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Review

Group 8 Bimetallic Complexes for Light-Driven Cancer Therapy

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Abstract

The incorporation of a second metal center with different biological targets and complementary physicochemical properties into metal-based compounds represents a promising strategy to enhance anticancer efficacy and overcome the limitations of conventional monometallic drugs. In recent years, increasing attention has been devoted to multitarget anticancer agents, including heterometallic complexes. This review provides an overview of recent advances in Group 8 bimetallic complexes containing iron, ruthenium, or osmium for light-driven cancer therapy. Particular emphasis is placed on their molecular design, photophysical and photochemical properties, mechanisms of action, and anticancer activity. The influence of the two metal centers on photoactivation, generation of reactive species, cellular targets, and therapeutic efficacy is discussed, together with emerging structure–activity relationships. Finally, current challenges and future perspectives for the development of these complexes as photoactivated anticancer agents are highlighted.

Keywords: bimetallic complexes; anticancer agents; phototherapy; multitarget therapy; Group 8 compounds

1. Introduction

The development of next-generation phototherapies is driven by the need to overcome the significant limitations of conventional photodynamic therapy (PDT). Despite the several advantages associated with traditional organic photosensitizers (PS), the first-generation clinical drugs such as Photodyn (Hematoporphyrin, HpD) and Photofrin (Porfimer Sodium) [1] suffer from several drawbacks, including poor aqueous solubility, low tumor selectivity, and prolonged skin photosensitivity. Furthermore, many organic dyes exhibit low photostability, leading to photobleaching during treatment. In addition, a fundamental hurdle is their extreme dependence on oxygen; they primarily operate through a Type II mechanism that requires molecular oxygen to generate cytotoxic singlet oxygen ($^1O_2$), rendering them ineffective against the hypoxic microenvironments typical of aggressive and drug-resistant solid tumors.

These challenges have spurred the development of metal complexes as the next-generation photosensitizers, which offer superior photostability, water solubility, and tunable and unique physicochemical and photochemical properties compared to organic PSs. Specifically, in the last two decades, 4d and 5d metal complexes—such as Ru(II), Ir(III), and Os(II)—have emerged as highly effective tools for PDT, as they can generate reactive oxygen species (ROS) through dual Type-I and Type-II mechanisms. The resulting strong spin-orbit

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Academic Editor: Xiaowei Zeng

Received: 12 October 2026
Revised: 6 November 2026
Accepted: 9 November 2026
Published: 18 November 2026

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coupling significantly increases the probability of intersystem crossing (ISC), allowing for the efficient population of reactive triplet excited states from the initial singlet states. Their modular, three-dimensional architecture provides high structural tunability, enabling a precise optimization of water solubility, cellular uptake, and absorption wavelengths across the biological transparency window (600–900 nm) by varying ligands and metal centers. Unlike visible light, which only penetrates a few millimeters, NIR light can reach depths of up to 10 cm [2], allowing for the treatment of larger or more deeply seated tumors while minimizing off-target damage to healthy tissues. Nevertheless, despite these advances, important challenges still remain, and there is still a long way to go.

Building on this, over the last decade there has been an increasing interest in developing polymetallic complexes as PDT-PSs, with various motivations and aims behind this approach [3–5]. The evolution from mononuclear design to bimetallic and polynuclear architecture represents a major shift toward multifunctional precision medicine. By combining two or more metal centers within a single molecular framework, such compounds can comprise two different functionalities, exhibiting unique photophysical properties—such as metal-to-metal charge transfer (MMCT) and coupled energy transfer processes—that are not attainable in mononuclear species.

As outlined above, a primary challenge in clinical PDT is the hypoxic microenvironment of solid tumors, which limits the effectiveness of oxygen-dependent Type II mechanisms. Bimetallic complexes can overcome this limitation by favoring Type I photochemical pathways that generate highly cytotoxic radicals, such as hydroxyl (·OH) and superoxide ($O_2 \cdot -$), under low-oxygen conditions. Furthermore, the incorporation of photocatalytic fragments enables the light-driven oxidation of essential coenzymes, such as NADH and NAD(P)H, thereby inducing metabolic and redox imbalance and triggering cell death even under severe hypoxia [6,7]. Selectivity can be further enhanced through subcellular targeting. In particular, the cationic nature of many Group 8 complexes promotes mitochondrial accumulation driven by the organelle's negative membrane potential. Thus, heterobimetallic architectures offer a sophisticated multimodal and potentially synergistic therapeutic approach, in which a single molecular platform can integrate multiple (photo)activation mechanisms to target cancer cells.

Besides, advanced conjugates go beyond direct destruction to induce immunogenic cell death (ICD) [8], stimulating the immune system through the release of damage-associated molecular patterns (DAMPs) like ATP and calreticulin, which helps prevent tumor recurrence and immune evasion.

In addition, the success of these multifunctional platforms relies on the engineering of bridging ligands -linkers, which serve as the structural and electronic scaffold between metal centers, as well as bioactive or targeting fragments. By utilizing rigid, extended conjugated linkers or Donor–Acceptor–Donor (D-A-D) architectures, photophysical properties can be precisely tuned, NIR absorption enhanced, and lifetimes of reactive triplet states prolonged.

Ultimately, the high performance of these complexes is driven by the heavy atom effect. The resulting strong spin-orbit coupling (SOC) facilitates efficient ISC, ensuring that absorbed light energy is effectively channeled into the triplet manifold for the generation of reactive oxygen species, thereby providing a potent light-triggered cytotoxic response while maintaining the dark stability required for clinical safety.

Herein, we provide a comprehensive review of bimetallic Group 8 complexes containing Fe, Ru, or Os for light-driven cancer therapy, with a particular focus on advances reported over the last decade. Both homo- and heterobimetallic, as well as multimetallic complexes are discussed. To better understand their design principles, particular attention is given to the nature of the linker and its influence on the properties of the resulting complexes, highlighting representative examples. Given the distinct physicochemical properties

and mechanisms of action associated with each metal center, the complexes are classified according to their metal composition.

2. Bridging Ligand Engineering: Design Strategies

The development of next-generation bimetallic PSs for cancer therapy relies heavily on the rational engineering of the bridging ligand—linker—which acts as the structural and electronic scaffold connecting the metal centers [9–11]. Unlike mononuclear complexes, bimetallic and multinuclear systems exhibit unique photophysical properties—such as photoinduced electron and energy transfer processes—that arise from the coupled interactions between the metal units. Therefore, the selection of the linker is crucial, as it dictates the absorption window, the degree of electronic communication, and the ultimate therapeutic mechanism of the assembly.

2.1. Enhanced Light Harvesting

Aiming to ensure deeper tissue penetration, the structural design of new PSs primarily relies on shifting their absorption profile toward the biological transparency window (600–1000 nm) [12,13]. For this purpose, many strategies have been developed worldwide, such as: extended-conjugation, D-A-D architectures and heterocyclic and polycyclic linkers. As reported by Liu, B. et al. in 2018, the incorporation of rigid, conjugated linkers such as fluorene has been shown to enhance molar extinction coefficients in the visible region [14]. Further expansion of the π-system using ethynyl (acetylene) connectors or alkenyl groups, as well as N-substituted carbazoles, has significantly shown red-shifted absorption bands and facilitation of intraligand charge transfer (ILCT) transitions (Figure 1a) [14,15]. Relating to D-A-D architectures, recent strategies have employed linkers such as diketopyrrolopyrrole (DPP)-based systems to achieve strong NIR absorption at approximately 700 nm [13]. This design enhances intramolecular charge-transfer efficiency and promotes the population of reactive triplet states even under hypoxic conditions. Finally, the use of pyrenyl, benzothiadiazole, and isoindigo linkers in Ru(II) metal–organic–metal triads has yielded some of the highest phototherapeutic indices (PI > 27,000) reported to date. These heterocyclic linkers have been shown to induce a significant ILCT character, which stabilizes low-energy transitions and improves $^1O_2$ generation [10,16].

2.2. Electronic Communication and Charge Transfer

The effectiveness of a bimetallic complex is often governed by how the bridging ligand mediates electron and energy transfer between the metal centers. To this end, efficient intramolecular energy transfer is highly desirable. As demonstrated by Wang et al. in 2023 [17], the linker enables nearly 100% efficient intramolecular energy transfer in a heterobimetallic Ru(II)–Re(I) system, from the Re(I) chromophore to the Ru(II) center, thereby drastically altering the photophysical properties of the assembly. Moreover, consideration of MMCT processes is essential when designing bimetallic systems. Innovative architectures, such as the Os(II)–Pt(II) system reported by Francés-Monerris et al. in 2022, in which the metal centers are bridged by the rigid 2,3-bis(2-pyridyl)pyrazine ligand, have revealed elusive MMCT excited states (Figure 1b) [18]. In this study, these states play a pivotal role in the synergistic activation of the platinum center, promoting photolabilization of the Pt–Cl bond and subsequent DNA binding [18]. In addition, the balance between conjugative communication and electronic decoupling is dictated by the geometry of the bridging ligand. For instance, a planar benzene linker promotes efficient conjugative communication between the metal centers, whereas a nonplanar biphenyl linker electronically decouples them, leading to blue-shifted, less intense absorption bands [16].

