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Theoretical Insight into the Medicinal World of Organometallics: Macro versus Nano

Ruby Srivastava

Abstract

Due to the unique physicochemical properties, organometallic complexes have been widely used in the medicinal world. These complexes have specific properties such as structural diversity, redox/catalytic activities, and possibility of ligand exchange. As the cancer therapies provided by these complexes are not always effective and have desired side effects, new treatment methods are needed for the successful therapies. Recent advances suggest that nanotechnology has also profound impact on the disease prevention, diagnosis, and treatment. The delivery system based on nanotechnology has faster drug absorption, controlled dosage release, and minimal side-effects. This technology is used for the treatment of cancer till now, but soon, it will find applications to other diseases also. The use of nanotechnology in the field of drug delivery is to develop a system that improves the solubility and bioavailability of hydrophobic drugs. It is used to increase specificity, developing delivery system for slow release, and to design delivery vehicles that can improve the circulatory presence of drugs. As the photophysics of organometallic complexes is still not clear, this topic is included to discuss the latest developments in this field, which allows the photochemical reactions at the nanolevel.

Keywords: organometallic complexes, nanotechnology, photophysics, drug delivery, upconversion luminescence

1. Introduction

Organometallic chemistry deals with three basic aspects as environmental concern, biological aspect, and medicinal chemistry. Medicinal organometallic chemistry continues to be a major application for these compounds in biology. Medicinal organic chemistry has therapeutics, diagnostics, and theranostics effects. Medicinal organometallic complexes consist of platinum, ruthenium, iron, titanium, and gold among other metals. Fundamental studies have been carried

out on the organometallic complexes in which the mechanism of action exert their medicinal effect (e.g., induce cell death in cancer cells), the synthesis of new organometallic compounds and the development of combination therapies containing organometallic components. Research has shown significant progress in utilization of transition metal complexes as

1.1. Anticancer agents

The development of metal complexes with platinum as a central atom such as cisplatin or carboplatin had an enormous impact on current cancer chemotherapy. Cisplatin has become one of the most widely used drugs and is highly effective in treating several cancers such as ovarian and testicular cancers. The limitations of cisplatin have stimulated research in the field of platinum antitumor chemistry by including the reduction in toxicity of cisplatin (nausea, ear damage, vomiting, loss of sensation in hands, and kidney toxicity), acquired drug resistance observed in certain tumors and inefficiency of the drug against some of the commonest tumors (e.g., colon and breast). Due to its particular chemical structure, cisplatin offers little possibility for improvement in tumor specificity and thereby reducing side effects. The other alternative complexes have at least one direct, covalent metal-carbon bond, having structural variety, diverse stereochemistry, provide control over major kinetic properties, kinetically stable, usually uncharged, and having low oxidation state of metal atom, so they can be used as ideal candidates for anticancer candidates [1–4]. Some examples are: metallocenes [5–9], organometallic ruthenium half-sandwich complexes [10–14], organometallic osmium half-sandwich complexes [15–17], organometallic iridium and rhodium complexes [18–21], rhenium organometallics [22–24], ruthenium, osmium, iridium, and platinum organometallics as scaffolds for protein kinase inhibitors, metal NHC complexes [25, 26], and metal carbonyl complexes [27, 28].

1.2. Antibacterial agents

The biggest challenge in the antibacterial market is the issues related to the drug-resistant pathogens. The remedy is now to search for new compounds with new mode of action to overcome the resistant strains. This can be done by either the organic derivatization of old drugs or completely new organometallic drugs, for example, new tamoxifen [19–21, 29], platensimycin [22–24], etc.

1.3. Anti-infectant agents

Transition metal as silver is being used as the antimicrobial agent due to its low toxicity as compared to the other metals. For example: silver (1) sulfazine, which is used to treat burns to prevent the bacterial infections. Silver nitrate is given to the infants to prevent the development of ophthalmia neonatorum. Chlorhexidine-silver sulfadiazine is an anti-infective metal complex against catheter infections. Organometallic complexes of Pt [30–32], Rh, Ir, Pd, and Os metal with active organic molecules have been reported to exhibit trypanocidal activity. Metal complexes of Pt (II) and Ru (II) with o-vanillin-(4-methyl thiosemicarbazone), and o-vinillin-(4-phenyl thiosemicarbazone), metal complexes of Ga (III), Al (III), and Fe are among the various other drugs [33–36].

1.4. Anti-inflammatory agents

These complexes are also used as anti-inflammatory and antiarthritic agents. Several inject-able transition metal complexes as sodium aurothiomalate, aurothioglucose, sodium auro-thiopropanol and gold and silver nanoparticles conjugated with heparin derivative possess antiangiogenesis properties [37–39]. Gold has been used for the treatment of peripheral psori-atic arthropathy. As a product of oxygen metabolism, superoxide anion can trigger oxidative injury to tissues. This activity is associated with riper fusion and inflammatory diseases as well as neurological disorders such as Parkinson's disease and Alzheimer's disease. However, excess use of these complexes in arthritis causes pain and fever. NO is excellent ligand for transition metal ions and these metal nitrosyls having therapeutic values. Sodium nitroprus-side is used to treat cardiovascular diseases by releasing NO with limited usage due to the toxicity of CN^-. Ruthenium poly aminocarboxylate complexes are also efficient NO scaven-gers [40, 41].

