ADVANCES IN METALLODRUGS
Preparation and Applications in Medicinal Chemistry

Edited by Shahid-ul-Islam, Athar Adil Hashmi, Salman Ahmad Khan
Advances in Metallodrugs
Emerging Trends in Medicinal and Pharmaceutical Chemistry

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Advances in Metallodrugs

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Over the past few decades, medicinal inorganic chemistry as an interdisciplinary sub-area of bioinorganic chemistry has received the growing attention of researchers in the search for promising antimicrobial, antimalarial, antiviral, and antitumor chemotherapeutic agents. An excellent compilation of reports on metal complexes has revealed the potency of metal complexes as better therapeutic agents. Metal-containing drugs have several promising advantages over organic ligands and have gained the trust of researches after the worldwide approval of the drug cisplatin. Their distinct mechanism of action makes them perfect candidates as alternatives to the conventional drugs to which resistance has already been shown. In this direction, a huge number of transition metal complexes have been synthesized and evaluated for their biological profiles.

This book is organized into 12 important chapters that focus on the progress made by metal-based drugs as anticancer, antibacterial, antiviral, anti-inflammatory, and anti-neurodegenerative agents, as well as highlights the application areas of newly discovered metalloids. It can prove beneficial for researchers, investigators, and scientists whose work involves inorganic and coordination chemistry, medical science, pharmacy, biotechnology, and biomedical engineering.

We are indebted to all the authors for their commitment and for bringing their knowledge and professional experience to making this project a reality. Last but not least, the editors would like to thank Mr. Martin Scrivener, President of Scrivener Publishing, USA, who accepted and supported this project.

Shahid-ul-Islam
Athar Adil Hashmi
Salman Ahmad Khan
April 2020
Metallo drugs in Medicine: Present, Past, and Future Prospects

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Department of Chemistry, Aligarh Muslim University, Aligarh, India

Abstract

Metal coordination complexes on account of their unique properties of metals which includes variable oxidation states, geometry, coordination numbers, redox behavior, and ability to bind to a wide variety of types of ligands offer a versatile platform for the design of novel therapeutic and diagnostic agents. The therapeutic potential of metal ions can be optimized by tethering it to a suitable framework that not only tune but synchronize the organic ligand scaffold to act in concord at the target site. Medicinal inorganic chemistry is a growing interdisciplinary field of pharmaceutical research which involves design of therapeutic and diagnostic agents with emphasis on medicinal use for the treatment of various chronic diseases. The serendipitous discovery of cisplatin, inorganic anticancer drug opened up new prospects in the area of medicinal inorganic chemistry that not only cured cancer but provided a continuous spur towards the development of new metallo drugs that can address the serious challenges in the drug regime. Thus, many metal-based therapeutics and diagnostic agents have been explored extensively for their diverse applications as artificial metalloenzymes, DNA foot-printing agents, and nucleic acid structural probes, etc. Given the premises of metallo drugs in the medicinal field, this chapter focuses on the progress made by metal-based drugs as anticancer, anti-bacterial, anti-viral, anti-inflammatory, and anti-neurodegenerative agents, as well as emphasis on the new strategies to be used in the development of new potential metallo drugs.

Keywords: Medicinal inorganic chemistry, metallo drugs, metal-coordination complexes, therapeutic and diagnostic agents, chronic diseases, drug delivery, prodrugs

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1.1 Introduction

Medicinal inorganic chemistry is an interdisciplinary sub-area of bioinorganic chemistry field which tethers the applications of inorganic chemistry and biological disciplines, thereby investigate the intriguing properties of metal ions, their complexes, and other metal binding compounds for the therapeutic and diagnostic purposes [1–6]. Conceptually, the field of medicinal inorganic chemistry includes the biomimetic chemistry of metal ions in metalloproteins [7, 8], identification of metal ions in pathogenic protein misfolding [9, 10], functions of endogenous and exogenous metal ions at the molecular level [11, 12], and the homeostasis of metal ions in living systems [13]. The use of several metals (Cu, Au, Ag, Hg, and As) can be traced back to ancient civilizations (Mesopotamia, Egypt, India, and China) [14] with the recognition by the Egyptians who used copper to sterilize water with an understanding of disinfection and the Chinese and Arabs utilized gold in the treatment of many chronic diseases [15]. Zinc was found to promote healing of wounds while mercurous chloride was used as a diuretic. Paul Ehrlich the “founder of chemotherapy” developed arsenical, Salvarsan, as a drug for the treatment of Syphilis in early twentieth century (Figure 1.1) [16]. Thus, a link between the discovery of a new elements and their application into the medicinal armamentarium (therapeutic and diagnostic) has been exploited since antiquity (Table 1.1).