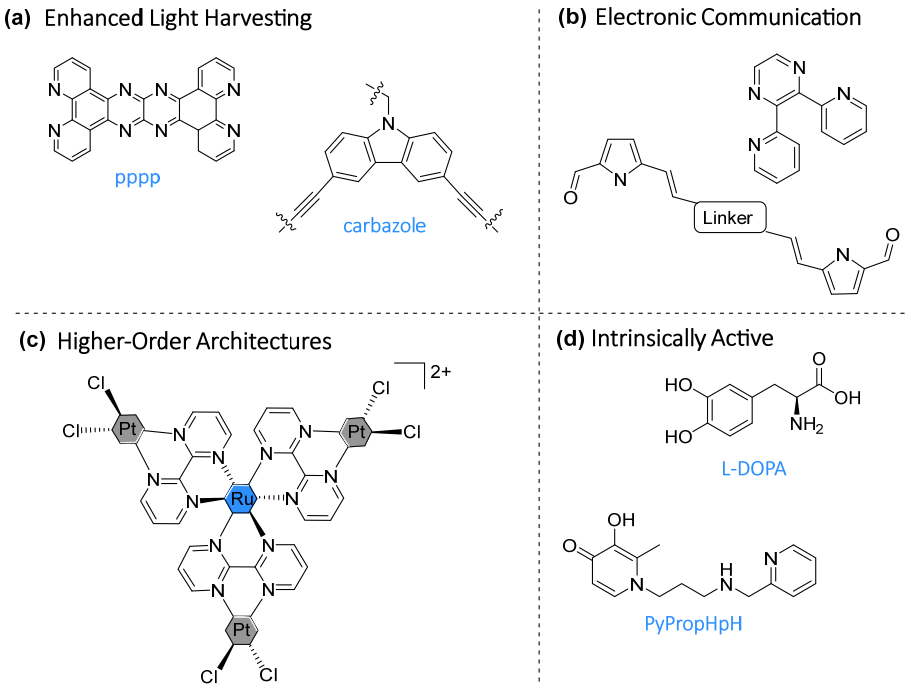


Figure 1. Design strategies of bridging ligands—linkers.

2.3. Higher-Order Architectures

Advanced structural strategies extend beyond simple binuclear designs to include higher-order and chiral architectures. In this context, the transition to tetranuclear architectures (e.g., Ru(II)–Pt(II) or Ru(II)–Re(I)) developed by J. Karges et al. using 2,2′-bipyrimidine bridges has opened new frontiers in multimodal therapy (Figure 1c) [19,20]. These systems can simultaneously release multiple therapeutic fragments or induce specific cell-death pathways like RIP3-regulated necrosis. In a similar manner, by incorporation of chiral and helical spacers like trans-1,2-cyclohexanediamine (DACH), optically pure Ir(III) metallohelices can be constructed. The chirality of these assemblies is a decisive factor in their biological performance, enabling enantiomer-dependent migration from the mitochondria to the nucleus after light irradiation [21].

2.4. Functional Ligands for Biocompatibility and Subcellular Targeting

Beyond serving as mere structural scaffolds, the strategic selection of ligands with intrinsic biological activity or biocompatibility has emerged as an effective approach to enhance the therapeutic efficacy and selectivity of bimetallic complexes. For example, the incorporation of L-DOPA (levodopa) as a biocompatible bridging ligand in red-light-activable Fe(III)–Ru(II) complexes has been demonstrated to provide a cohesive molecular framework for dual-modality PDT, while exploiting the natural uptake pathways of this amino acid derivative [22]. Likewise, Tran et al. reported in 2024 the development of PyPropHpH, a rationally modified derivative of deferiprone (dhpH), an FDA-approved iron chelator used to treat iron overload. When incorporated into Co(III)–Ru(II) heterobimetallic complexes, PyPropHpH functions as a hypoxia-activated prodrug that, upon bioreductive release, depletes the labile iron pool and inhibits ribonucleotide reductase, thereby enhancing anticancer activity (Figure 1d) [23].

This concept of functional ligands also extends to the axial positions of Pt(IV) prodrugs within heterometallic frameworks. For example, the incorporation of the kinase inhibitor ceritinib as an axial ligand in Os(II)–Pt(IV) conjugates, or phenylbutyrate, a histone deacetylase (HDAC) inhibitor, in Ru(II)–Pt(IV) assemblies, enables multimodal

therapeutic activity [8,24]. These bioactive ligands can decondense chromatin or inhibit pro-survival signaling pathways, thereby sensitizing cancer cells to the primary photodynamic or chemotherapeutic effects of the metal centers. Similarly, the incorporation of targeting moieties such as biotin (vitamin B7) has been shown to enhance the selective uptake of Ir(III)–Pt(IV) conjugates by cancer cells while minimizing accumulation in healthy tissues [25].

A further design strategy involves subtle structural modifications to the bridging ligand, which can profoundly influence the subcellular localization of bimetallic complexes. For example, replacing the dipyrido[3,2-a:2′,3′-c]phenazine (dppz) ligand with benzo[i]dipyrido[3,2-a:2′,3′-c]phenazine (dppn) increases the amphiphilicity of the complex, redirecting its accumulation from the nucleus to the mitochondrial membranes, as demonstrated for a Ru(II)–Re(I) heterobimetallic complex reported by Saeed et al. in 2023 [26]. This redistribution alters the dominant mechanism of action, shifting it from chemotoxicity to phototoxicity, underscoring the importance of ligand selection.

3. Multi-Pharmacophore and Group 8 Containing Bimetallic Complexes

3.1. Ruthenium(II)-Based Bimetallic Complexes

Over the past two decades, Ru(II)-based metal complexes have attracted considerable attention as photosensitizers for PDT owing to their ability to meet many of the key requirements for effective treatment [27–29]. Moreover, the clinical progress of the Ru(II)-based photosensitizer TLD-1433, which is currently undergoing Phase II clinical trials for the treatment of non-muscle-invasive bladder cancer (NMIBC), further highlights the translational potential of this class of compounds [30,31].

Particularly, Ru(II) polypyridyl complexes are highly effective photosensitizers in PDT due to their modular 3D architecture, which allows for precise tuning of their photophysical and photochemical properties through the careful design and selection of ligands [30,32,33]. They possess ideal excited-state dynamics, including efficient ISC to exceptionally long-lived triplet states, which significantly increases the probability of interacting with molecular oxygen to generate cytotoxic ROS [30,32]. Their versatility allows them to operate through both Type I and Type II pathways, ensuring therapeutic efficacy even in hypoxic tumor environments where traditional organic photosensitizers often lose potency [30,33,34]. Furthermore, these complexes exhibit high chemical stability, negligible dark toxicity, and massive phototherapeutic indices, with modern designs enabling activation by tissue-penetrating deep-red or near-infrared light to treat large or deep-seated tumors effectively [35].

3.1.1. Homobimetallic Ruthenium(II) Complexes

A Second Ru(II) Nucleus: Advantages

Integrating a second Ru(II) center into a bimetallic system transforms its therapeutic potential by enabling properties unattainable by mononuclear complexes.

Ru(II) binuclear complexes are characterized by high chemical and light stability, meaning they are resistant to degradation during treatment. They also exhibit highly efficient intersystem crossing (ISC)—converting nearly all absorbed energy into long-lived triplet excited states (sometimes exceeding 1.000 µs), which maximizes the opportunity for the complex to interact with oxygen or other substrates.

A hallmark of these systems is their ability to generate singlet oxygen ($^1O_2$) with very high quantum yields. This efficiency makes them powerful photosensitizers for Photodynamic Therapy (PDT), where $^1O_2$ acts as the primary cytotoxic agent to destroy malignant cells. Their modular 3D structure allows the tuning of their photophysical properties through a specific choice of ligands. This includes shifting light absorption into the optical window (650–900 nm) for deeper tissue penetration or enhancing properties like

two-photon absorption for targeted therapy. Finally, these complexes generally exhibit negligible toxicity in the absence of light, only becoming lethal to cancer cells when triggered by specific wavelengths. This selectivity results in outstanding phototherapeutic indices (PI), ensuring that the treatment is highly potent against tumors while sparing healthy, non-irradiated tissue.

π-Extended Bridging Ligands

The most common binuclear complexes are designed featuring bridging ligands with delocalized π-electron density, like tetrapyrido[3,2-a:2′,3′-c:3″,2″-h:2‴,3‴-j]phenazine (tpphz) [36–38], imidazophenanthroline-derivatives [39], benzimidazoles [40], or 2,3-bis(2-pyridyl)pyrazine (dpp)/2,3-bis(2-pyridyl)pyrazine (dpq) [41].

Related to bimetallic Ru-tpphz complexes, novel Ru–Ru binuclear complexes bearing [1,10]phenanthrolino[5″,6″:5′,6′]pyrazino[2′,3′:5,6]pyrazino[2,3f][1,10]phenanthroline (pppp) and different N^N ligands were designed with suitable features as PSs for PDT/PTT (Figure 2a). The highly conjugated and electron-rich bridging ligand favors a low-energy excited state, which is easier to reach. At 808 nm, the complexes were able to generate singlet oxygen (PDT effect) and to increase the temperature of aqueous solutions (PTT effect). One of the complexes displayed special features in cells, with PI values of 784 in A375 cells under two-photon irradiation at 808 nm. In vivo studies revealed that the tumor temperature increased by 10 °C and the size was reduced by 90% [12].