1.5. Anti-diabetic agents

Diabetes is the most suffering disease among human beings. This is the disease in which the body do not produce insulin hormone, which is used for absorption of glucose in cells. The control of glucose level is done by vanadium complexes with organic ligands which are less toxic and have improved solubility and lipophilicity [42]. These complexes show involvement in the activation of prominent key components of insulin-signaling pathways [43]. Chromium supplementation also improves glycemia among patients of diabetes [44]. Similarly, higher zinc intake also lowers the risk of type 2 diabetes in women [45].

1.6. Neurological drugs

Neurological disorders are also treated by transition metal complexes. Lithium is used for Huntington's chorea, tardive dyskinesia, spasmodic torticollis, Tourette's syndrome, L-dopa induced hyperkinesia, Parkinsonism, organic brain disorders, drug induced delusional disor-ders, migraine and cluster headache, periodic hypersomnolence, epilepsy, Meniere's disease, and periodic hypokalemic paralysis. Lithinium inhibit the scavenging pathways for capturing inositol in the resynthesis of polyphosphoinositides in the brain. Zinc is also used as transmitter in neuronal signaling pathways.

1.7. Delivery probes and diagnostic tools

Organometallic complexes have unique properties as redox activity, Lewis acidity, electro-philicity, valency, geometry magnetic spectroscopic, and radiochemical properties which can be used to measure cellular functions. Gold nanorods has been used for photoacoustic molecular imaging with simultaneous multiple targeting as they are less reactive and less toxic. The nanoparticles injected in the tumor cells increases their ability to absorb radiation of specific wavelength. The property is used in lymphotropic nanoparticle-enhanced magnetic resonance imaging of prostate cancer. As iron oxide has superparamagnetic properties so

they can act as negative contrast agent in magnetic resonance imaging (MRI) which is used to detect the sensitivity of inflamed tissues.

Transition metals exhibit different oxidation states and can interact with several negatively charged molecules. Due to their vital role in medicinal chemistry, we have included both the macro and the nanoorganometallic complexes and their structural and photophysical behavior in detail.

Metallocene compounds have two π-bonded cyclopentadienyl (Cpa) ligands on a metal atom. These compounds are also called "sandwich complexes" due to their symmetrical nature. Other metal complexes with cyclic π-perimeters are also named as metallocenes. Compounds with only one π-perimeter are classified as "half sandwich metallocenes." The bis-cyclopentadienyl complexes are divided in two categories: (a) "classical" with parallel Cp rings and (b) "bent" metallocenes, which have other ligands bonded to the metal in addition to the Cp rings. Ferrocene was the first organometallic compound with antiproliferative properties, so the medicinal properties of the complex were investigated [3]. Ferrocene is nontoxic compound and can be injected, inhaled, or taken orally. It cannot cause major health problems [4, 5]. Another ferrocene-containing compound chloroquine (derivative) is used as antimalarial drug. Ferroquine has an activity-like chloroquine on the malaria parasite *P. falciparum*. The p-methoxybenzyl substituted titanocene show very good activity against renal cell cancer and pleura mesothelioma cell lines. Ruthenium complexes have low toxicity and it has the same mechanism (ligand exchange kinetics) to those of platinum(II) antitumor drugs [10]. A class of ruthenium(II)-arene complexes that are weakly cytotoxic *in vitro*, [Ru(η6-p-arene)Cl$_2$(1,3,5-triaza-7-phosphaadamantane)] termed as RAPTA, interact strongly with proteins, with the ability to discriminate binding to different proteins, but show a relatively low propensity to bind DNA, which is considered to be the main target of many metal-based drugs. Dyson et al. recently described the preparation of a series of RAPTA-type complexes with fluoro-substituted η6-arene ligands [46] (**Figure 1**). The active Pt-drug seems to be *cis*-coordinated by bidentate amine ligands or two amines (at least one -NH group on the amine) and two leaving groups with an intermediate binding strength (e.g., Cl$^-$, SO$_4^{2-}$, citrate or oxalate) to platinum. Nonplatinum metals may have some different chemical behavior (oxidation state, redox potential, coordination geometry, additional coordination sites, binding preferences to biomolecules as the HSAB (hard and soft (Lewis) acids and bases), rate of hydrolysis or kinetics of ligand exchange reactions and the ability to replace essential metals. Due to these differences, the nonplatinum metal-based compounds may have different mechanisms of action, biodistribution, and biological activity.