Numerous metal ions and their complexes have been routinely administered to patients for therapeutic and diagnostic benefit such as platinum and ruthenium complexes in cancer therapy [17–20], gold complexes as anti-arthritis agents [21, 22], cobalt complexes as antiviral [23], and gadolinium and technetium as magnetic resonance imaging (MRI) contrasting agents [24–26] (Figure 1.2).

Metal ions can serve many important functions in the biological systems; (i) functional role, i.e., the biological activity is due to direct binding

Figure 1.1 Structures of arsenic-based therapeutic drug, salvarsan (3-amino-4-hydroxyphenyl-arsenic(III) compounds).
Table 1.1  The use of metal salts and their compounds as therapeutic and diagnostic agents.

<table>
<thead>
<tr>
<th>Metal</th>
<th>Metal-based salt/compound</th>
<th>Therapeutic/diagnostic use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag</td>
<td>Silver sulphadiazine</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>Al</td>
<td>Al(OH)₃</td>
<td>Antacid</td>
</tr>
<tr>
<td>As</td>
<td>Salvarsan, Melarsen, Tryparsamide</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>Au</td>
<td>Gold(I) thiolates</td>
<td>Antitumour</td>
</tr>
<tr>
<td></td>
<td>Auranofin</td>
<td>Antiarthritis</td>
</tr>
<tr>
<td>Ba</td>
<td>Barium sulphate</td>
<td>X-ray contrast</td>
</tr>
<tr>
<td>Bi</td>
<td>Bismuth subsalicylate, colloidal bismuth citrate</td>
<td>Antacid, antiulcer</td>
</tr>
<tr>
<td>Cu</td>
<td>Copper histidine complex</td>
<td>Menkes disease</td>
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<tr>
<td></td>
<td>Casiopeinas</td>
<td>Anticancer</td>
</tr>
<tr>
<td>Co</td>
<td>Coenzyme B₁</td>
<td>Supplement</td>
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<td></td>
<td>Doxovir</td>
<td>Antiviral</td>
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<tr>
<td>Fe</td>
<td>Sodium nitroprusside</td>
<td>Vasodilator</td>
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<td></td>
<td>Fe(III) desferrioxamine chelates</td>
<td>Antimicrobial</td>
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<tr>
<td>Gd</td>
<td>Gd metallotexaphyrin (Magnevist, Dotarem)</td>
<td>MRI contrast agent</td>
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<td></td>
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<td>Radiopharmaceuticals</td>
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<td>Hg</td>
<td>Mereurochrome</td>
<td>Antiseptic</td>
</tr>
<tr>
<td>Li</td>
<td>Li₂CO₃</td>
<td>Manic depression</td>
</tr>
<tr>
<td>Pt</td>
<td>Cisplatin, carboplatin, oxaliplatin, nedaplatin etc</td>
<td>Anticancer</td>
</tr>
<tr>
<td>Ru</td>
<td>NAMI-A, KP10109, RAPTA-C etc</td>
<td>Anticancer</td>
</tr>
<tr>
<td>Sb</td>
<td>Pentostam, N-methylglucamine antimonate</td>
<td>Antileishmanial</td>
</tr>
<tr>
<td>Tc</td>
<td>⁹⁹ᵐ⁹⁹ᵐ₇₀Tc (V) propyleneamine oxime</td>
<td>Diagnostic imaging</td>
</tr>
<tr>
<td>Ti</td>
<td>Titanocene dichloride, bis(β-diketonato) Ti(IV)</td>
<td>Anticancer</td>
</tr>
</tbody>
</table>

(Continued)
Table 1.1 The use of metal salts and their compounds as therapeutic and diagnostic agents. (Continued)