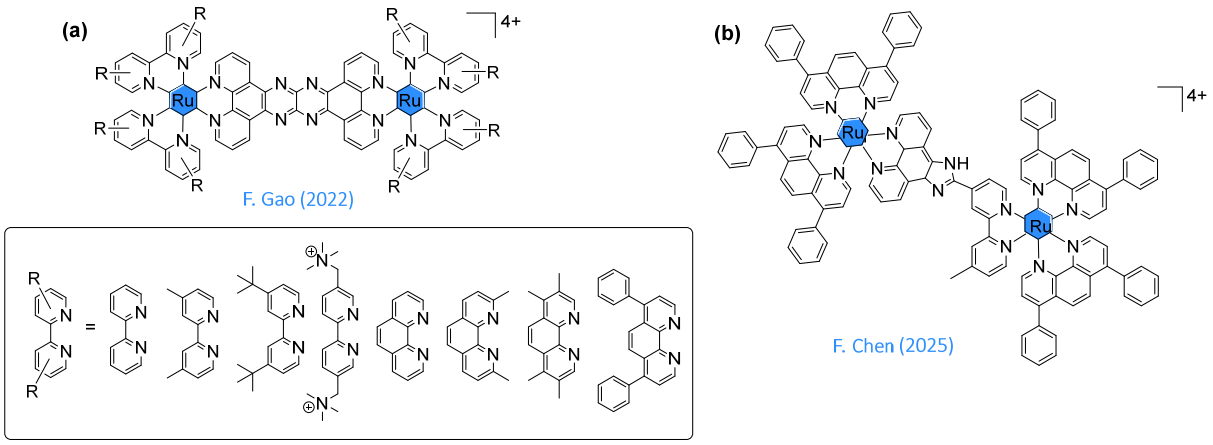


Figure 2. Chemical structures of Ru–Ru homobimetallic complexes bearing π-extended ligands (**a**) F. Gao and coworkers [12], and (**b**) F. Chen and coworkers [9].

A Ru–Ru binuclear complex bearing a bipyridyl imidazophenanthroline ligand showed interesting properties as a potential ferroptosis photoinduction photosensitizer (Figure 2b). This complex can generate singlet oxygen, a 24-fold increase regarding $[Ru(bpy)_3]^{2+}$ under blue light irradiation, as well as $OH^{\bullet}$ and $O_2^{\bullet-}$. The complex was not dark toxic, but phototoxic under blue light with IC_{50} values of 2.33 μM and 3.10 μM for A549 and MGC-803, leading to PI values of >21 and >16, respectively. Further testing in healthy cells revealed selectivity indices (SI) of 2.62 and 1.96, highlighting good selectivity between cancer and healthy cells. These data, along with the perturbation of NADH and GSH levels, positioned the Ru–Ru complex as a promising Type I and II photosensitizer for cancer treatment [9].

Ru Triads

BODIPYs, pyrrolides, and carbazoles are organic molecules that absorb energy in the visible region of the spectrum and can work as light-harvesting chromophores and linkers to transfer electronic density in Ruthenium–Chromophore–Ruthenium triads. There are

many examples of mononuclear Ru–BODIPY or Ru–pyrrolide complexes described in the literature that take advantage of the chromophore to achieve absorption in the green or even red window for their use in PDT.

The addition of a second Ru(II) fragment frequently causes not only a bathochromic shift, but also a hyperchromic shift, therefore enhancing singlet oxygen quantum yields and phototoxicity.

One of the first examples known is the complex Ru–BODIPY–Ru designed and prepared by M. Draper and coworkers (Figure 3a) [42]. The BODIPY linker, along with the second Ru(II) fragment, causes a bathochromic shift with a maximum at 570 nm and extends the lifetime to over 1 μs, when compared with the mononuclear complex. Their promising photodynamic effect is based on the high singlet oxygen quantum yield (79.4%), low dark toxicity in HeLa cells, and uptake in the cytosol.

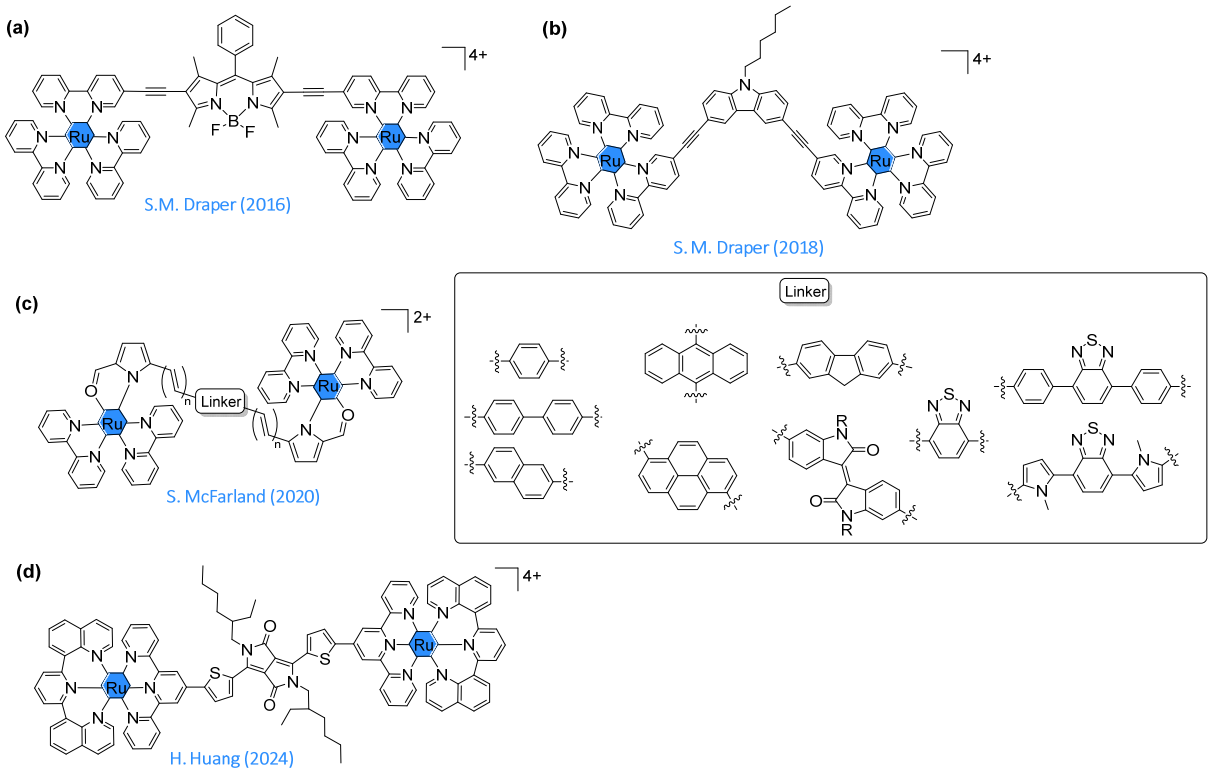


Figure 3. Chemical structures of Ru–Ru homobimetallic complexes bearing different chromophores and linkers. (**a**) Draper and coworkers [42], (**b**) S.M. Draper and coworkers [15], (**c**) S. McFarland and coworkers [16], and (**d**) H. Huang and coworkers [10].

Carbazoles are organic molecules composed of pyrrole fused with two benzene rings. The lone pair of the N-atom delocalizes along the planar system, causing this structure to behave as an electron-rich fragment. When used as a linker connected through alkynyl groups between two Ru(II) fragments, the π-extension becomes even higher, leading to a stabilization of the LUMO, which reduces the HOMO–LUMO gap, bathochromically shifting the absorption. A bimetallic complex designed by M. Draper (Figure 3b) shows an excellent singlet oxygen quantum yield of 83.3% using DPBF as the probe [15].

Pyrrolide ligands form strong Ru(II)–N(η^1) bonds, which stabilize the MLCT excited states while preventing ligand dissociation through dissociative ^{3}MC states. Different examples of bis[Ru(II)–pyrrolide] triads have been reported in the literature [16] by extending or modifying the conjugation of the linkers, leading to absorption patterns expanding up to 600 nm with a several-fold increase in the extinction coefficient (Figure 3c). When the

linker was benzothiadiazole or isoindigo, the absorption shifted bathochromically up to 700 nm. These systems can generate singlet oxygen with values ranging from 5 to 77%, and apparently non-emissive ^{3}IL or ^{3}ILCT states could be involved in the high values obtained. A good correlation was obtained between the singlet oxygen quantum yields and the photocytotoxicities of the complexes, with one of the complexes (the one bearing pyrenyl) standing out with a PI = 5439 when using visible light (16 h, visible light irradiation, 28 J/cm^2, 7.8 mW/cm^2) and PI = 261 with red light (16 h, 625 nm, 100 J/cm^2, 42 mW/cm^2).

Some theoretical studies performed on these bimetallic complexes confirmed the experimental results and revealed that the π-extended ligands induce ILCT states in the bimetallic complexes, favoring singlet oxygen and ROS generation [10].

It is well-known that some types of chromophores can shift the absorption intrinsically to the red. This is the case of diketopyrrolopyrrol (DPP) ligands. A tridentate binuclear Ru(II) complex bearing a DPP ligand linker (Figure 3d) exhibited an outstanding visible/NIR absorption with a maximum around 700 nm. This complex was able to produce both singlet oxygen (Type I) and $OH^{\bullet}$ and $O_2^{\bullet -}$ (Type II). Their phototoxicity indices of 101 and 10 in the 4T1 cell line under normoxia and hypoxia, respectively, upon irradiation at 700 nm, make it a promising photosensitizer [13].