Studies were carried out on complexes with iron, cobalt or gold, titanium, ruthenium, or gallium central atoms, which have shown the promising results in preclinical studies. Other metal complexes which have shown potential anticancer activity are the complexes of Rh (I), Rh (III) [22, 23, 47], Ir (I), Ir (II), Ir (IV) [48, 20, 21], Os (II), and Os(III) [18, 49–52]. Ferrocifenes [53] exhibit anticancer activity against hormone dependent and hormone-independent breast cancers. Ferrocene derivatives as curcuminoids [54], androgen derivatives [55], and antiandrogens derived from the nilutamide lead structure [56],
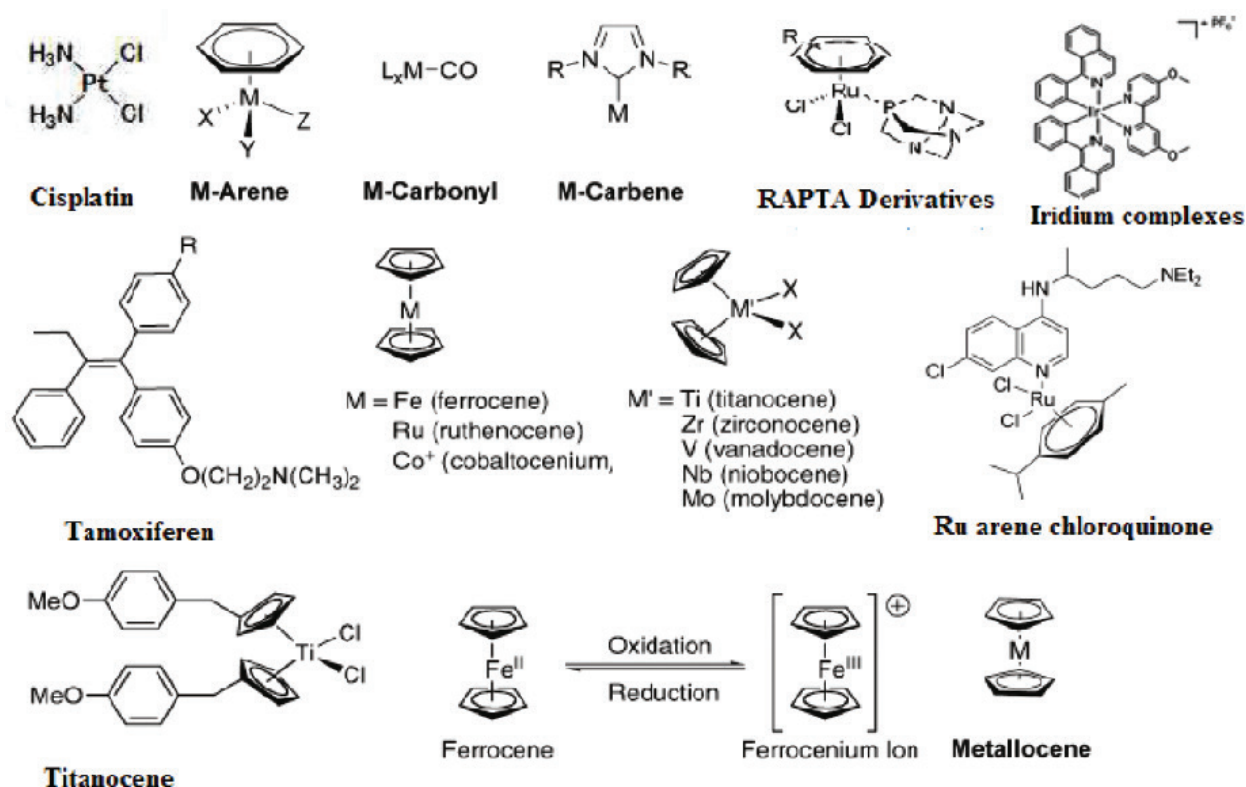
Figure 1. Schematic diagram of few organometallic complexes.

indolones [57], and ferrocenophane polyphenols [58] has also been used for antiproliferative activities.

Transition metal carbene complexes also feature a divalent organic ligand, which is coordinated to the metal center. As these complexes are highly stable and easily derivatize, they can be the suitable candidates for drug development [8, 59].

Metal NHC complexes are also having pharmacological properties as novel antibacterial and antitumor drugs. Their mode of action is both coordinated metal–respective biological target-dependent thioredoxin reductase or other enzymes containing (seleno) cysteine residues in their active site for gold or DNA for copper NHC complexes (half-sandwich) [60, 32], ruthenium [27], or manganese [28, 61] bioorganometallic species and complex containing an acetylsalicylic acid (aspirin) derived ligand emerged as cytotoxic drugs.

An enormous work has been carried out by my mentor Prof. G. Narahari Sastry and group in the field of anticancer treatment. The research group has focused their attention to the biochemical aspects of the clinical application of aromatase inhibitors with designing strategies on toxicity profile, pharmacokinetics, relative potency of aromatase inhibitors, and pharmacophores models [62–73].

As the side effects of these complexes are unavoidable, the research was shifted to the nanotechnology which will have a profound impact on disease prevention, diagnosis, and treatment.