<table>
<thead>
<tr>
<th>Metal</th>
<th>Metal-based salt/compound</th>
<th>Therapeutic/diagnostic use</th>
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<td>V</td>
<td>Bis(maltolato) oxovanadium(IV)</td>
<td>Antidiabetic</td>
</tr>
<tr>
<td></td>
<td>Bis(glycinato) oxovanadium (IV)</td>
<td></td>
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<td></td>
<td>Bis(methylpicolinato oxovanadium (IV)</td>
<td></td>
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<tr>
<td>W</td>
<td>PolyoxometalJates</td>
<td>Anti-HIV activity</td>
</tr>
<tr>
<td>Zn</td>
<td>ZnO</td>
<td>Skin ointment</td>
</tr>
<tr>
<td></td>
<td>Zn(II)bicyclam complexes</td>
<td>Antiviral</td>
</tr>
<tr>
<td></td>
<td>Zinc citrate/sulphate</td>
<td>Supplement</td>
</tr>
<tr>
<td>Zr</td>
<td>Zr(IV) glycinato</td>
<td>Antiperspirant</td>
</tr>
</tbody>
</table>

Figure 1.2 Prominent examples of metal-based drug in medicinal inorganic chemistry: (a) Cisplatin, (b) MS–325, (c) Darinaparsin, and (d) Auranofin.
of the metal fragment to the target site [27], (ii) structural role, i.e., the shape of the complex is determined and binding to the biological target occurs through non-covalent interactions [28–30], (iii) act as a carrier for active ligands that are delivered in vivo [31, 32] and protect the ligand before its delivery at the target site, (iv) metal complexes behave as a catalyst in vivo by the production of reactive oxygen species (ROS) that cause cell damage [33, 34], and (v) metal complexes which are photoactive can act as photosensitizers [35, 36]. Metal ions once introduced into a bio system for therapeutic or diagnostic effect can also be removed from back by the judicious use of the chelating ligands (chelation therapy). Many proteins and enzymes bind one or more metal ions to perform their functions where the metal ion is involved in the catalytic mechanism or stabilizes the tertiary and quaternary structure of proteins.

Whereas the small organic drug molecules rely purely on carbon, their binding geometry in space is dictated by the hybridization, viz., sp (linear), sp² (trigonal-planar), and sp³ (tetrahedral) as compared to the diverse geometry in 3D space open to metal-based drugs [37]. Besides linear, square planar, and tetrahedral geometries, pyramidal, trigonal bipyramidal, and octahedral shapes can be created and even higher coordination numbers and geometries with larger metal ions are possible, all of these geometries exhibit a tremendous importance for biological phenomena that allow the fine-tuning of their chemical reactivity in terms of both kinetics (rates of ligand exchange) and thermodynamics (strengths of metal-ligand bonds, redox potentials, etc). Not only the metal but also the ligands can play important roles in biological activity, ranging from outer-sphere recognition of the target site to the activity of any released ligands and ligand centered redox processes. Modification of substituents or ligands around the metal center, thus modulates drug entities to perform manifold functions and at specific target sites to combat chronic diseases, viz., cancers, HIV-AIDS, cardiovascular, cerebrovascular diseases, and respiratory disorders [38]. Since metal ion can participate in biological redox reactions, and many transition metals (Pt, Ru, Fe, Cu) possessing variable oxidation states offer many possibilities for strategic designs of new chemotherapeutics. Many literature reports reveal that the redox properties of the metal ions or the ligands can influence the mechanism of action of metal-based anticancer chemotherapeutic drugs [39–41]. Thus, in metal complexes, it is possible to trigger a desired biological response at the site of action and at the optimum time by controlling the activation process by substitution (ligand exchange) and/or redox processes.
Advances in Metallodrugs

One of the biggest challenges in enhancing the therapeutic potential of a metallodrug is its delivery to the selective targets. It is imperative for a prospective drug to demonstrate sufficient reactivity towards the selective biological target but less affinity towards other biomolecules encountered on the way which render its deactivation. Prodrugs are drug derivatives that can undergo in vivo transformation to release the active species, with improved physiochemical, biopharmaceutical, and pharmacokinetic properties [42, 43]. The application of prodrug strategy encompasses the use of polymeric conjugate materials and other inclusions of metallodrug in liposomes, protein macromolecules, lipid-based systems, and dendrimers as drug carriers that limit its interaction with biomolecules other than the selected targets [44]. For metal-based therapeutics, this prodrug activation can be accomplished by in vivo ligand substitution, photochemical process and/or redox reactions before reaching the target site. It is thus important to ascertain the active part of the metal complex which is essential for therapeutic activity; the metal itself, the ligands and the intact delivery system. Thus, a rational state-of-art design of therapeutic and diagnostic agents is required to achieve specific targeting features and control toxicity (side effects) which can be achieved by controlling thermodynamic and kinetic processes of metal complexes.