Some other chromophores, like porphyrins, are interesting molecules that have strong absorption peaks in the visible region of the spectra (Soret band around 420 nm) and smaller bands between 560 and 600 nm (Q-bands). These porphyrins allow designing higher-order architectures by the inclusion of even four metal fragments. The complex, prepared by S. Draper in 2019 (Figure 4) [43], shows a red-shifted absorption compared with the Zn–porphyrin and a high singlet oxygen quantum yield (40%), even higher than that of the respective monometallic complex (20%). Finally, the complex is not toxic in dark conditions, whereas upon irradiation with red light its toxicity increases, inducing a decrease in cell viability of 77% at 0.25 μM, which makes it a good candidate for PDT.

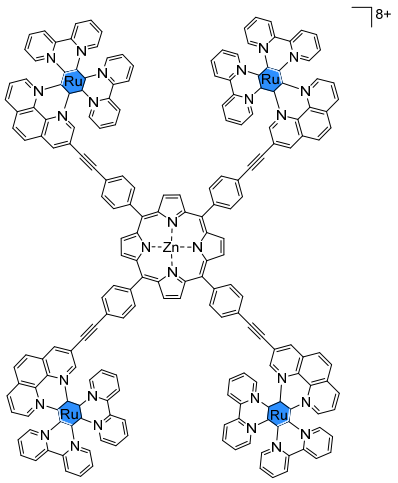


Figure 4. Chemical structure of a high-order architecture of Ru homometallic complexes bearing porphyrin.

3.1.2. Heterobimetallic Ruthenium(II) Complexes

Extending the advantages of homobimetallic Ru(II) complexes, the incorporation of Ru(II) into heterometallic frameworks has emerged as a promising strategy for the development of next-generation light-activated anticancer agents. By combining the well-established photophysical and photobiological properties of Ru(II) with the complementary characteristics of a second metal, these systems offer opportunities to achieve synergistic therapeutic effects beyond those attainable with monometallic complexes. As discussed in

this section, heterobimetallic Ru(II)-based PSs can integrate efficient ROS generation with additional functionalities, such as mitochondrial targeting, hypoxia modulation, redox-active cooperation, and the combination of photodynamic and chemotherapeutic mechanisms.

Ruthenium–Platinum Complexes: Combining Chemo- and Phototherapy

The anticancer activity of cisplatin stems from its ability to form covalent adducts with DNA, thereby disrupting DNA replication and transcription and ultimately triggering apoptosis [44,45]. However, the widespread emergence of platinum-resistant tumors has driven the search for alternative metal-based chemotherapeutics. As outlined above, Ru(II) arene and polypyridyl complexes are among the most promising candidates, which exhibit distinct mechanisms of action and favorable photophysical properties.

In this context, Ru–Pt heterometallic conjugates have become the most extensively investigated class of bimetallic complexes. These systems are designed to combine the well-established DNA-binding and cytotoxic properties of Pt with the photoactivatable characteristics of Ru, enabling light-controlled therapeutic activity while potentially overcoming platinum resistance through complementary or synergistic mechanisms.

One of the earliest strategies, introduced during the first decade of the 2000s, involved the design of trinuclear and tetranuclear heterometallic architectures, with the aim of integrating the complementary properties of ruthenium and platinum within a single molecular scaffold. Early examples include the trinuclear Ru(III)–Pt(II) complex AH-197 (Figure 5a) [46], reported in 2008, which incorporates structural motifs derived from both cisplatin and NAMI-A, the first ruthenium-based anticancer agent to enter clinical trials in the late 1990s. This design sought to combine the potent DNA-binding activity of Pt with the antimetastatic properties associated with Ru, illustrating the potential of multinuclear metal architectures to achieve multimodal anticancer activity. More recently, in 2025, tetranuclear Ru(II)–Pt(II) complexes activated by red light—630 nm—have been developed by the Karges group (Figure 5b) [19]. Upon irradiation, these systems release Pt(II) moieties that accumulate in the nucleus to trigger chemotherapy, while the Ru(II) core remains in the cytoplasm to act as a photocatalyst for $^1O_2$ generation.

A complementary strategy has focused on improving tumor selectivity while overcoming Pt resistance. In 2011, two Ru(II)–Pt(II) complexes utilizing 4,7-diphenyl-1,10-phenanthroline (Ph_2phen, also called bathophenanthroline) ligands demonstrated dramatically enhanced DNA photocleavage efficiency via oxygen-dependent pathways, providing a structural motif that binds to and cleaves DNA at low light flux (Figure 5c) [47]. Similarly, a bimetallic Ru(II)–Pt(II) conjugate was reported in 2025, showing, once again, upon light activation, improved production of singlet oxygen compared with its monometallic congeners (Figure 5d) [48]. This system was encapsulated within polymeric nanoparticles and demonstrated the capacity to eradicate human breast adenocarcinoma monolayer cells and multicellular tumor spheroids under 450 nm (power: 20%, 10 min, 1.2 J cm^{-2}) at nanomolar concentrations. The same year, but using a Pt(IV) complex derivative, an advanced Ru(II)–Pt(IV) conjugate was designed to overcome drug resistance through a dual-action mechanism. In this system, Gibson and Gasser reported a Ru(II) photosensitizer that selectively accumulates in the Golgi apparatus and mediates PDT upon irradiation in the 480–595 nm range, while intracellular reduction of the Pt(IV) prodrug releases cisplatin, which subsequently targets nuclear DNA [24]. To preserve the individual photophysical and biological properties of both metal-based components, the Ru(II) and Pt(IV) units were connected through a long aliphatic linker and, as anticipated, the absorption and emission spectra of the Ru precursor and the Ru–Pt conjugate showed no significant differences, indicating that the Pt(IV) center exerts insignificant influence on the photophysical behavior of the Ru(II) chromophore (Figure 5e).

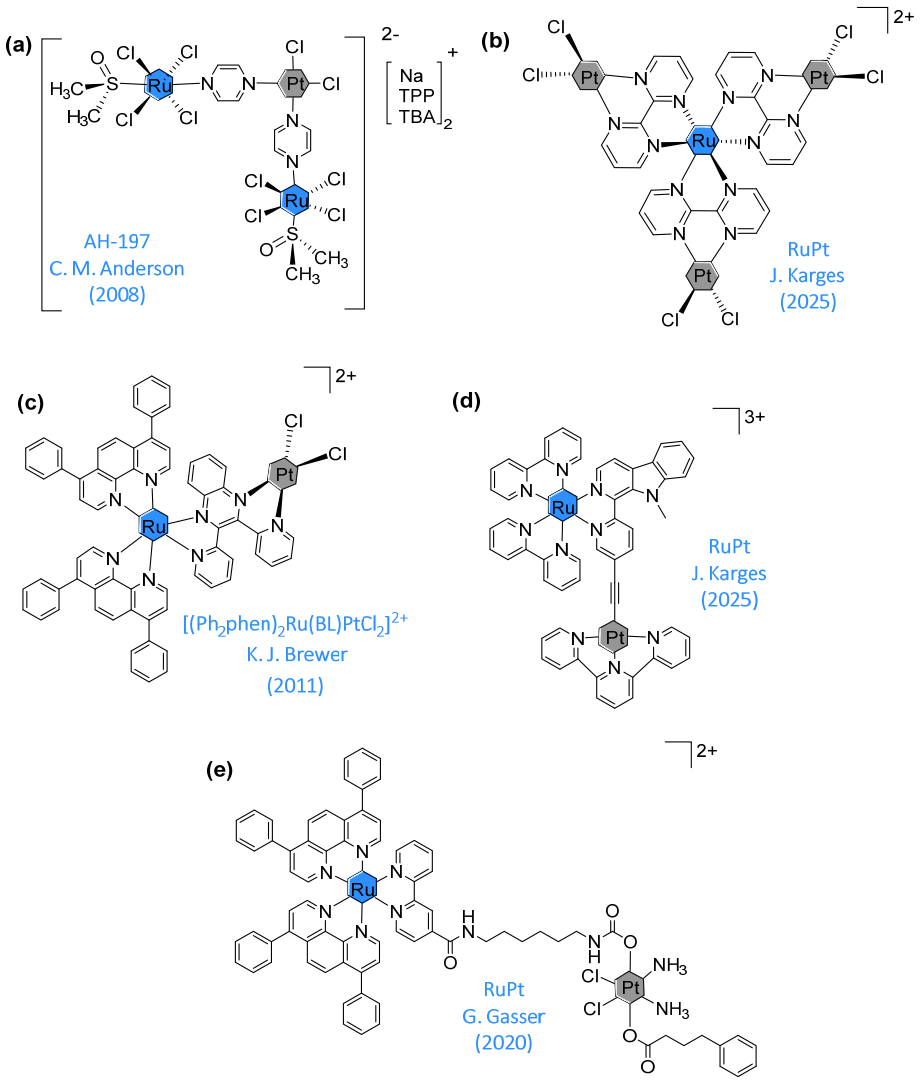


Figure 5. Chemical structures of Ru–Pt heterobimetallic complexes. (**a**) C.M. Anderson and coworkers [49], (**b**) J. Karges and coworkers [19], (**c**) K.J. Brewer and coworkers [47], (**d**) J. Karges and coworkers [48], and (**e**) G. Gasser and coworkers [24].