Few advantages of nanotechnology techniques are:

1. Protect drug from degradation

2. Easily changeable physical properties due to nanosizes

3. Reduced dose size

4. Ease of drug targeting due to nanosize

5. Allow delivery of insoluble drugs

6. Longer circulation time

7. Maintain its therapeutic activity

8. Improve the oral bioavailability of the agents

9. Passive targeting of drugs to the macrophages (liver and spleen)
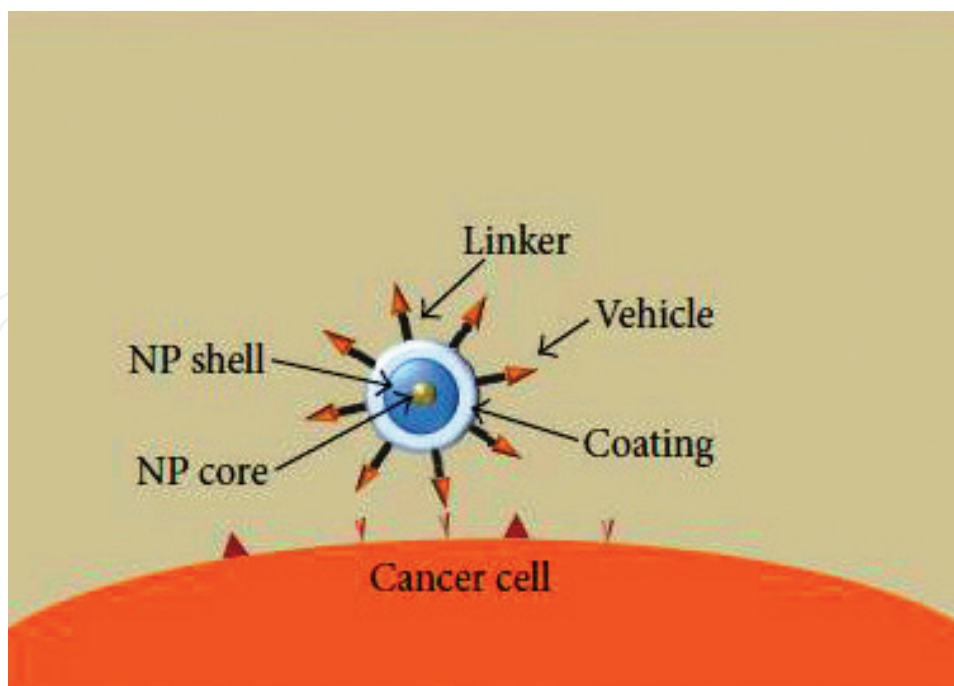
2. Nanoorganometallic complexes

Recent advances suggest that nanotechnology will give a better solution for disease prevention, diagnosis, and treatment. It is an ideal targeting system, should have long circulating time, be present at appropriate concentrations at the target site, and should not lose its activity or therapeutic efficacy while in circulation. The increased vascular permeability coupled with an impaired lymphatic drainage in tumor allows an enhanced permeability and retention effect of the nanosystems in the tumor or inflamed tissue. Nanotechnology offers a solution for using the numerous chemical entities for treating brain disorders that are not clinically useful because of the presence of the blood-brain barrier.

The advantage of nanoparticles with potential MRI-related medical applications comprise of various materials, such as metals (gold, silver, and cobalt) or metal oxides (Fe_3O_4, TiO_2 and SiO_2) (**Figure 2**). Magnetic nanoparticles coated with dimercapto succinic acid (DMSA) were toxic to neurons in a dose-dependent manner. Cobalt (Co), gold (Au@Fe), and platinum (Pt@Fe) are the other types of nanomaterials that show potential application in antimicrobial and anticancer treatment. Several studies on nanoparticles shown them to be cytotoxic [72], genotoxic [73], and potentially carcinogenic [74] and are used to induce apoptosis and inhibit cell proliferation [75].

These nanomaterials contain the sphere and core-shell structures, two-dimensional (2D) grapheme nanosheets have great potential for high drug loading efficiency and conjugation of proteins, drugs, and fluorescent probes.
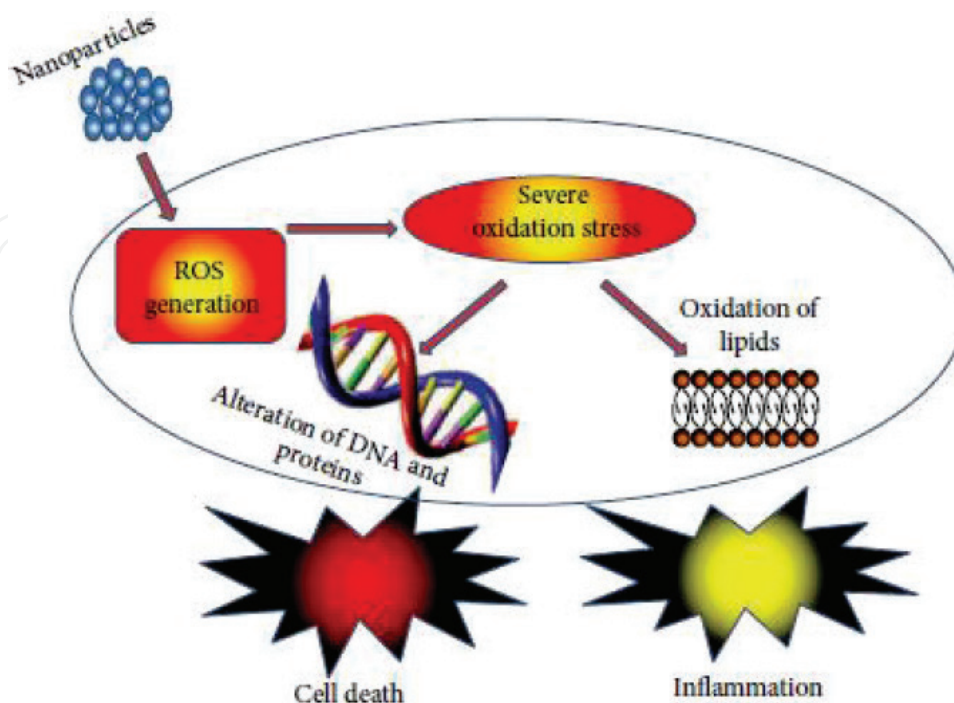
The molecular imaging applies to various techniques such as positron emission tomography (PET), computed tomography (CT), or ultrasound and magnetic resonance imaging (MRI) which gives the best spatial resolution and is either noninvasive or minimally invasive. As MRI is not applied in full potential due to low specificity, so it can be alternatively taken to use as cell markers. The unique paramagnetic and superparamagnetic properties of nanoparticles (NP) can be utilized for the detection with MRI in small quantities. Nanoparticles with potential MRI-related medical applications comprise various materials, such as metals (gold,