1.2 Therapeutic Metallodrugs

1.2.1 Anticancer Metallodrugs

Cancer is a class of disease in which a group of cells display uncontrolled growth (division beyond the normal limits), invasion (intrusion and destruction of adjacent tissues), and sometimes metastasis (spread to other locations in the body via lymph or blood) [45]. Current statistics indicate that one in every three people will develop some form of cancer during their lifetime. It is estimated that by 2030, there will be 21.4 million new cases diagnosed every year [46]. Most cancerous cells divide uncontrollably to form lumps or masses of tissue called tumors but some like leukemia (where cancer prohibits normal blood function by abnormal cell division in the blood stream) do not [47]. The complexity of the disease however, arises mainly due to the fact that cancers evolve from different tissues of origin, shows multiple etiologies or endless combinations of genetic or epigenetic alterations. The primary treatment modalities include surgery, chemotherapy, radiations, and immunotherapy, etc [48]. However, the mainstay treatment is based on chemotherapy which a viable alternative
involving various natural and synthetic origin compounds that can kill or halt the unwanted proliferation of cancerous cells.

Metal-based antitumor chemotherapeutics gained prominence after the phenomenal serendipitous discovery of the archetypical inorganic drug, cisplatin (\textit{cis}–diamminedichloroplatinum(II), [\textit{cis}–(\text{NH}_3)_2\text{PtCl}_2]) by B. Rosenberg in 1965 [49]. Cisplatin is one of the most effective chemotherapeutic drug used for treating solid malignancies, \textit{viz.}, bladder, melanoma, non–small cell lung, small cell lung, head and neck, cervical, ovarian, and testicular cancers (>90% cure rate) [50]. Currently, it is used in 32 of 78 treatment regimens in combination with a wide range of other drugs including: topoisomerase II inhibitors (doxorubicin, etoposide, and bleomycin), mustards (cyclophosphamide, melphalan and ifosfamide), and antimetabolites [51].

\subsection*{1.2.1.1 Mechanism of Anticancer Action}

Cisplatin initially enters inside the cell \textit{via} both passive diffusion and active uptake where it undergoes a ligand substitution event prior to DNA binding. Noticeably, inside the bloodstream (extracellular), cisplatin is relatively stable and maintains its neutral state, due to the high concentration of chloride ions (~100 mM). However, inside the cell (intracellular), the relatively low chloride ion concentration (~4–12 mM) causes cisplatin to undergo aquation, in which a chloride ligand is replaced by a water molecule resulting in the formation of cis–\([\text{Pt(NH}_3)_2\text{Cl(H}_2\text{O)}]\)^+ species having half-life of ca. 2 h for the aquation reaction. The positive charged platinum complex is a potent electrophile that is attract to the negatively charged nuclear DNA at the N7 position of purine bases of DNA with a release of the water molecule [52]. The remaining cis-monochloride species ([Pt(NH}_3)_2\text{Cl(H}_2\text{O)}]) is then subsequently aquated diaqua species ([Pt(NH}_3)_2\text{H}_2\text{O}_2]\)^+ allowing the cisplatin to cross-link to another purine. Moreover, the square-planar geometry of cisplatin facilitates ligand substitution, which is necessary for it to form the DNA lesions that characterize its activity. Cross-linking between adjacent guanine residues is considered to be crucial to the cytotoxicity of cisplatin. Such cross-links can occur between deoxyguanosines on the same strand or on different strands, giving rise to intrastrand and interstrand DNA cross-links, respectively. The 1,2–d(GpG) intrastrand cross-link is the most prevalent lesion (65%), but 1,2–(ApG) (25%) and 1,3–d(GpTpG) (10%) intrastrand cross-links also form along with small amounts of GG interstrand crosslinks [53]. These adducts interfere with cellular DNA replication and transcription processes causing eventual cell cycle arrest and potentially activation of pro-apoptotic signals (Figure 1.3) [54].
Regardless of the therapeutic success of cisplatin in the treatment of several types of tumors, its effectiveness is severely hindered by adverse side effects, viz., alopecia, ototoxicity, neurotoxicity, myelosuppression, and nephrotoxicity [55]. Another major drawback is tumor resistance, either acquired or intrinsic resistance [56]. However, considerable efforts are being made by many research groups around the world to mitigate the severe side effects, provide oral bioavailability, and overcome resistance issues of cisplatin; and consequently, a plethora of second generation platinum analogs were envisaged, viz., carboplatin, oxaliplatin, nedaplatin, heptaplatin, and satraplatin (Figure 1.4) [57].