Ruthenium–Iridium Complexes: Mitochondria Targeting and Hypoxia Management

Following the development of Ru-based metal complexes, Ir(III) complexes have emerged as another highly promising class of metal-based anticancer agents, owing to their remarkable photophysical properties, high photostability, and intrinsic mitochondrial affinity [49,50]. Consequently, the combination of Ru(II) and Ir(III) within a single heterometallic platform has also attracted considerable interest as a strategy to exploit the complementary advantages of both metal centers. In this section, we highlight recent advances in Ru(II)–Ir(III) heterobimetallic complexes, with particular emphasis on their application in mitochondria-targeted therapy and their potential to overcome the limitations imposed by hypoxic tumor microenvironments.

The first hetero-binuclear Ir(III)–Ru(II) complex designed as a dual-modal agent utilized the Ir(III) moiety for mitochondrial localization and PDT, while the Ru(II) complex acted as a PACT agent to induce mitochondrial DNA (mtDNA) damage (450 + 405 nm) (Figure 6a). This combination was reported by Hui Chao's group in 2019 and successfully bypassed cisplatin resistance by triggering mitochondria-mediated apoptosis independently of nuclear DNA repair mechanisms [39]. More recently, in 2024, to address the limitations of oxygen-dependent PDT in solid tumors, the same research group developed a hetero-

bimetallic Ru(II)–Ir(III) photosensitizer that functions through dual Type I and Type II mechanisms (light 450 nm) [11]. Unlike homogeneous complexes, these heterometallic systems can generate multiple ROS, including hydroxyl radicals and superoxide anion radicals, allowing them to kill tumor cells even under severe hypoxia (1%). This study presents the first example of a hetero bimetallic Type-I and Type-II dual photosensitizer (Figure 6b).

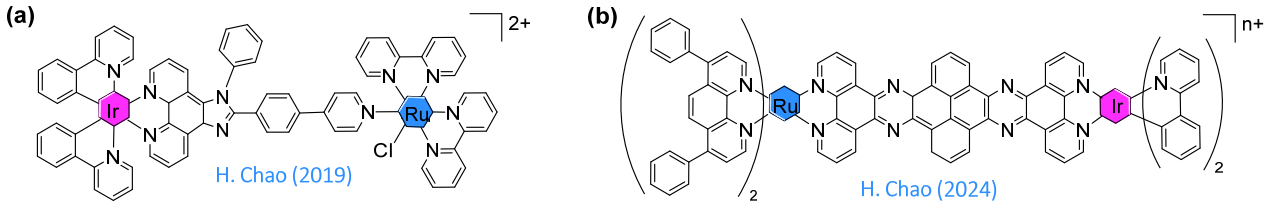


Figure 6. Chemical structures of Ru–Ir heterobimetallic complexes. (**a**) H. Chao and coworkers [39] and, (**b**) H. Chao and coworkers [11].

Ruthenium–Iron and Ruthenium–Cobalt Complexes: Redox-Active Synergy

Earth-abundant 3d transition metals have attracted considerable attention in medicinal inorganic chemistry because of their natural abundance, low cost, reduced toxicity, and diverse redox properties. In particular, iron (Fe) [51] and cobalt (Co) [52–54] possess unique chemical characteristics that enable them to participate in biologically relevant redox processes, making them attractive candidates for the design of multifunctional anticancer agents. Their ability to catalyze ROS generation and regulate iron-dependent cell death pathways has highlighted their potential to overcome some of the limitations associated with conventional PDT. Consequently, in this section, we will discuss the coupling of Ru(II) photosensitizers with earth-abundant 3d transition metals to exploit complementary photophysical and redox properties.

Recently, in 2024, the group of Péter Buglyó designed two Co(III)–Ru(II) heterobimetallic complexes [23], differing in the tetradentate nitrogen ligands (tren—tris(2-aminoethyl)amine—or tpa—tris(2-pyridylmethyl)amine-), as iron-sequestering prodrugs under both normoxia and hypoxia (Figure 7a). In these systems, the Co(III) core acts as a hypoxia-activated "cage" that, upon reduction to Co(II), releases the active iron-chelating ligand (PyPropHpH) to deplete the labile iron pool in cancer cells, while the Ru(II)-*p*-cymene moiety enhances the anticancer activity. Besides, as previously discussed in Section 2, PyPropHpH is a hypoxia-activated deferiprone prodrug able to deplete the labile iron pool and inhibit ribonucleotide reductase in cancer cells upon bioreductive activation. One year later, Mithun Roy and Aarti Upadhyay developed a novel Fe(III)–Ru(II) heterobimetallic complex that integrates an Fe(III)-catecholate moiety, acting as a Type I PS through $^{\cdot}OH$ generation, with a Ru(II)–*p*-cymene moiety that functions as a Type II photosensitizer via $^1O_2$ production [22]. Upon red-light irradiation (600–720 nm), the complex exhibited potent phototoxicity against A549 and HeLa cancer cells while maintaining negligible dark toxicity. Notably, the two metal centers are linked through L-DOPA, a biocompatible catechol-containing amino acid that not only serves as a molecular bridge but also stabilizes the Fe(III)-catecholate coordination environment, contributing to the complex's efficient dual photodynamic activity (Figure 7b).

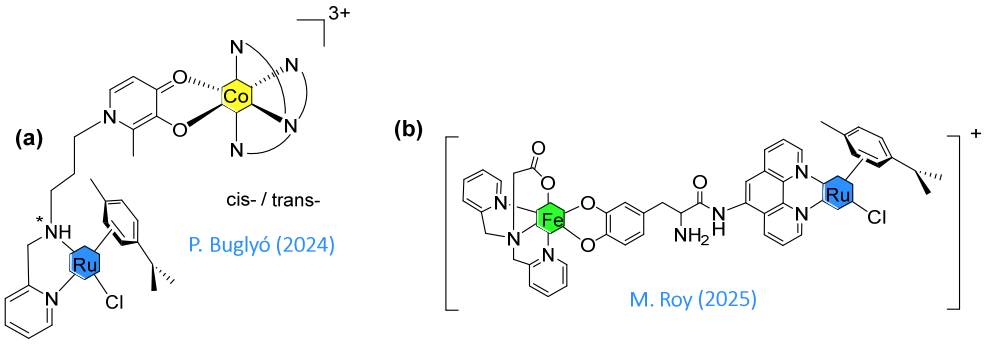


Figure 7. Chemical structures of Ru-(Earth-abundant 3d transition metals) heterobimetallic complexes. (**a**) P. Buglyó and coworkers [22], and (**b**) M. Roy and coworkers [23].

Ruthenium–Rhenium Complexes: Energy Transfer and Emerging Architectures

Rhenium(I) tricarbonyl complexes have long attracted interest as potential anticancer agents, exhibiting cytotoxic activities comparable to or even exceeding those of cisplatin [55,56]. Beyond their chemotherapeutic potential, these complexes have also demonstrated promising performance as PSs in PDT [57,58]. Moreover, integrating a Ru(II) complex with a Re(I) tricarbonyl unit within a single molecular framework has been reported to promote efficient intramolecular energy transfer, thereby improving the photophysical properties of the resulting complexes [59,60]. Consequently, the incorporation of both heavy-metal centers into a single Ru(II)–Re(I) heterobimetallic scaffold represents an attractive design strategy, as it is expected to enhance spin-orbit coupling and ISC efficiency, ultimately improving ROS generation and photodynamic performance. To the best of our knowledge, the first example of a binuclear Ru(II)–Re(I) complex featuring a tripodal coordination mode at the Re center was developed in 2023 by Gasser and coworkers (Figure 8a) [17]. The electronic coupling between the two metal centers was designed to potentially induce a shift in the absorption spectrum of the resulting complex, thereby providing access to enhanced photophysical properties. Despite the limited stability exhibited by the bimetallic complex, the parent Ru(II) complex exhibited strong and selective mitochondrial phototoxicity toward cancer cells, surpassing PPIX. In the same year, the group of J.A. Thomas showed how minor structural modifications, such as substituting dppz with dppn ligands, could redirect heterodinuclear Ru(II)–Re(I) systems from the nucleus to mitochondrial membranes [26]. This shift effectively transitions the therapeutic mechanism from classical genotoxicity to mitochondria-targeted PDT (Figure 8b). Moreover, following the previously cited strategy of higher-order multinuclear metal architectures, in 2025, Karges' group developed the first tetranuclear Ru(II)–Re(I) complex bridged by 2,2′-bipyrimidine (Figure 8c). This system induced cell death via RIP3-regulated necrosis and demonstrated superior efficacy in eradicating 3D multicellular tumor spheroids compared to traditional cisplatin [20].

Similarly, a series of heterodinuclear Ru–Os complexes have been investigated lately. Particularly interesting is the work reported by F.Gao et al. in 2023 (Figure 8d) [61]. This complex demonstrated enhanced PDT/PTT activity compared with its homonuclear analogs, efficiently eradicating PDT-resistant melanoma and cisplatin-resistant lung tumors in mice with low metal accumulation and minimal toxicity to normal cells. Its mitochondrial targeting, IR-induced singlet oxygen generation, and photothermal effects highlight its potential for the treatment of large and deep tumors.