Figure 2. Schematic representation of the targeted contrast agent used for MRI approaching of the cancer cell and specific proteins.

silver, and cobalt) or metal oxides (Fe_3O_4, TiO_2, and SiO_2). While diagnostic is a common medical application of nanoparticles, they can also be used for therapy [76–80] (**Figure 3**).

Nanoparticles can be categorized in two parts:

Figure 3. Representation of toxicological mechanisms of NM to eukaryotic cells.

2.1. Inorganic nanoparticles

Silver (Ag), iron oxide (Fe_3O_4), titanium oxide (TiO_2), copper oxide (CuO), and zinc oxide (ZnO) are used for highly potent antibacterial effect. The property is exhibited through reactive oxygen species (ROS) generation or by physical structure and metal-ion release. Though the mechanism is not clear, nonetheless high surface energy may compromise their efficacy. Another important aspect is that how to define and determine the silver minimal inhibitory concentration (MIC) and breaking point, the ease of emergence of resistant strains [81–83]. Silver really kills biofilm or planktonic cells and finally the side effects of silver and its complexes [84–87] remains the same. Yet till now it is the most promising antibacterial nanometal. Titanium oxide (TiO_2) has shown its efficiency against various viral species and parasites [88–90]. Copper oxide (CuO) is less expensive and used for efficacy enhancement [91–93]. Iron oxide (Fe_3O_4) [94], zinc oxide (ZnO) and Magnesium oxide (MgO) [95–97] nanoparticles show antibacterial activities. Gold nanoparticles and nanorods have been used as bactericidal in photothermally functionalized form [98]. Pt nanoparticles diffuse through membranes and induce DNA damage, accumulation of cells at the S-phase of the cell cycle, and apoptosis [99]. The properties of Al_2O_3 are unclear about the antibacterial treatment [100], while SiO_2, Au, Fe_2O_3, and TiO_2 are biocompatible.

