to cisplatin. Upon intracellular reduction, the complex releases cisplatin and two molecules of estrogen derivative. The latter induces upregulation of the high-mobility group domain protein HMGB1 in a human breast cancer cell line. The HMGB1 protein shields platinated DNA from nucleotide-excision repair.

In an attempt to overcome cisplatin resistance, a similar approach has been used to inhibit glutathione-*S*-transferase (GST), the main cellular defence against xenobiotics. For this, Dyson *et al.* [70] attached the GST inhibitor ethacrynic acid to a Pt^{IV} complex (ethacraplatin, Fig. 4i).

In recent years, effort has also been given to the design of novel drug delivery systems that are capable of increasing the cellular uptake, as well as directed delivery, of metallodrugs only to tumor cells. Interesting approaches include attachment of a platinum drug to a pH-sensitive polymer [71], attachment of a Pt^{IV} prodrug noncovalently to single-walled carbon nanotubes [72], encapsulation of platinum drugs in lipid-based nanocapsules [73] and attachment of the SV4-40T antigen nuclear localization signal to metallocenes [74].

Concluding remarks

Metal coordination complexes offer a versatile platform for the design of novel anticancer agents. Their properties can be distinct from those of purely organic compounds. Particularly attractive for study are the first-, second- and third-row transition metals, which have variable oxidation states, coordination numbers and the ability to bind to a wide variety of types of ligands (e.g. halides, O, S, N, P and C). In particular, metals in the second and third rows often exchange their ligands slowly, on minutes-to-hours timescales that enable 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 prodrugs; ligand substitution can activate the metal complex toward 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 that can occur *in vivo*; for example, the aquation of metal–chloride bonds as the chloride concentration diminishes from extracellular to intracellular (cytoplasmic and nuclear) compartments.

In addition, both metal-centered and ligand-centered redox processes are of interest. The former can trigger activation by ligand release (e.g. reduction of substitution-inert Co^{III} to labile Co^{II}), and the latter can trigger 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 that can overcome some of the disadvantages associated with cisplatin therapy, including the reduction of side-effects, widening the spectrum of activity, and resistance.

Finally, it is worth emphasizing the subtlety with which ligands control the reactivity of transition metal ions and, also, the reciprocal effects that metal ions can have on the properties of ligands. Both the metal and the ligands can have important roles in the recognition of target sites. The subtle effects exerted by ligands can be both steric and electronic in nature. Modern theoretical methods (e.g. Amsterdam Density Functional Theory) and techniques (e.g. high-resolution electrospray mass spectrometry and multinuclear polarization transfer NMR spectroscopy) are likely to aid our understanding of the chemical and biochemical reactivity of metal complexes and the construction of meaningful structure–activity relationships. For this purpose, studies of the chemistry of metal complexes under physiologically relevant conditions (e.g. biological screening conditions) become very important.

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