Carboplatin and oxaliplatin have entered worldwide in chemotherapeutic drug regimens as a first-line treatment for colorectal cancer [58]. Carboplatin is primarily used against ovarian cancers; however, it has also found use in treating a diverse type of cancers including retinoblastomas, neuro- and nephroblastomas, brain tumors, as well as cancers of the head, neck, cervix, testes, breast, lung, and bladder [59]. Carboplatin has the same implications as that of cisplatin, but with a different toxicity profile [60]. Another
front-line platinum anticancer drug oxaliplatin has gained global approval for combination chemotherapy treatment against colon cancers [61] and was subsequently approved for clinical use in countries like France and the United States [62]. Oxaliplatin features two chelating ligand groups with oxalate and \( R,R \)-diaminocyclohexane (DACH) as leaving and non-leaving groups, respectively. Nedaplatin has been mainly used to treat head, neck, and esophagous cancers besides small cell lung and non-small cell lung cancers in Japan [63]. The drug possesses \textit{cis} ammine as non-leaving group along with a chelating leaving group ligand as glycolate, which confers greater water solubility than cisplatin. Heptaplatin was developed in Korea and is being used against gastric cancer under the market name SunPla. The drug contains two types of chelating ligands, a malonate as a leaving group and 2-(1-methylethyl)-1,3-dioxolane-4,5-dimethanamine as its non-leaving ligand.

However, the search for efficacious drugs that overcome the limitations of platinum compounds such as severe side effects, high systemic toxicity, and incidence of drug resistance have motivated researchers to introduce non-platinum drugs into the drug regimens. No-platinum drug entities are likely to have different mechanism of action, bio-distribution, toxicity profile, and could be effective against human cancers that are poor chemo-sensitive or have become resistant to conventional platinum drugs.

Three-dimensional transition metals particularly Ti, Fe, Co, Cu, and Zn have invoked considerable interest as antitumor chemotherapeutics as these metal ions are site selective at physiological pH and are compatible to the biological system in contrast to platinum-based anticancer agents. Although essential metal ion that escapes from its normal metabolic

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structure.png}
\caption{Structure of anticancer platinum metallodrugs; carboplatin and oxaliplatin (approved), Carboplatin, Lobaplatin, heptaplatin, and satraplatin (in clinical trials).}
\end{figure}
pathway could show toxic effects in an organism, complexes of such metals can serve as effective cytotoxic agents. Among first row transition metal ions titanium complexes, viz., titanocenedichloride, (Cp₂TiCl₂) and budotitane (Figure 1.5) have demonstrated pronounced antitumor properties and low toxic side effects [64]. Cp₂TiCl₂ which has entered in phase II clinical trial inhibits DNA synthesis rather than RNA and protein synthesis and titanium accumulates in nucleic acid rich regions in tumor cells after in vivo or in vitro administration [65]. The complex also showed weaker affinity to DNA bases and binds more strongly to phosphate backbone. Budotitane, which was the first non-platinum transition metal anticancer agent to be tested in clinical trials, was quite effective against a number of ascites tumors and induced colorectal tumors [66]. Clinical trials indicated that it was fairly well tolerated by patients with the dose limiting side effects being cardiac arrhythmia [67, 68].