Even cytotoxic NM can be converted into biocompatible materials through slight variation in their surface structure. Therefore, we can say that nanomaterials possess a broad level of biological properties that are highly dependent upon their size, structure, quantity, and receptor cell type. Though, the nanomaterials that penetrate the body through the skin by respiration or by inhalation directly affect the major body organs (lungs, heart, and brain).
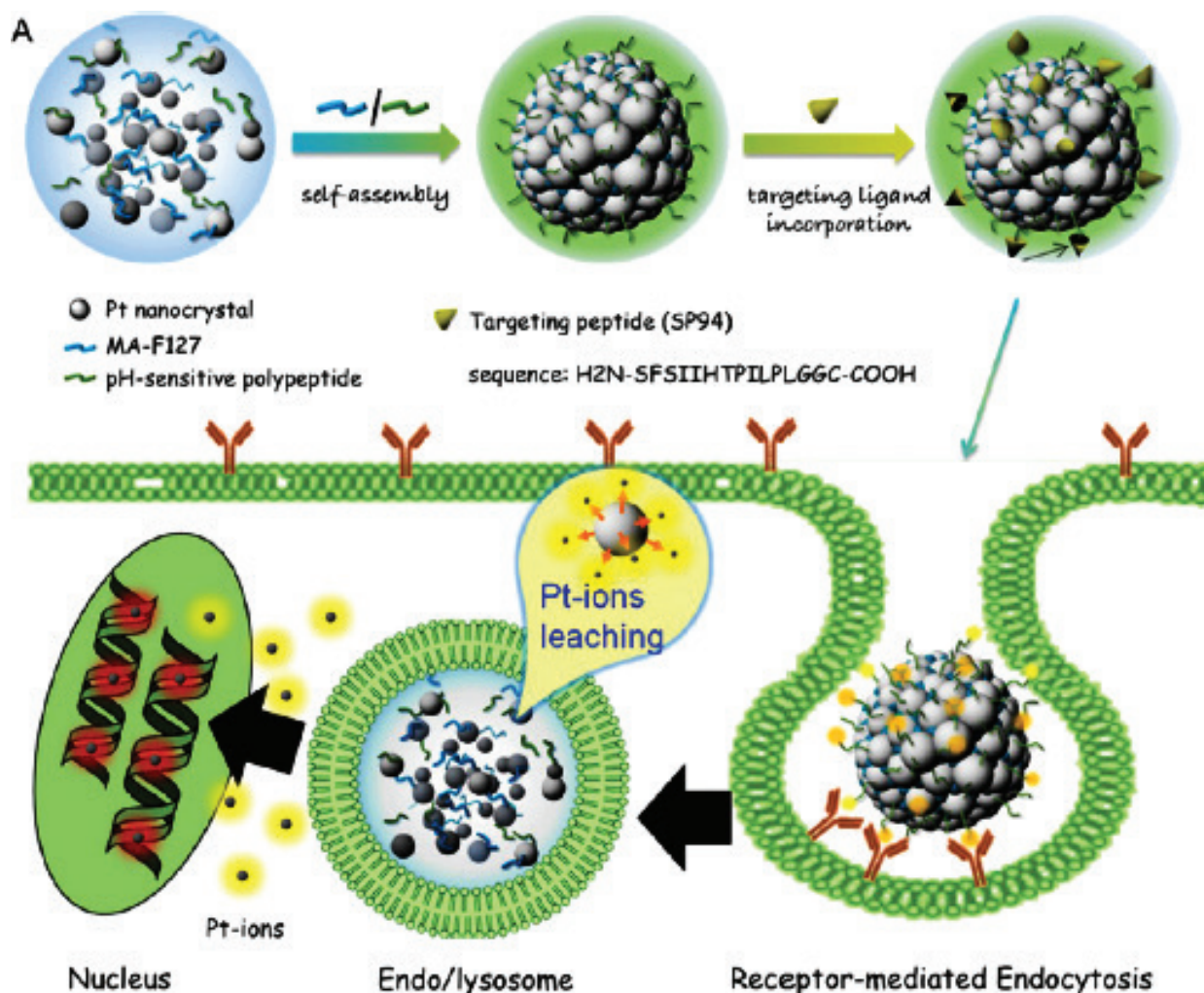
2.2. Organic nanoparticles

Quaternary ammonium compounds, imidazole derivatives, alkyl pyridiniums, copolymers of N-vinylimidazole and phenacyl methacrylate, benzoic acid, phenol, and p-Hydroxy benzoate esters, quaternary phosphonium or sulfonium groups, triclosan, 5-chloro-8-hydroxy-quinoline, chitosan, or quaternary phosphonium are the polymeric nanoparticles that are used to kill microorganisms either by releasing antibiotics, antimicrobial peptides, and antimicrobial agents or by contact-killing cationic surfaces. Organic antibacterial materials are less stable than inorganic materials at high temperatures [101, 102]. Still some phenomena such as several NM killing pathways, effects of NM's treatment combinations and bacterial intrinsic pathways of programmed cell death in NM's dependent killing are yet to be understood.

As we all know, hepatocellular carcinoma (HCC) is the leading cause of cancer-associated death and the conventional treatment is still not satisfactory due to chemoresistance and recurrence. In a recent study, Pt nanocluster assembly (Pt-NA) composed of assembled Pt nanoclusters was synthesized incorporating a pH-sensitive polymer and HCC-targeting peptide [103] .

The advantage of Pt nanocluster medicine is that Pt-NA is active in peripheral blood and readily targets tumor cells including CLSC because of (i) the surface-targeting peptide; (ii) protonation of pH-sensitive polymers in an acidic intracellular environment triggers Pt-NA disassembly into extremely small Pt nanoclusters; and (iii) the resulting extremely small Pt

nanoclusters with large specific surface accelerate the release of toxic Pt ions inside the cells for an effective cancer treatment (**Figure 4**).

Numerous efforts have been devoted to synthesize nanostructured materials with specific morphology as their size and shape play an important role in determining their functions. It was seen that the cationic nanoparticles with metals (gold, silver, and cobalt) or metal oxides (Fe_3O_4, TiO_2, and SiO_2) were moderately toxic than their anionic nanoparticles. The studies reflect that DMSA coated nanoparticles are nontoxic to HeLa cells or RAW macrophages. The incorporation of chlorotoxin onto functionalized Fe_3O_4 nanoparticles resulted in a significant increase in the total uptake within the brain tumors of mice. Substituted magnetic spinel ferrites of the general formula MFe_2O_4 (where M = Zn^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, and Mg^{2+}) offer the opportunity to fine-tune the magnetic properties of the inorganic nanoparticle core as a function of the kind of divalent ion.