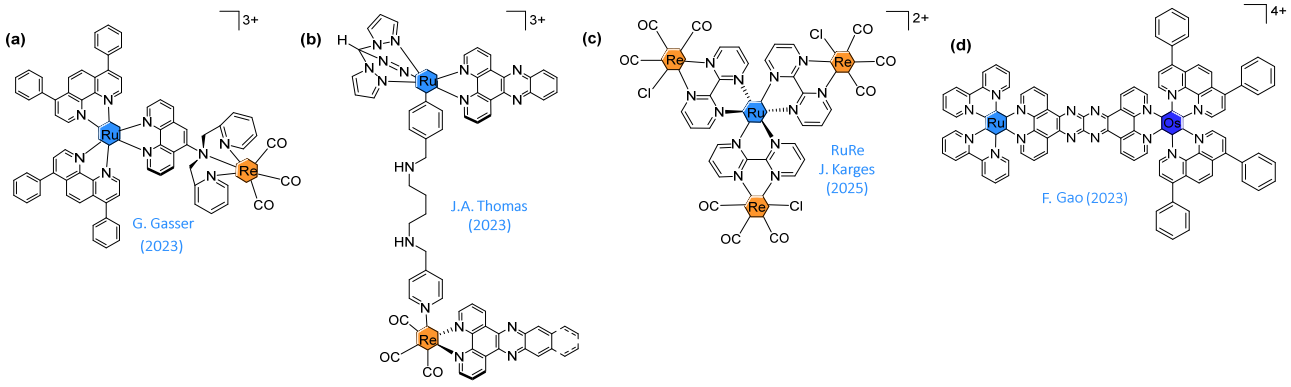


Figure 8. Chemical structures of Ru–Re heterobimetallic complexes. (**a**) G. Gasser and coworkers [17], (**b**) J.A. Thomas and coworkers [26], (**c**) J. Karges and coworkers [20] and, (**d**) F. Gao and coworkers [61].

3.2. Iron (III)-Based Bimetallic Complexes

As previously discussed, Fe(III) complexes, particularly those coordinated with catecholate or phenolate/carboxylate ligands, have emerged as pivotal agents in the development of Type I PDT as well as promising agents in the regulation of iron-dependent cell death pathways [27,62].

Their therapeutic effect is driven by a ligand-to-metal charge transfer (LMCT) process. Upon irradiation with red light (600–720 nm), excitation of the Fe(III)–O bond induces photodecarboxylation and the in situ reduction of Fe(III) to Fe(II). This photoredox process simultaneously generates highly cytotoxic $^{\cdot}$OH radicals (Fenton reaction), enabling efficient photocytotoxicity under both normoxic and hypoxic conditions and making it especially promising for microenvironments where O_2-dependent therapies are limited.

3.2.1. Heterobimetallic Iron (III) Complexes

Iron–Manganese Complexes: Synergy of Type I PDT and PACT

The combination of Fe(III) and Mn(I) within a single photoactive heterobimetallic architecture was, for the first time, developed by Mithun Roy in 2025, combining the Type I PDT capabilities of Fe(III) with PACT mediated by Mn(I) (Figure 9a) [62]. In this platform, the Fe(III) moiety generates $^{\cdot}$OH upon light exposure, while the Mn(I) tricarbonyl unit facilitates the photoactivated release of carbon monoxide (CO). CO acts as a potent cytotoxic agent by inducing mitochondrial dysfunction and apoptosis. This combination ensures high therapeutic efficacy regardless of oxygen levels, as PACT (CO release) does not depend on O_2 to produce its effects. The same group reported in 2026 the development of another Mn(I) tricarbonyl complex functionalized with Prussian blue nanoparticles (PBNPs) as a dual modality therapeutic nanoplatform for combined PACT and PDT (Figure 9b) [63]. PBNPs represent a sophisticated application of Fe(II/III) in nanomedicine, utilizing an FDA-approved iron hexacyanoferrate framework ($Fe_4[Fe(CN)_6]_3{\cdot}nH_2O$) [64]. These systems are characterized by their intervalence charge transfer between the Fe(II) and Fe(III) centers, which grants them strong absorption in the red and near-infrared (NIR) regions. This intrinsic optical activity allows PBNPs to serve as multifunctional platforms for dual-mode phototherapy: (a) as efficient photothermal (PTT) agents, converting light into heat to destroy tumor cells; and (b) as effective PDT systems, thanks to their ability to generate $^1O_2$ under red-light activation. Furthermore, their porous structure and cyanide ligands provide stable coordination sites for anchoring other therapeutic cargos, such as metal carbonyls, to enhance therapeutic synergy. The integration of these PBNPs with the Mn(I) carbonyl complex in a single molecular framework confirmed the dual photoresponsive functionality

of this nanohybrid system, demonstrating efficient red-light-induced controlled CO release, enhanced by the photothermal properties of PBNPs and $^1O_2$ generation.

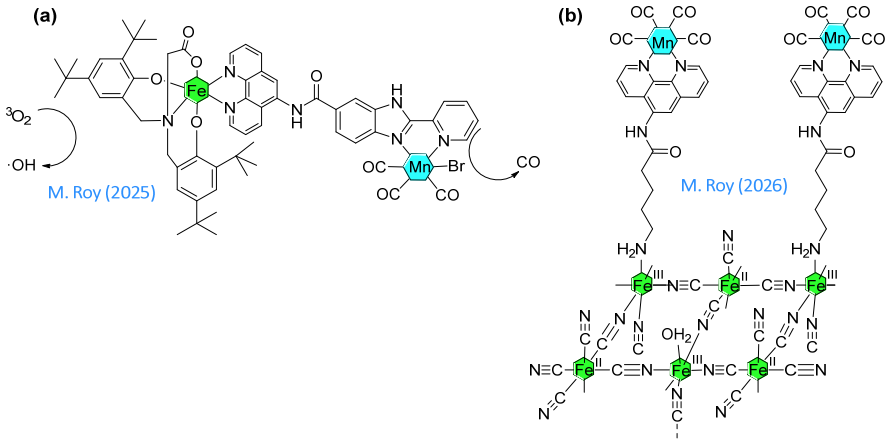


Figure 9. Chemical structures of Fe–Mn heterobimetallic complexes. (**a**,**b**) M. Roy and coworkers [62,63].

Iron–Ruthenium Complexes: Dual Type I/Type II Platforms

As described above for Ru-based systems, heterobimetallic Fe(III)–Ru(II) complexes have been designed as dual-modality PDT tools that accumulate diverse ROS [22]. Within this cohesive framework, the Fe(III) catecholate moiety acts as a Type I agent (·OH generation), while the Ru(II) *p*-cymene moiety functions as an efficient Type II agent. This bimodal strategy maximizes oxidative stress and triggers caspase-dependent apoptosis more effectively than the individual metal components.

3.3. Osmium(II)-Based Bimetallic Complexes

Osmium complexes have recently shown interesting properties as PDT agents. Osmium derivatives serve as potent panchromatic photosensitizers that absorb light deep into the near-infrared (NIR) biological window and possess remarkable resistance to photobleaching [65–67]. They provide a critical advantage by maintaining high phototoxicity in hypoxic tumors through oxygen-independent mechanisms, such as superoxide radical release and the induction of ferroptosis [65]. Furthermore, these systems are biologically stable, useful for NIR cellular imaging, and have demonstrated successful tumor reduction in mouse models [67]. Conversely, disadvantages include low singlet oxygen quantum yields in aqueous environments and shorter excited-state lifetimes compared to their ruthenium analogs [66]. Additionally, while designed for light-triggered activity, some osmium derivatives or their photolytic products can exhibit dark cytotoxicity, behaving as chemotherapeutic agents [68] or photothermal agents for photothermal therapy (PTT) [69] rather than purely light-controlled photosensitizers.

3.3.1. Homobimetallic Osmium(II) Complexes

Panchromatic Absorption in the NIR Region

The combination of two osmium centers outperforms monometallic versions by offering superior light-harvesting properties and intense absorption in the near-infrared region, facilitating deeper tissue penetration. Their larger molecular skeletons enable unique excited states and powerful multielectron redox capacity through coupled electronic interactions between the two metal centers [69,70]. One of these examples (Figure 10) is a powerful photothermal agent when irradiated at 808 nm [69].

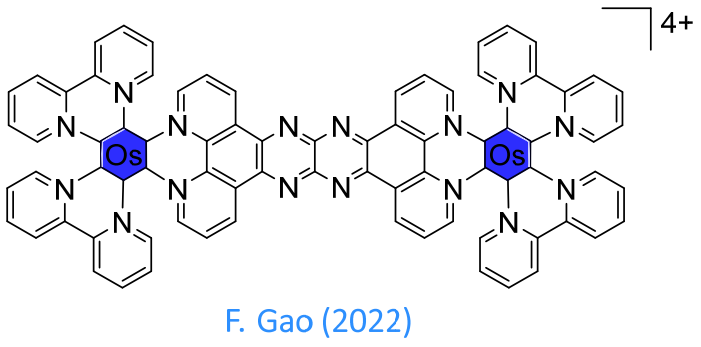


Figure 10. Chemical structure of an Os–Os homobimetallic complex for photothermal therapy (PTT) [69].

To the best of our knowledge, the only bimetallic Os–Os complex reported to date (Figure 11) as a PDT agent [70] is the one described by Lu and Chen, and it shows better cellular uptake than the monometallic complex, due to enhanced lipophilicity. Although the photoactivation of the complexes is limited in most of the cell lines tested, and only one gastric cancer cell line has a higher PI value of around 10, the complex can produce singlet oxygen and has an extended absorption up to 750 nm, a relevant feature for PDT.