Iron is the most significant essential metal ion in biology which serves as important cofactors of many redox enzymes [69]. Iron is vital for wide variety of metabolic processes including oxygen transport, DNA synthesis, and electron transport reactions. Many synthetic iron complexes have been reported displaying anticancer activities that are often linked to the redox reactions of Fe(II) or Fe(III) under physiological conditions [70]. One of notable example of anticancer compounds involving iron complexation is bleomycin which was clinically used to treat testicular carcinoma with high cure rates [71]. Bleomycin is a glycopeptide comprising a N-terminal metal-binding domain that coordinates to Fe(II) ion through five nitrogen donor atoms of amines, pyrimidine, and imidazole [72]. The coordination of dioxygen to Fe(II) is followed by one-electron oxidation which generates a bleomycin-Fe(III) OOH species. This species induced DNA damage as well as production of ROS, leading to apoptotic cell death [73]. Recently,

Figure 1.5  Structure of Titanium anticancer agents: (a) Titanocene dichloride and (b) Budotitane.
an organometallic compound Ferrocifen, an analog of Tamoxifen (which has been widely used in the clinic for the treatment of hormone dependent breast cancers) was discovered indicating a distinguished mode of antiproliferative activity (Figure 1.6) [74]. Another noteworthy example of iron complexes is a polypyridine iron(II) complex, Fe(II)–N₄Py {N₄Py = N,N–bis(2–pyridylmethyl)–N–bis(2–pyridyl)methylamine} which is synthetic bleomycin mimetic [75]. The complex was reported to cleave DNA efficiently under aerobic conditions and induced cell death and caused nuclear DNA damage [76].

Copper is one of widely distributed in the biological system and is the most familiar redox metal accessible within the cellular potential range [77]. Due to the plasticity and participation of copper as an integral part of the active site of metalloproteins (superoxide dismutase, ceruloplasmin, cytochrome oxidase, and tyrosinase), it familiarizes its coordination with the human body’s functions [78]. Copper binds to electron rich nucleic acids (DNA/RNA) with higher affinity than any other divalent cation and induces conformational changes in polynucleotides and bio-membranes. The altered metabolism of cancer cells and the differential response between normal and tumor cells to copper is the basis for the development of copper complexes endowed with antitumor properties [79].

Ruiz-Azuara et al. have synthesized a series of Cu(II) complexes with diimine ligand donors having the trade name “Casiopeinas®, (Cas)” as antitumor chemotherapeutics (Figure 1.7) [80, 81]. These compounds are mixed chelate copper(II) complexes with a general condensed formula [Cu(N–N)(A–A)][NO₃], where N–N represents neutral diimine donors, either phen or bipy, A–A stands for uninegative N–O or O–O donors, either aminoacidates or acetylacetonate. The activity of Cas II–gly, [Cu(1,4–dimethyl–1,10–phenanthroline)(glycine)NO₃], a novel anticancer agent, was tested against two cell lines, L1210 (murine leukemia)

![Figure 1.6](image_url)  
**Figure 1.6** Examples of some iron anticancer agents: (a) Ferrocifen (ferrocene derivative of tamoxifene) and (b) Iron(II) pentapyridyl complexes.
and CH1 (human ovarian carcinoma). It was observed Cas II–gly was highly active against these cell lines, including cell lines resistant to cisplatin and mechanism of cell death was both via apoptosis and necrosis [82]. Another variant of the “Casiopeina” series, [Cu–(acetylacetonato) (4,4′–dimethyl–2,2′–bipyridine)(NO₃)], (CasIII–ia), was found to exhibit antineoplastic effects on glioma C6 [83].

Ruthenium(II) complexes are rapidly becoming a prime focus for the development of new more efficacious metal-based anticancer drug entities due to their unique spectroscopic and electrochemical properties [84, 85]. Ruthenium is well suited for pharmacological applications as it offers various oxidation states (II, III, and IV) under physiologically conditions [86]. Plethora of ruthenium complexes have been synthesized and have successfully demonstrated significant cytotoxic and antimetastatic properties with reduced side effects [87]. The first successful breakthrough in the area of ruthenium-based chemotherapeutics was achieved by B. K. Keppler et al. who synthesized imidazolium [trans–RuCl₄(1H–imidazole)(DMSO–S)] (NAMI–A) and indazolium [trans–RuCl₄(1H–indazole)]₂ (KP1019), as a substitute to platinum-based drugs (Figure 1.8). These drugs have successfully completed phase I clinical trials and are now undergoing further clinical evaluation [88, 89].