Figure 4. Schematic representation of HCC targeted Pt nanocluster assembly (Pt-NA). Adapted with permission from American Chemical Society [103].
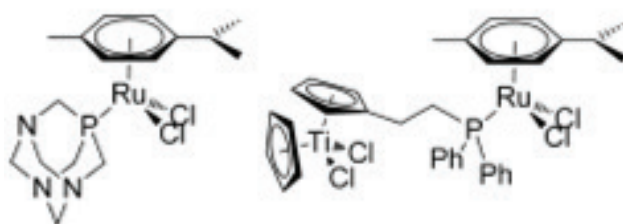
3. Photophysics of the bioactive molecules

In the recent years, new experimental and theoretical developments have occurred in the field of photoactivatable metal complexes which play active role in the field of medicine and biotechnology. Some metal-DNA complexes possess favorable emission properties, while some complexes also provide site-directed therapy. These properties help in oncology, where metal-based precursors generate excited state drugs with different mechanisms.

In this section, the computational techniques (time-dependent density functional theory) and ultrafast-pulsed radiation techniques will be discussed.

The delivery of light depends on the efficiency of light source. It should be efficient to activate the complex. The irradiation should occur in the strong MLCT transitions. However, in medicinal world the UV radiations are harmful but red region is preferred as it deeply penetrates the tissues. Two and three photon absorption can be achieved as the desirable condition is to activate complexes that absorb at shorter wavelength using laser beam that penetrates tissues deeply.

The use of organometallics has become a topic of interest for design of tractable therapeutic agents and theranostics [104]. The most promising organometallic complexes (and motifs) used in cancer therapy is RAPTA-C: [Ru(η6-p-cymene)Cl$_2$(pta)] (pta = 1,3,5-triaza-phosphatricyclo [3.3.1.1]-decane; **Chart 1**), along with its osmium analogue and their corresponding function-alized derivatives [105]. These complexes exhibit antimetastatic properties *in vivo*. The quite strongly bonded phosphine and arene ligands, the chloride ligands rapidly interchange with water molecules. Arene-ruthenium derivatives can react with N- and S-donors so that they can bind to both nucleotides and proteins [106].

Porphyrins and their metalloderivatives are used for photodynamic therapy [107] and optical imaging and as theranostic agents [108]. Gold (III), Palladium (II), Palladium (III) inside the porphyrin rings and their derivatives can act as anticancer agents [109]. It is based on the concept of "optical bi-theranostic" (two modalities for therapy and one for optical imaging). Further as the intramolecular interactions between the two moieties alter their activities so this should be considered for designing and testing. Ruthenium and Iridium possess favorable photophysi-cal properties which allow functional imaging of cells and tissues (e.g., DNA interactions) and provide site-directed therapy. The electronic transitions can be metal-centered (MC), ligand-

Chart 1. Structure of [Ru(η^6-p-cymene) Cl$_2$(pta)] (left) and [(η^5-Cp)Ti((η^5-C$_5$H$_4$-(CH$_2$)$_4$-PPh$_2$-[Ru(η^6-p-cymene)Cl$_2$(pta)] (right).
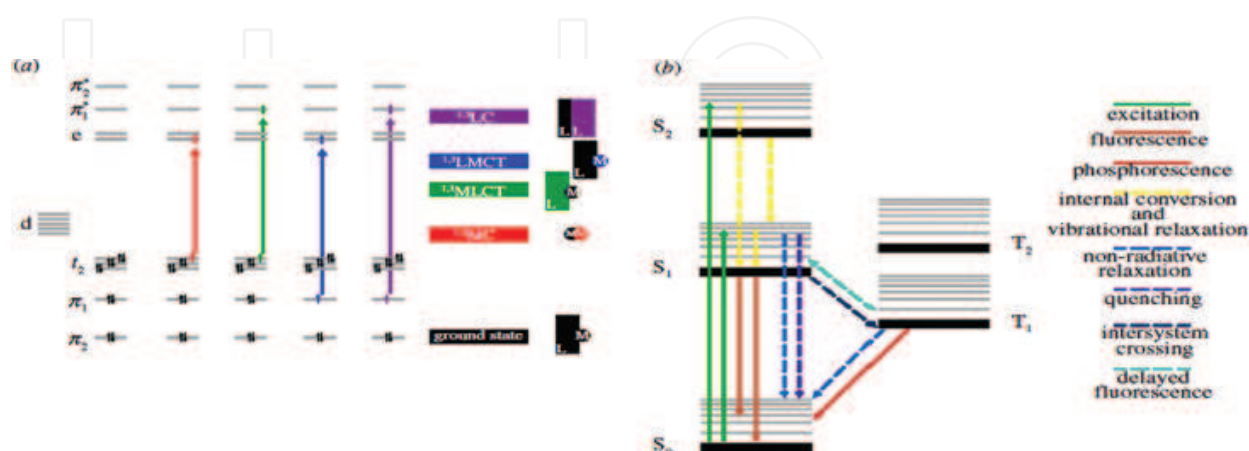
centered (LC) or involve both the metal and the ligands: metal-to-ligand charge transfer (MLCT) (for readily oxidized metal ions and ligands with low-lying acceptor orbitals), or ligand-to-metal charge transfer (LMCT) (for readily reduced metal ions with strong donor ligands) (**Figure 5**).