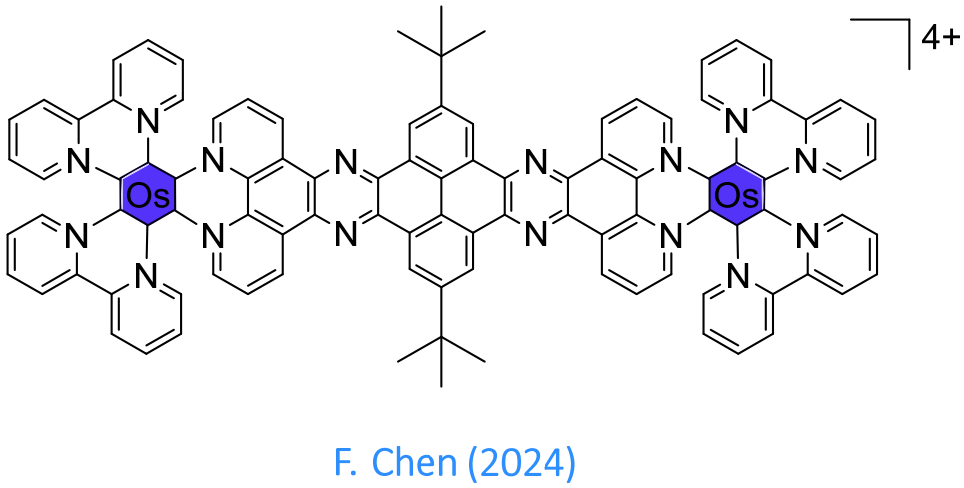


Figure 11. Chemical structure of Os–Os homobimetallic complex for PDT [70].

3.3.2. Heterobimetallic Osmium(II) Complexes

Osmium–Iron Complexes: Photocatalytic Cancer Therapy (PCT) and Strong Visible Absorption

The combination of Os(II) with ferrocene, Fe(III) (Figure 12), merges the panchromatic absorption of osmium complexes with the hyperchromism of ferrocene, thus enhancing the absorption in the visible region, with a maximum at 530 nm and weak absorption extending up to 900 nm. This bimetallic complex stands out for its great stability. Although it can generate small amounts of singlet oxygen, it mainly produces Type I ROS and can oxidize NADH to NAD^+. Its negligible dark toxicity, along with a promising PI value of 50, makes this combination strategically interesting for PCT [71].

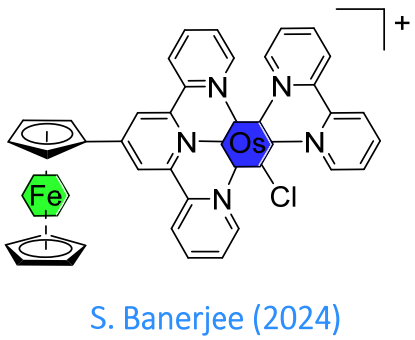


Figure 12. Chemical structure of Os–Fe heterobimetallic complex [71].

Osmium–Platinum Complexes: PDT and Chemotherapy Synergy

Platinum complexes have been used as anticancer agents for decades, since the discovery of cisplatin. Therefore, the combination of different transition metal complexes with Pt-based fragments, both Pt(II) and Pt(IV), has emerged as a promising strategy for cancer treatments [72–74]. The architecture of Os–Pt bimetallic complexes has recently been described. The first example reported by Alberto and Francés-Monerris depicts an Os(II)–Pt(II) complex (Figure 13a) with a dual mechanism studied by theoretical methods: light activation causes the photoexcited hydrolysis of the Pt–Cl bond in the triplet state, whereas the Os fragment activates the classical Type II PDT [18].

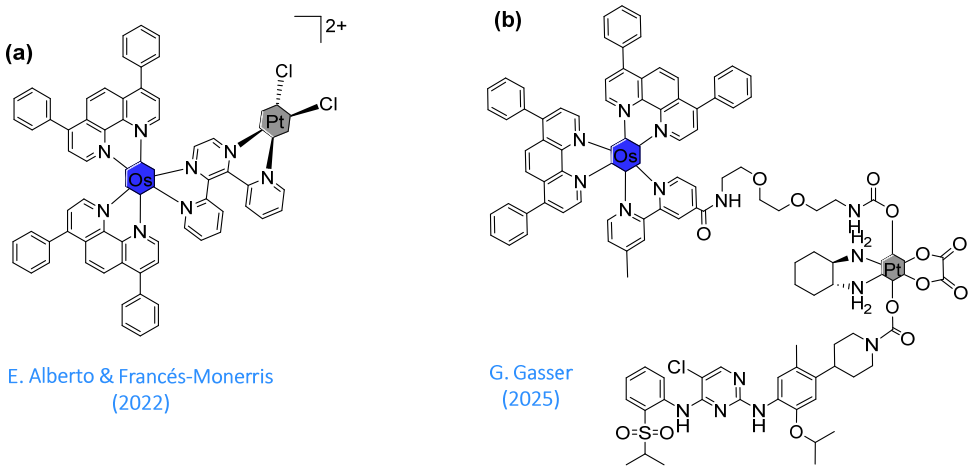


Figure 13. Chemical structures of Os–Pt heterobimetallic complexes. (**a**) E. Alberto and Francés-Monerris [18] and (**b**) G. Gasser and coworkers [8].

A very recent example of an Os(II)–Pt(IV) complex (Figure 13b) reported by M. Redrado et al. was designed to undergo a triple mechanism: PDT, chemotherapy and immunogenic cell death (ICD) [8]. Thus, the Os fragment acts as the PS that is activated under 740 nm light irradiation; then the Pt(IV) fragment releases oxaliplatin after self-reduction to a Pt(II) species; ceritinib, a kinase inhibitor chemotherapeutic agent, was conjugated to an axial position of the Pt center to be released after reduction of the Pt center. This conjugate displays phototoxicity in the low nanomolar range in ovarian cancer cells and reduced cancer-cell migration. It also shows evidence of hallmarks of immunogenic cell death, including enhanced phagocytosis.

Table 1 gathers the properties and results of the homo and heterometallic Fe, Ru and Os complexes for comparative purposes.

Table 1. Photoinduced effects, excitation wavelengths and phototoxicities (IC_{50} and PI) of the homo and heterometallic complexes of Fe, Ru and Os described above.

Metal	Oxidation State	Photoinduced Effects	Excitation Wavelength (nm)	Cell Line ($IC_{50light}$)	PI [a]	Figures	Ref.
			Iron (Fe)				
Heterometallic	**Fe(III), Mn(I)**	$^1O_2$ + cytotoxic CO	600–720	MCF-7 (76 µg/mL); MDA-MB-231 (82 µg/mL); Hep-G2 (92 µg/mL)	>2.7; >2.4; >2.2	Figure 9b	[63]
		$^{\cdot}OH$ + cytotoxic CO	400–700	A549 (2.3 ± 0.4 µM)	~35	Figure 9a	[62]
	Fe(III), Ru(II)	$^1O_2$ + $^{\cdot}OH$ + DNA binding	600–720 (30 J/ cm^2)	A549 (1.4 ± 0.7 µM); HeLa (2.9 ± 0.8 µM)	35; >5	Figure 6b	[22]
			Ruthenium (Ru)				
Homometallic	**Ru(II), Ru(II)**	PDT+PTT	450 (50 mW/cm^2, 30 J/ cm^2) 808 (0.1 W/cm^2, 30 J/ cm^2)	A375 (OP [b]: 0.262–>500 µM) (TP [b]: 0.262–>500 µM)	OP: 3.848–227 TP: 16.2–784	Figure 2a	[12]
	Ru(II), Ru(II)	$^1O_2$ + $^{\cdot}OH$ + ferroptosis	465 (13 mW/cm^2)	A549 (2.33 µM) MGC-803 (3.10 µM)	>21 >16	Figure 2b	[9]
	Ru(II), Ru(II)	$^1O_2$	600 (0.2 W/cm^2)	HeLa (10 µM → viability reduction)	-	Figure 3a	[42]
	Ru(II), Ru(II)	$^1O_2$	436	-	-	Figure 3b	[15]
	Ru(II), Ru(II)	$^1O_2$	visible light (28 J cm^2, 7.8 mW/cm^2) 625 (42 mW/cm^2, 100 J/ cm^2)	HL-60 (visible light: 0.01–10.8 µM). HL-60 (red: 0.14–10.2 µM).	Visible: 2–5439 Red: 2–261	Figure 3c	[16]
	Ru(II), Ru(II)	$^1O_2$ + $^{\cdot}OH$ + $O_2^{\cdot-}$	700 (47.4 J/ cm^2)	(Normoxia—21% O_2) 4T1 (0.66 ± 0.0043 µM) A549 (0.26 ± 0.058 µM) (Hypoxia—1% O_2) 4T1 (3.73 ± 0.016 µM) A549 (3.18 ± 0.09 µM)	 101 356 19 30	Figure 3d	[13]
	Ru(II), Ru(II)	$^1O_2$	620–630 (55 mW/cm^2, 33 J/ cm^2)	SKBR-3 (0.25 µM → 77% decrease in cell viability)	-	Figure 4	[43]