Both NAMI–A and KP1019 are ionic Ru(III) compounds bearing structural novelty possessing negatively charged octahedral metal center coordinated to heterocyclic nitrogen donor ligands and equatorial chlorides; a protonated form of the heterocyclic nitrogen ligands as counter ions that are replacable by sodium or other cations [90]. NAMI–A in solution phase involves both loss of Cl⁻ and DMSO. NAMI–A is the most intensively studied ruthenium anticancer complexes because of its ability to prevent the metastasis formation or inhibit the growth of secondary tumor cells while KP1019 is active only against primary cancers [91]. KP1019 has entered in the clinical trials after it demonstrated in vitro cytotoxic activity against
cisplatin-resistant human colon carcinoma cell lines [92] along with efficient in vivo activity against various tumor types. Pertinent to mention, Ru(II) compounds that are administered to the patient are not as the active species rather Ru(III) complexes are first reduced into a more active Ru(II) form (Scheme 1.1). The plausible mechanistic hypothesis for Ru(III) compounds was attributed on “activation by reduction” mechanism, according to which the Ru(III) complexes act as prodrugs that can be reduced to Ru(II) active species in the hypoxic (therefore reducing) environment of cancer cells [93]. The hydrolysis reaction of Ru–X bonds to give ruthenium–aqua species (aquation) is an important aspect of the therapeutical behavior for ruthenium complexes. The corresponding aqua species

![Figure 1.8](image_url)

**Figure 1.8** Ru(III) anticancer compounds currently in clinical trials: (a) imidazolium [trans-RuCl₄(1H–imidazole)(DMSO–S)] (NAMI–A) and (b) indazolium [trans-RuCl₄(1H-indazole)$_2$] (KP1019).

![Scheme 1.1](image_url)

**Scheme 1.1** A generalized scheme depicting possible action for Ru(III) prodrugs invoking "activation by reduction" hypothesis (X = Cl⁻, Br⁻, I⁻).
exist over a wide range of pH, but for pH > pKa, the hydroxo species formed by deprotonation are predominant. Since, the hydroxide is a less labile ligand than water, it will not so easily be displaced by biomolecule targets. “Aquation” of the chloro complexes may be suppressed extracellularly due to high chloride concentrations (0.1 M) but because of lower intracellular Cl⁻ concentrations (4–25 mM), the aquation reaction is highly possible.

Many ruthenium compounds have been found are non-toxic and have been quite selective for cancer cells. This has been attributed to the ability of ruthenium to mimic iron in binding to biomolecules. As cancer cells overexpress transferrin receptors to satisfy their increased demand for iron, ruthenium-based drugs have been found to be delivered more efficiently to cancer cells [94].

In recent years, half-sandwich–configured organoruthenium(II)–arene scaffold have emerged as a versatile tool for the design novel anticancer agents because their biological activity and pharmacological properties can easily be modulated by ligand selection [95]. The different mode of action is a consequence of their high lipophilicity that favor better cellular uptake; and the presence of labile ligands, viz., chlorido/carboxylato, favor the extracellular binding with the drug target. Besides possessing supposedly low general toxicity and high selectivity of ruthenium-arene complexes towards cancer cells, the big reasons for the flourishing design of arene-ruthenium–based anticancer drugs are the amphiphilic properties of the arene ruthenium unit, which provides the hydrophobic nature to the arene ligand counter balanced by the hydrophilic metal center [96]. The pioneering work of Paul J. Dyson and P. J. Sadler in the field of anticancer organometallics led to successful revelation of two lead Ru(II)–arene anticancer agents, RAPTA–C, and RAED which are at an advanced preclinical development stage (Figure 1.9) [97, 98].

![Figure 1.9](image)

**Figure 1.9** Structures of anticancer organoruthenium complexes (a) RAPTA–C ([Ru^II(cym)(PTA)Cl]_2, PTA = 1,3,5–triaza–7–phosphatricyclo[3.3.1.1]decane; cym = η⁶–p–cymene) and (b) RAED ([Ru^II(η⁶–biphenyl)(en)Cl]^+).