A lot of research is carried out in the delivery of small molecules, which can act as second messengers and transmit signals into cells, for example, NO, carbon monoxide (CO), and hydrogen sulfide (H_2S). Photoactive Pt (IV) diazido complexes also offer potential dual mode activity; excited singlet and triplet states can release reactive or biologically active ligands and form Pt (II) species which can bind to DNA. The introduction of extended conjugation into the amine ligands of square–planar Pt (II) complexes has allowed two-photon activation of ligand exchange using red and near-infrared (NIR) light. The wavelength for two-photon activation of cis-[$PtCl_2(MOPEP)_2$], where MOPEP is the π-conjugated ligand 4-[2-(4 methoxyphenyl)ethynyl]pyridine, is shorter than twice the single-photon absorption wavelength [110].

Another important optical phenomenon is "upconversion luminescence," which is discussed here.

3.1. Upconversion luminescence

It is a nonlinear optical phenomenon, which absorb two or more photons and emit one photon. Compared with traditional luminescent materials, upconversion nanostructures have many advantages, such as weak background interference, long lifetime, low excitation energy, and strong tissue penetration, which are used in bioimaging and sensing. Similarly producing shorter wavelength light from longer wavelength irradiation involves the use of upconverting nanoparticles. For example: YF3 doped with lanthanide ions (Yb^{3+} and Tm^{3+}). Lanthanide-doped upconversion nanoparticles are used to mediate nitric oxide (NO) release from Roussin's black salt anion [$Fe_4S_3(NO)_7$]$^-$ in NIR light from a simple diode laser operating at 980 nm [110]. Cr (III) sensitizers around a central Er (III) acceptor also favor efficient nonlinear energy transfer and upconversion luminescence [111].

Figure 5. Schematic representation of the orbital and excited state diagram for (d^6) metal complex. Spin is represented by arrows (↑↓) for electronic transitions. (a) Spin up is represented for electronic transition in singlet state whereas spin down is represented for electronic transition in triplet state. (b) Jablonski diagram.

3.2. Imaging and binding of photo-triggered DNA

The simple and powerful strategy for selective destruction of cancer cells is to target the metal complexes to the tumor cells by photoactivation. Peptides releases the aqua species, $[(\eta6\text{-}p\text{-cym})Ru(bpm)(H_2O)]^{2+}$ in the visible range which bind to DNA. The other example is the cyclometalated iridium (III) polypyridine indole complexes, which have the intense luminescence (λ_{em} = 540–616 nm, τ = 0.13–5.15 µs) [112]. Another interesting feature of these complexes is that they can deliver CO in the body [113], for example, MnI carbonyl complex [Mn(pqa)(CO)3]$^+$ (pqa =(2-pyridylmethyl)(2-quinolylmethyl)amine) [114] and manganese complexes [115]. The release of CO from these complexes is visibly monitored by time-resolved IR spectroscopy [116]. This property is also used to deliver other biologically active species also. [Rh(bpy)2(chrysi)]$^{3+}$ targets single-base mismatches in DNA by noncovalent binding in UV/visible region. As there is deficiency of mismatch repair in cancer cells, this technique can be used to detect the cancer cells [117, 118]. The other luminescent N-heterocylic carbene (NHC) cyclometalated platinum(II) complexes, which are localized in cytoplasmic structures, do not interact with nucleotides [119].

4. Conclusions

Unfortunately, like the macro organometallic complexes, the nanoparticles also carry some serious adverse effects. Though the adverse effects of nanoparticles depend on individual factors such as genetics, existing disease conditions, exposure, nanoparticle chemistry, size, shape, agglomeration state, and electromagnetic properties, the key to understanding the toxicity of nanoparticles is their size. Thus, it is very essential to understand the basic nature, structure, and the photophysics behind these particles. Nanoparticles are smaller than mammalian cells and cellular organelles, which allows them to penetrate these biological structures and disrupt their normal function. Nanoparticles are effective in glycoma treatment. This brain cancer is particularly difficult to treat as neurosurgery is ineffective, while chemotherapy suffers from the inability of therapeutics to cross the blood. Although the lack of self-error-correcting mechanism result in defect sites in these nanostructures, the high efficiency and relative simplicity of the novel approach demonstrates the potential power of using irreversible covalent bonds to generate adverse range of shape-persistent and robust nanostructures that is likely to enrich the repertoire of self-assembled nanomaterials and multidrug delivery. Finally, toxicity of nanoparticles could also be potentially utilized to destroy the cancer cells. Bioorganometallic compounds offer hope in the fight against the deadly diseases such as Malaria, HIV/AIDS, and EVD that have continued to devastate humans. There are expected challenges in this area of collaborative research as organometallic compounds are ideally synthesized under inert atmosphere in the absence of oxygen and water. These challenges are not too difficult to surmount, we therefore implore researchers to orient more into this relatively new multidisciplinary research area in the search for novel and potent anticancer and other drug candidates with reduced side effects, which can be a great service to the mankind.

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