Table 1. *Cont.*

Metal	Oxidation State	Photoinduced Effects	Excitation Wavelength (nm)	Cell Line ($IC_{50light}$)	PI [a]	Figures	Ref.
Heterometallic	**Ru(II), Pt(II)**			CCRF-CEM (4.3 μM) HOP-62 (5.0 μM) BT-549 (14.4 μM) HT29 (18.8 μM) COLO 205 (5.5 μM)	-	Figure 5a	[46]
		$^1O_2$ + DNA binding	595	HeLa (0.13 ± 0.07 μM) RPE-1 (0.45 ± 0.18 μM) A2780 (0.16 ± 0.05 μM) A2780 cis (0.19 ± 0.06 μM) A2780-ADR (0.17 ± 0.04 μM)	10.8 5.5 12.3 13.8 12.6	Figure 5b	[24]
		$^1O_2$ + DNA binding	460–540	-	-	Figure 5c	[47]
		$^1O_2$ + DNA binding	630	CT-26 (11.4 ± 0.6 μM) MCF-7 (9.7 ± 0.8 μM) GM-5657 (18.9 ± 2.3 μM)	1.96 2.11 1.41	Figure 5d	[19]
	Ru(II), Ir(III)	$^1O_2$ + DNA binding + mitochondria targeting	405–450	A549 (0.52 ± 0.1 μM) A549R (0.45 ± 0.1 μM) SCG-7901 (0.44 ± 0.2 μM) SCG-7901DDP (0.37 ± 0.2 μM)	12.2 25.2 12.3 9.5	Figure 6a	[39]
		$^1O_2$ + $^{\cdot}OH$ + $O_2^{\cdot-}$	450 (20 mW/cm^2)	(Normoxia—21% O_2) A549R (1.40 ± 0.98 μM) (Hypoxia—1% O_2) A549R (3.48 ± 0.66 μM)	21.9 -	Figure 6b	[11]
	Ru(II), Co(III)			MCF-7 [c]	-	Figure 7a	[23]
	Ru(II), Fe(III)	$^1O_2$ + $^{\cdot}OH$ + DNA binding	600–720 (30 J/cm^2)	A549 (1.4 ± 0.7 μM); HeLa (2.9 ± 0.8 μM)	35; >5	Figure 7b	[22]

Table 1. *Cont.*

Metal	Oxidation State	Photoinduced Effects	Excitation Wavelength (nm)	Cell Line ($IC_{50light}$)	PI [a]	Figures	Ref.
	Ru(II), Re(I)	Necrosis	-	CT-26 (11.5 ± 1.8 μM) MCF-7 (12.3 ± 2.3 μM) PT-45 (22.1 ± 3.3 μM) GM-5657 (17.4 ± 2.5 μM)		Figure 8c	[18]
		Phototherapy + cytotoxic CO	broad-spectrum light (0, 8, 24, 48 J/cm)	A2780 (<4 μM)	>28	Figure 8b	[26]
	Ru(II), Os(II)	PDT + PTT	808 (100 mW/cm^2)	A375 (0.0236 ± 0.0025 μM) A549R (0.0871 ± 0.0075 μM)	907 772	Figure 8d	[61]
			Osmium (Os)				
Homometallic	**Os(II), Os(II)**	$^1O_2$ + NADH oxidation	640 (red) and 465 (blue)	A549 (red: 25.29 ± 2.14 μM, blue: 27.73 ± 2.53 μM) Caco-2 (red: 3.66 ± 0.25 μM, blue: 3.51 ± 0.45μM) MGC-803 (red: 11.84 ± 1.42 μM, blue: 6.88 ± 1.20 μM) HGC-27 (red: 7.14 ± 1.51 μM, blue: 1.83 ± 0.49 μM)	R:1.63 B: 1.55 R: 1.01 B: 1.06 R: 1.4 B: 2.4 R: 2.5 B: 9.7	Figure 10	[70]
Heterometallic	**Os(II), Fe(II)**	PCT	400–700 (10 J/cm^2)	MDA-MBE-231 (1.1 ± 0.2 μM) HEK 293 (>50 μM)	>50	Figure 12	[72s]
	Os(II), Pt(IV)	PDT + Chemotherapy + Immunogenic cell death (ICD)	670 (13.5 J/cm^2) 740 (12.6 J/cm^2)	A2780 (0.42 ± 0.04 μM) A549 (5.89 ± 0.91 μM) MCA205 (3.21 ± 0.67 μM) RPE-1 (1.73 ± 0.2 μM)	24 >17 >31 8	Figure 13b	[8]

[a] Phototherapeutic index(PI) = IC_{50}(dark)/IC_{50}(light); [b] OP = one-photon; TP = two-photon; [c] No light activation.

4. Strengths, Future Challenges and Conclusions

The rapid evolution of metal-based phototherapeutics has established these complexes as a promising class of PSs for next-generation phototherapeutic systems. Unlike conventional organic chromophores, metal-based systems exploit the unique electronic and coordination properties of metal ions to combine efficient light absorption, tunable excited-state behavior, enhanced ROS generation, and additional therapeutic functionalities within a single molecular platform. This multifunctionality offers significant opportunities to address longstanding challenges in light-driven cancer therapy, including poor tumor selectivity, hypoxia, multidrug resistance, and the limited efficacy of single-target therapies.

Despite these advances, significant challenges remain before metallic PSs can achieve widespread clinical translation. A deeper mechanistic understanding of their photoinduced biological activity, including the interplay between the metal center, ligand environment, excited-state processes, and cellular targets, is still needed to enable the rational optimization of therapeutic efficacy and safety. Equally important, the establishment of robust structure–activity relationships (SAR) to guide molecular design while ensuring favorable pharmacokinetic, pharmacodynamic, and toxicological profiles represents an important future research direction for guiding and facilitating the clinical translation of these structures.

Looking forward, the convergence of inorganic chemistry, photophysics, chemical biology, and nanotechnology is expected to accelerate the development of increasingly sophisticated metal-based systems with programmable and synergistic modes of action. The integration of therapeutic, diagnostic, and targeting capabilities into single molecular structures offers exciting prospects for precise photomedicine. Continued interdisciplinary efforts will therefore be crucial to transform these promising molecular architectures into clinically relevant photoactivatable agents capable of overcoming the current limitations of conventional PSs.

This review highlights the emerging potential of polymetallic photoresponsive complexes as a next-generation platform for photo-activated therapies, addressing critical limitations associated with conventional mononuclear systems. By bringing together recent advances in the rational design of Group 8 polymetallic complexes, this work provides a comprehensive overview of how the incorporation of multiple metal centers can synergistically integrate complementary photophysical, photochemical, and biological functions within a single molecular architecture. Beyond summarizing current developments, the review establishes structure–property–activity relationships that connect molecular design with therapeutic performance, highlighting strategies to improve light harvesting, ROS generation, tumor targeting, and multimodal mechanisms of action. The main breakthrough areas identified in this review include the use of metal–metal interactions and cooperative effects between metal centers to enhance photoactivity, modulate excited-state properties and, thus, promote more efficient ROS generation. The integration of several metal centers has been shown to achieve complementary or synergistic therapeutic strategies to improve tumor selectivity and therapeutic efficacy. Jointly, these developments offer new opportunities and show the potential of polymetallic architectures to move beyond the limitations of conventional mononuclear photosensitizers. Importantly, it also identifies the remaining challenges, including the incomplete understanding of the molecular mechanisms underlying photoinduced cytotoxicity, which continues to limit the rational development and clinical translation of these systems. By critically discussing both opportunities and challenges, this review offers a timely framework for the future design of multifunctional (poly)metallic-based PSs capable of overcoming the intrinsic limitations of traditional systems.

Author Contributions: M.M.-A. and M.J.M.P.: writing—review and editing, validation, formal analysis, tables, figures, data curation, methodology, conceptualization, critically reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: The authors used ChatGPT-6 to design the structure of the review, for a very first draft of the introduction, and for language polishing. All content was carefully reviewed, verified, and edited by the authors, who take full responsibility for the manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

D-A-D	Donor-Acceptor-Donor
DAMP	Damage-associated molecular patterns
DPBF	1,3-Diphenylisobenzofuran
dpp	2,3-Bis(2-pyridyl)pyrazine
DPP	Diketopyrrolopyrrol
dppn	Benzo[i]dipyrido [3,2-a:2′,3′-c]phenazine
dppz	Dipyrido [3,2-a:2′,3′-c]phenazine
dpq	2,3-Bis(2-pyridyl)pyrazine
GSH	Glutathione
HDAC	Histone deacetylase
HpD	Hematoporphyrin
ICD	Immunogenic Cell Death
IL	Intraligand
ILCT	Intraligand charge transfer
ISC	Intersystem Crossing
L-DOPA	L-3,4-dihydroxyphenylalanine / levodopa
LMCT	Ligand-to-metal charge transfer
MLCT	Metal-to-ligand charge transfer
MMCT	Metal-to-metal charge transfer
NADH	Nicotinamide adenine dinucleotide
NIR	Near-Infrared
NMIBC	Non-muscle-invasive bladder cancer
PACT	Photoactivated chemotherapy
PBNPs	Prussian Blue Nanoparticles
PCT	Photocatalytic Cancer Therapy
PDT	Photodynamic Therapy
phpH	Deferiprone
PI	Phototoxicity index
PS	Photosensitizer
PTT	Photothermal therapy
ROS	Reactive Oxygen Species
SOC	Spin-orbit Coupling
tpa	Tris(2-pyridylmethyl)amine
tpphz	Tetrapyrido [3,2-a:2′,3′-c:3″,2″-h:2‴,3‴-j]phenazine
tren	Tris(2-aminoethyl)amine

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